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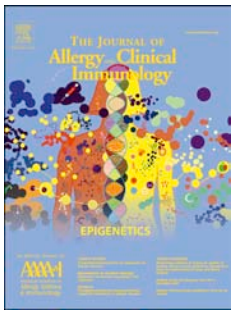

Epigenome-wide Meta-analysis of DNA Methylation and Childhood Asthma

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EPIGENOME-WIDE META-ANALYSIS OF DNA METHYLATION AND CHILDHOOD ASTHMA

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ABSTRACT

Background: Epigenetic mechanisms, including methylation, may contribute to childhood asthma. Identifying DNA methylation profiles in asthma may inform disease pathogenesis.

Objective: To identify differential DNA methylation in newborns and children related to childhood asthma.

Methods: Within the Pregnancy And Childhood Epigenetics (PACE) consortium, we performed epigenome-wide meta-analyses of school-age asthma in relation to CpG methylation (Illumina450K) in blood measured either in newborns, in prospective analyses, or cross-sectionally, in school-age children. We also identified differentially methylated regions (DMRs).

Results: In newborns (8 cohorts, 668 cases), 9 CpGs (and 35 regions) were differentially methylated (epigenome-wide significance, FDR<0.05) in relation to asthma development. In cross-sectional meta-analysis of asthma and methylation in children (9 cohorts, 631 cases), we identified 179 CpGs (FDR<0.05) and 36 differentially methylated regions. In replication studies of methylation in other tissues, most of the 179 CpGs discovered in blood replicated, despite smaller sample sizes, in studies of nasal respiratory epithelium or eosinophils. Pathway analyses highlighted enrichment for asthma-relevant immune processes and overlap in pathways enriched both in newborns and children. Gene expression correlated with methylation at most loci. Functional annotation supports regulatory impact on gene expression at many asthma-associated CpGs. Several implicated genes are targets for approved or experimental drugs, including *IL5RA* and *KCNH2*.

Conclusion: Novel loci differentially methylated in newborns represent potential biomarkers of risk of developing asthma by school age. Cross-sectional associations in children may reflect both risk for and effects of disease. Asthma-related differential methylation in blood in children substantially replicated in eosinophils and respiratory epithelium.

Abstract Word Count: 249

Key Messages: This large-scale genome-wide meta-analysis of DNA methylation and childhood asthma identified novel epigenetic variations related to asthma in newborns and children.

Capsule Summary:

This large-scale genome-wide meta-analysis identified variation in DNA methylation related to childhood asthma, prospectively in newborns and cross-sectionally in children; these biomarkers of asthma development and biologic effects that may shed light on disease mechanisms.

Key words: epigenetics, methylation, asthma, childhood, newborn, drug development.

Abbreviations:

CpG – C phosphate G site

OR – odds ratio

CI – confidence interval

GWAS – Genome-Wide Association Study

INTRODUCTION

Asthma is the most common chronic disease of childhood[1], but the underlying mechanisms remain poorly understood. GWAS meta-analyses have identified many loci related to asthma[2], but these explain only a modest proportion of variation in asthma risk[3]. Increasing evidence suggests that epigenetic variation may play a role in asthma pathogenesis[4]. DNA methylation is the most studied epigenetic modification in humans. Prospective examination of methylation patterns in newborns in relation to asthma development may identify genes and mechanisms involved in the developmental origins of asthma[5].

Epigenome-wide association studies (EWAS) of DNA methylation in blood in relation to asthma (number of cases range from 16 to 149)[6-12] have identified differential methylation at some specific gene regions. The only meta-analysis of epigenome-wide methylation in childhood asthma included 392 cases but did not examine newborn methylation[13]. Larger meta-analysis, including both methylation in newborns and at later ages, would increase power for identification of novel loci.

Using the Illumina HumanMethylation450K BeadChip (Illumina450K), we performed a large-scale meta-analysis of childhood asthma in relation to whole blood DNA methylation in newborns to evaluate whether methylation patterns at birth relate to disease development. We separately examined cross-sectional associations between whole blood DNA methylation and the presence of asthma in children, at least of school age. We investigated the association of DNA methylation in blood and asthma at both individual sites and over genomic regions and evaluated the potential functional impact of findings by integrating gene expression, pathway

analyses, detailed functional annotation, and searching for druggable targets of differentially methylated loci. We also followed up our findings using methylation data in eosinophils and from nasal respiratory epithelium.

METHODS

The Online Repository provides additional details on methods.

STUDY POPULATION

Pregnancy and Childhood Epigenetics (PACE) is an international consortium of cohorts with Illumina450K DNA methylation data at birth (newborns) or in childhood[14]. In prospective analyses, we evaluated childhood asthma at school age in relation to blood DNA methylation data from newborns (8 cohorts: ALSPAC, CHS, EDEN, Generation R, GOYA, MoBa1, MoBa2, NEST). We also conducted cross-sectional analyses of methylation measured in children in relation to asthma status at that same time point (9 cohorts: BAMSE EpiGene, BAMSE MeDALL, CHOP, GALA II, ICAC, NFBC 1986, PIAMA, Raine Study, STOPPA). To avoid problems from small numbers, we set a minimum of 15 cases for participating cohorts to perform analyses.

HARMONIZATION OF CHILDHOOD ASTHMA VARIABLES

We developed a harmonized definition of asthma based on the questionnaire data available in each cohort. Asthma was assessed at school age, defined as age 5 years or older and varied by cohort. Asthma was defined by doctor diagnosis of asthma and the report of at least one of the following: (a) current asthma, (b) asthma in the past year, or (c) asthma medication use in the last year. Non-cases were children who had never had asthma.

METHYLATION DATA MEASUREMENTS AND QUALITY CONTROL

DNA methylation was measured using the Illumina450K platform. Cohorts performed their own quality control, normalization, and analyzed untransformed beta values. We previously found that the use of different pre-processing or normalization methods did not influence meta-analysis results[15, 16]. Probes on the X and Y chromosomes were removed as were those where a SNP was present in the last 5 base pairs of the probe which could interfere with binding. Rather than remove probes a priori that have appeared on various published lists of potentially cross-reactive probes or probes nearby SNPs, we examined post hoc those that appear in statistically significant results[17, 18].

ANNOTATION OF CPGS

Tables include the UCSC RefGene name from Illumina's annotation file and enhanced annotation to UCSC Known Gene. UCSC Known Gene annotations include the nearest gene within 10 Mb of each CpG and fill in many missing gene names. All annotations use the human February 2009 (GRCh37/hg19) assembly.

COHORT SPECIFIC STATISTICAL ANALYSES

The association of methylation and asthma was assessed using logistic regression. Covariates included in adjusted models were maternal age, sustained maternal smoking during pregnancy[15], maternal asthma, socioeconomic status, and child's sex. Cohorts adjusted for batch effects using ComBat[19], SVA[20], or by including a batch covariate in their models. We also adjusted for potential cell type confounding by including estimated proportions calculated using the Houseman method[21] with a cord blood reference panel[22] for newborn cohorts or an

adult blood reference panel[23] for child cohorts. The primary models presented include adjustment for covariates and cell type; reduced models are presented for comparison.

META-ANALYSES

As in other consortium genomic analyses[24, 25], we meta-analyzed the study specific results using inverse variance-weighting, also referred to as fixed effects meta-analysis, with METAL[26]. We accounted for multiple testing by controlling for the false discovery rate (FDR) at 0.05[27]. To enable readers to assess whether the results across studies are consistent, we provide forest plots of the study specific effect estimates and 95% confidence intervals. As another way to visualize meaningful heterogeneity or influential results, we also provide plots, for all significant CpGs, of regression coefficients and 95% confidence intervals where we leave out one cohort at a time. Although inverse-variance weighted meta-analysis does not require the assumption of homogeneity[25], where there is even nominal evidence for heterogeneity (P-value for heterogeneity <0.05, without correction for multiple testing) for any CpG we report as genome wide significant, we also provide meta-analysis P-values from standard random effects meta-analysis using METASOFT[28].

ANALYSES OF DIFFERENTIALLY METHYLATED REGIONS (DMRS)

Differentially methylated regions (DMRs) were identified using two methods, comb-p[29] and DMRcate[30]. To correct for multiple comparisons, comb-p uses a one-step Šidák correction[29], while DMRcate uses an FDR correction[30]. Each method requires the input of parameters to be used in selecting the regions. DMRcate[30] has default values for the minimum number of CpGs in

a region (=2) and minimum length=1000 nucleotides; we used these values in comb-p to maximize comparability. To be conservative, we set the significance threshold at 0.01, rather than 0.05, and only considered a DMR to be statistically significant if it met this threshold in both packages (Šidák corrected P-value<0.01 from comb-p and FDR<0.01 from DMRcate). DMRcate annotates DMRs to UCSC RefGene from the Illumina annotation file.

FUNCTIONAL FOLLOW-UP OF SIGNIFICANT DNA METHYLATION FINDINGS

Correlation of differentially methylated sites with expression of nearby genes

To examine whether differentially methylated sites impact gene expression, we analyzed paired methylation and gene expression data, both measured in blood, from several datasets[31-37] (see Online Repository): two with methylation and gene expression in newborns[32-34] (GEO [GSE62924 and GSE48354], N=38 and IoW, N=157), one with newborn methylation and gene expression at age four years[35] (INMA, N=113), another with gene expression and methylation both measured at age four[35] (INMA, N=112), one with both measured at age 16[38] (BAMSE, N=248), and the largest with both measured in adults[36, 37] (BIOS, N=3,096). For each of our significant CpGs, we examined the association with expression of transcripts within a 500kb window (+/-250kb from the CpG). For differentially methylated regions, we used a window 250kb up- and down-stream of the end and start site of each region. A given CpG or region may have more than one gene transcript in this window. In the smaller datasets of paired gene expression and methylation in newborns or children, we report nominal evidence for significance (P<0.05); for the much larger adult dataset, we report associations based on FDR<0.05.

Functional annotation

To identify tissue or cell type specific signals in significant EWAS results, we used eFORGE[39]. Pathway and network analyses were conducted using Ingenuity Pathway Analysis (IPA) (QIAGEN Inc., Venlo, the Netherlands) (https://www.qiagenbioinformatics.com/products/ingenuity-pathway-analysis)[40]. Due to possible uncertainty regarding genome annotation of probes flagged in the literature as potentially cross-reactive[41], we excluded those from pathway analyses. We also compared our methylation findings to published studies of methylation in relation to asthma and evaluated whether the implicated genes overlap with loci identified in GWAS[42, 43]. Additionally, we matched the genes to which our asthma-associated CpGs and DMRs annotated against the ChEMBL database (v22.1) to identify whether any are targets of approved drugs or drugs in development[44].

LOOK-UP REPLICATION OF SIGNIFICANT DNA METHYLATION FINDINGS IN NASAL RESPIRATORY EPITHELIUM AND EOSINOPHILS

We examined the cell-type specificity of significant findings in whole blood in childhood by doing a look-up in two datasets with methylation measured with the Illumina450K in respiratory epithelium collected by nasal brushing [455 16-year-old Dutch children (37 with asthma) from the PIAMA study[13] and 72 African-American children (36 asthmatics, 38 non-asthmatics)[45]] and in a study with methylation measured with the Illumina450K in eosinophils isolated from blood[46] [16 asthmatics and 8 non-asthmatics aged 2-56 years from the Saguenay-Lac-Saint-Jean (SLSJ) region in Canada[13, 47]].

RESULTS

The prospective analysis of newborn methylation in relation to asthma development included eight cohorts; the cross-sectional analysis of methylation in children in relation to asthma included 9 cohorts with mean ages at assessment of both asthma status and methylation ranging from 7 to 17 years (Table 1 contains counts by cohort; Table E1 in the Online Repository contains descriptive statistics). As newborn DNA methylation is measured at birth, the age at asthma assessment is the time between assessment of methylation and asthma status in the prospective analyses. All models included covariates and cell type unless otherwise noted. Some studies oversampled asthma cases within their population-based cohorts using a nested case-control or case-cohort design for methylation measurement, hence the case-control ratio varies across studies.

ASTHMA IN RELATION TO NEWBORN DNA METHYLATION

Meta-analysis of asthma and newborn methylation (668 cases, 2,904 non-cases, 8 cohorts, ALSPAC, CHS, EDEN, Generation R, GOYA, MoBA1, MoBa2, and NEST), identified 9 statistically significant (FDR<0.05) individual CpGs (Manhattan and volcano plots in Figure 1). The 9 CpGs include two that have appeared on a list of poorly hybridizing probes[41] and thus must be regarded with caution (ch.11.109687686R and ch.6.1218502R). The other seven CpGs annotated to the following genes: *CLNS1A*, *MAML2/Mir_548*, *GPATCH2/STATA17*, *SCOC/LOC100129858*, *AK091866*, *SUB1*, and *WDR20* (Table 2). We identified 35 significant DMRs (Table 3; Table E2 for individual CpGs within DMRs); DMRs did not overlap the significant CpGs. Seven of the 9 significant CpGs showed higher methylation in children who developed

asthma than in non-cases. All 9 CpGs had $P \leq 3.55 \times 10^{-3}$ in a crude model and $P \leq 4.16 \times 10^{-4}$ in the covariate-adjusted models that did not include cell-type (Table E3 in the Online Repository). None of the 9 CpGs had been previously reported in the literature (Table E4 in the Online Repository).

Forest plots, showing the cohort specific odds ratios and 95% confidence intervals for the 9 CpGs, are shown in Figure E1 in the Online Repository. Two cohorts in the newborn analysis include individuals of non-European ancestry (NEST and CHS), therefore we evaluated whether these were influential. The forest plots (Figure E1) suggest that for just 1 of the 9 CpGs (cg07156990), the size of the effect estimate was larger in NEST than in other studies, but the P-value for heterogeneity was not close to statistically significant ($P_{heterogeneity}=0.26$) and after removing NEST, the meta-analysis p-value was attenuated only slightly to 2.8×10^{-6} from 9.5×10^{-7}. When we repeated the meta-analysis removing both NEST and CHS, results were very consistent with those from all cohorts (correlation of the regression coefficients = 0.996). With respect to tests of heterogeneity, only one of the 9 CpGs, cg13289553, gave a p-value for heterogeneity that was even nominally significant ($P_{heterogeneity}=0.04$, Table E3 in the Online Repository includes $P_{heterogeneity}$ for all 9 CpGs and the random effects meta-analysis results for this CpG); GOYA had the largest magnitude of association but effect estimates were in the same positive direction across studies (Figure E1). Analyses leaving out one cohort at a time does not suggest that any of the results are driven by a single cohort (plots of untransformed effect estimates and 95% CI are in Figure E2 in the Online Repository).

ASTHMA IN RELATION TO CHILDHOOD DNA METHYLATION

In meta-analysis of asthma in relation to DNA methylation measured in childhood (631 cases, 2,231 non-cases, 9 cohorts, BAMSE EpiGene, BAMSE MeDALL, CHOP, GALA II, ICAC, NFBC, PIAMA, Raine Study, and STOPPA), we identified 179 CpGs at genome-wide significance (FDR<0.05) (Manhattan and volcano plots in Figure 2; results for all 179 CpGs in Table E5 in the Online Repository). Nearly all (173 of 179) showed decreased methylation in asthma versus non-cases; similar predominant directionality was seen in a recent study[13].

As in the newborn analysis, results were consistent across studies for the 179 significant CpGs (forest plots in Figure E3, plots of regression coefficients and 95% confidence intervals from analyses leaving one cohort out at a time in Figure E4 in the Online Repository). Two of the cohorts were adolescents (NFBC: mean age=16.0, SD=0.4; Raine: mean age=17.0, SD=0.2); repeating the meta-analysis without these two cohorts gave high correlations with the values for our FDR significant findings from all cohorts (correlation of coefficients = 0.96). Because two studies included individuals who were not of European ancestry – ICAC and GALA – we compared significant results with and without including these two studies and found them to be very similar (correlation of coefficients = 0.99). Table E5 in the Online Repository provides P-values for heterogeneity and, where those are even nominally significant ($P_{heterogeneity}$ <0.05), random effects meta-analysis results.

Of the 179 FDR significant CpGs, 34 CpGs were not singletons (i.e., more than one significant CpG annotated to a given gene). These 34 non-singleton CpGs correspond to 13 genes: *ACOT7*, *LOC100189589*, *IL5RA*, *SLC25A26*/*LRIG1*, *RPS6KA2*, *KCNH2*, *ZNF862*/*BC045757*, *AK096249*, *PRG2*, *EVL*/*AX747103*, *KIAA0182*, *ZFPM1*, and *EPX* (Table 4). We identified 36 significant DMRs by both

458 calling methods (Table 5). Of the 179 FDR significant CpGs, 31 fell within one of these 36 DMRs,
459 and 21 of the 36 DMRs contained at least one FDR significant CpG.

460 Three studies in our meta-analysis of asthma in relation to childhood methylation (PIAMA,
461 BAMSE-MeDALL, and BAMSE-Epigene) also contributed to a recent meta-analysis of both
462 preschool and school-aged asthma outcomes[13]; these studies contributed only a quarter
463 (n=155) of the 636 cases in our meta-analysis. That EWAS meta-analysis of asthma at preschool
464 and school-age[13] identified 14 CpGs at genome-wide significance; seven were among our 179
465 genome-wide significant findings for childhood methylation (cg13835688, cg14011077,
466 cg03131767, cg13628444, cg10142874, cg01901579, cg01445399) and six others represented
467 in our dataset (cg15344640, cg11456013, cg01770400, cg19764973, cg08085199, cg16592897),
468 were nominally statistically significant (P<0.05) and direction matched for all 13. When
469 repeating the meta-analysis excluding those three studies, 13 out of the 14 CpGs had P<0.05
470 and directions of association matched; only cg06483820 gave no evidence for association
471 (P=0.74). In additional comparison to the literature, differential methylation in *ACOT7* and
472 *ZFPM1* was previously identified in EWAS of blood in relation to immunoglobulin E[48] and in two
473 of our contributing studies, ICAC and ALSPAC, to asthma[10, 12] as well as in an EWAS of nasal
474 epithelium to asthma[45].

475 Comparing newborn and childhood methylation models, none of the 9 FDR-significant CpGs for
476 newborn methylation were nominally significant (p<0.05) in the childhood methylation analysis.
477 Only 6 of the 179 CpGs significant for asthma in relation to childhood methylation were at least

nominally significant for newborn methylation; two of these had consistent directions of effect [cg16409452 (*EVL*) and cg09423651 (*NCK1*)].

REPLICATION OF FINDINGS FOR ASTHMA IN RELATION TO CHILDHOOD METHYLATION IN NASAL EPITHELIUM

We assessed whether the 179 CpGs differentially methylated in blood in relation to asthma in childhood were also differentially methylated in relation to current asthma in nasal epithelium from two studies (Table E6 in the Online Repository). Among 455 Dutch children (37 with asthma) studied at age 16[13], we found evidence for replication for 20 CpGs: matching direction of effect estimates and nominal significance ($P<0.05$). Among African-American children aged 10-12 with persistent asthma plus atopy (36 cases) compared with 36 non-asthmatic, non-atopic children, 128 of the 179 CpGs gave effect estimates for asthma in the same direction and also had $P<0.05$ for association.

REPLICATION OF FINDINGS FOR ASTHMA IN RELATION TO CHILDHOOD METHYLATION IN EOSINOPHILS

We looked up the 179 CpGs differentially methylated in childhood in relation to asthma in EWAS of 16 asthma cases and 8 non-cases in whom methylation had been measured in purified eosinophils. Of the 177 CpGs included in this dataset, all directions of association with asthma were the same as in PACE and 148 gave $P<0.05$ (Table E7 in the Online Repository).

FUNCTIONAL ANNOTATION

For the newborn analysis, among the 7 significant CpGs (after removing the 2 “ch”-probes), all 7 were near a transcription factor binding site and 6 were in a DNase hypersensitivity site,

identified in at least one ENCODE cell line, supporting a potential functional relevance to transcriptional activity (Figure E5 in the Online Repository).

Among the 179 CpGs significantly differentially methylated in childhood in relation to asthma, there was significant depletion of localization to CpG islands (17 CpGs, 9.5%, $P=1.09x10^{-11}$) and promoters (34 CpGs, 19.0%, $P=1.10x10^{-4}$). Functional annotation plots are shown in Figure E6 in the Online Repository for the 13 gene regions to which the 34 nonsingleton CpGs annotate. Among the 179 CpGs, 113 were in DNAse hypersensitivity sites. Using eFORGE[39] to examine enrichment of all 179 significant CpGs for histone marks (H3K27me3, H3K36me3, H3K4me3, H3K9me3, and H3K4me1), we found significant enrichment for H3K4me1 in blood and lung and H3K36me3 in blood (Figure E7 in the Online Repository).

ASSOCIATION OF METHYLATION AND GENE EXPRESSION

For the CpGs and regions we identified as differentially methylated in either newborns or children in relation to asthma, we assessed association between paired levels of blood DNA methylation and whole blood gene expression for nearby transcripts, defined as within a 500kb window of the significant CpG or DMR, in newborns (GEO n=38, INMA n=113, IoW n=157), children (4-year-olds in INMA n=112, 16-year-olds in BAMSE n=248) and adults (BIOS n=3,096).

Among 9 CpGs differentially methylated in newborns in relation to asthma, three CpGs were associated with expression of a nearby transcript in three datasets (cg17333211 in newborns, 4-year-olds, and adults, and cg02331902 and cg07156990 in two newborn datasets and 4-year-olds) and an additional three CpGs were associated with expression in two datasets

(cg13427149 in 16-year-olds and adults, and cg13289553 and cg21486411 in newborns and 4-year-olds) (Table E8-A in the Online Repository). All regions differentially methylated in newborns in relation to asthma were related to expression in at least one dataset (Table E8-B in the Online Repository).

For methylation in childhood, nearly all (176/179) CpGs related to asthma also associated with expression in at least one dataset (Table E8-C in the Online Repository). CpGs annotated to *IL5RA* were significantly associated with expression in four cohorts (BIOS, INMA, IoW, and BAMSE). All 36 regions differentially methylated in childhood were associated with expression of a nearby transcript in at least one dataset (Table E8-D in the Online Repository).

PATHWAY ANALYSIS

Using IPA, we identified pathways, as well as disease processes and biological functions, significantly enriched ($P<0.05$) for the genes to which the significant individual CpGs or DMRs annotated in the meta-analysis of asthma in relation to newborn or childhood methylation (Tables E9 and E10 in the Online Repository). The genes to which the 7 significant CpGs (after removing "ch"-probes) and 35 significant DMRs in the newborn methylation analysis were annotated were significantly enriched ($P<0.05$) for canonical pathways relevant to immune function in asthma including eNOS signaling, the inflammasome, and NF-κB signaling (Table E9). Enriched disease processes and biologic functions included several involving immune function and others involving immune and organ development (Table E9). Given the larger number of implicated genes for childhood methylation, many more pathways, disease processes, and biological functions were enriched (Table E10 in the Online Repository). There was substantial

overlap in newborns and children in the significantly enriched pathways and diseases and biological function relevant to immune function, immunologic disease and development (Figure E8). As an example, Figure 3 illustrates the network of four overlapping disease and biological processes between newborns and children – tissue morphology, immunological disease, inflammatory disease, and cell-mediated immune response.

DRUGGABLE TARGETS

Among regions differentially methylated in newborns in relation to later asthma, *RUNX1* is the target of the agent CHEMBL2093862 and *CASP8* is the target of CHEMBL2105721 (Nivocasan), an inhibitor of this caspase and two others (1 and 9). Among genes with individual CpGs significantly differentially methylated in childhood in relation to asthma, *KCNH2* (3 significant CpGs) is a target of several approved drugs with mechanism of action of blocking *HERG* (human *Ether-à-go-go*-Related Gene), including the anti-arthymic agents amiodarone hydrochloride, dofetilide, and sotalol. Notably, sotalol is also a beta-adrenergic receptor antagonist. *IL5RA* (2 significant CpGs) is the target for a drug approved for use in severe asthma, benralizumab, whose mechanism of action is antagonism of this gene[49]. Several other genes implicated by either individual CpG (16 genes) or DMR analysis (5 genes, including *IGF1R*) are targets for approved or potential drugs (Tables E11 and E12 in the Online Repository).

DISCUSSION

This epigenome-wide meta-analysis of the association between childhood asthma and DNA methylation measured at birth or childhood identified numerous novel CpGs and regions differentially methylated in relation to this common health outcome. The 9 CpGs and 35 regions significantly differentially methylated in relation to asthma in newborn blood DNA are potential markers of risk for disease development. There were many more statistically significant associations of asthma in relation to childhood DNA methylation, with 179 CpGs and 36 regions; these may reflect both risk for and effects of this disease[50].

Among the significant CpGs in newborns, 6 were in DNAse hyper-sensitivity sites supporting potential regulatory impact on gene function. Additionally, genes to which cg13427149 (*GPATCH2*/*SPATA17*) and cg16792002 (*MAML2*) annotate have previously been associated with obesity phenotypes[51, 52]; conditions that are related to childhood asthma. This supports the potential functional importance and asthma relevance of our newborn findings.

Some CpGs on the 450K array have been reported as potentially polymorphic by virtue of location near SNPs[41]. Given that many of the nearby SNPs are low frequency and most will not interfere with probe binding, which would generate a truly spurious result, rather than filter these in advance, in PACE we examined statistically significant CpGs post-hoc for occurrence on lists of potentially problematic CpGs in the literature as recently recommended by others[17, 18]. Lists of potentially problematic probes change over time as do underlying gene annotations[53]. We note that two of the 9 significant CpGs in newborn methylation (ch.11.109687686R and ch.6.1218502R) were flagged as potentially non-specific ("ch") probes by Chen, et al. [41]. We

provide association results for these as they may be useful to others but, acknowledging this caveat, do not include them in downstream analyses that assume certainty regarding gene localization. With respect to the issue of CpGs previously reported as near SNPs, we visually assessed plots of all significant CpGs in 3 of our largest cohorts [MoBa1 and Generation R for newborn methylation (Figure E9) and STOPPA for childhood methylation (Figure E10)] to verify unimodal distributions.

We identified many more CpGs and DMRs associated with later asthma, likely because these also capture disease effects. Our findings may also reflect different pathophysiological mechanisms related to newborn vs childhood methylation and asthma. A comprehensive search for methylation signals at birth that predict later development of asthma likely requires much larger sample sizes given the intervening effects of exposures and developmental processes that may outweigh effects of small methylation differences present at birth[54]. However, while overlap at the level of specific CpGs or DMRs was low, there was substantial overlap at the pathway and network level (Figure 3 and Figure E8).

To follow-up our differentially methylated signals for potential functional impact, we examined correlations with gene expression. Because of the relatively small sizes of the paired gene expression datasets in newborns or children, we also examined a much larger dataset of adults to increase power. Although the number of subjects in datasets of newborns or children with both gene expression and methylation data were modest (range 38 to 248), limiting power to find correlations, we found that a high proportion of CpGs and DMRs related to asthma were

596 also correlated with gene expression in at least one dataset in this age range. This further
597 supports the functional impact of our methylation findings.

598 Our search for druggable targets identified two genes from the newborn DMR analysis that are
599 targets for either approved or potential drugs. The childhood analysis identified more drug
600 targets. One of these genes, *IL5RA*, already has an approved asthma drug that inhibits its
601 product. This analysis further supports the relevance to asthma pathogenesis and potential
602 clinical usefulness of these findings. Investigating the potential to repurpose approved drugs for
603 new indications has been recently highlighted as cost-effective way to develop new therapeutic
604 modalities[55].

605 We meta-analyzed results across studies using fixed effects meta-analysis with inverse variance
606 weighting. Rice, et al. [25] have recently summarized issues regarding the choice of meta-analytic
607 models for combining study specific results in genomic analyses and show that inverse-variance
608 weighted average estimates a reasonable and interpretable parameter, even under the
609 assumption that effect sizes differ[25]. Further, they point out that fixed effects meta-analysis
610 does not require the assumption of homogeneity. Rice, et al. [25] also emphasize the importance
611 of evaluating meta-analyses effect estimates and significance tests along with visualization of
612 study specific estimates rather than relying on a single statistical estimate of heterogeneity.
613 Accordingly, we provide forest plots, to show the consistency of study specific findings for all
614 significant meta-analysis results (Online Repository Figure E1 for newborn methylation and
615 Figure E3 for childhood methylation). Further, we performed a systematic leave-one-out meta-
616 analysis for all significant CpGs, where we leave each cohort, out one by one (Figure E2 for

newborn and E4 for childhood methylation in the Online Repository). In addition, where there is even nominal evidence for heterogeneity ($P_{heterogeneity}<0.05$), we provide random effects results in Tables E3 (newborn methylation) and E5 (childhood) in the Online Repository.

We recognize various limitations. As in most EWAS[13], as well as GWAS meta-analyses[56], asthma was defined by questionnaires. As in Xu, et al. [13], we used reported doctor diagnosis combined with symptoms and medication use. While the use of self-reported outcomes can lead to misclassification, this should be non-differential with respect to methylation and thus should lead to bias toward the null rather than create false positive findings. We did not stratify the analyses by allergic status because most cohorts do not have objective measures of atopy and, in many cohorts, sample size would have been inadequate for stratification. We also note that the diverse cohorts included in the analysis could have introduced heterogeneity based on ancestry or, in the analysis of methylation in older children, two studies in older adolescents. However, in the studies of older children, non-European ancestry of older children did not appear to be influential in sensitivity analyses. While magnitudes of the associations are modest, this is consistent with other genome wide analyses of methylation in newborns and children in relation to various exposures[15, 57, 58]. These effect sizes are not surprising given that highly reproducible genetic signals discovered in asthma GWAS, such as *ORMDL3*[59], are also modest.

We used logistic regression in the prospective analyses of newborn methylation in relation to asthma rather than Cox regression, which is not commonly used in high dimensional genomic studies. If time to asthma were available or could be estimated reliably, a Cox model would be more efficient. However, for asthma, the exact time to disease development is poorly

638 estimated. Thus, epidemiologic studies generally use age at diagnosis, but there can be a very
639 long lag between disease onset and diagnosis. In our scenario, where the exact time to asthma
640 is unknown, using error-prone outcomes can actually result in larger bias. Thus, considering the
641 tradeoff between bias and efficiency, logistic regression is the better option. We also note that
642 where the condition under study has lower than 10% prevalence, as is the case for our outcome,
643 asthma diagnosed at school age, the odds ratio is a good approximation of the hazard ratio[60].
644 To address the important aspect of age at diagnosis of asthma, we used the diagnosis age for
645 the harmonized definition of asthma. With the exception of a couple of studies, where
646 sensitivity analyses removing them did not suggest undue influence, the range of mean ages is
647 not large.

648 Unmeasured confounding is a concern in all analyses of observational data. With high
649 dimensional genomic data, variability due to batch effects is an additional potential source of
650 unmeasured confounding[61]. In this meta-analysis, each cohort corrected for batch effects using
651 methods most suitable for their own data. In most studies, methylation analyses were
652 completed over a short period of time which greatly reduces batch effects[61]. When using
653 methods such as adjustment for batch variables or ComBat, one must specify the putative
654 batch variables. To the extent that there are unknown factors contributing to laboratory
655 variability, there may be residual confounding. Various methods have been proposed to
656 attempt to address unmeasured confounding in high dimensional data. However, in meta-
657 analysis, findings, tend to be significant because they are consistent across studies. Thus, the
658 chance that in studies done in different countries, with methylation measured in different
659 laboratories and at different times, that unmeasured confounding is operating in the same

660 manner across studies, resulting in false positive significant associations in the meta-analysis, is
661 greatly reduced. Further in the childhood methylation analysis, we have substantial replication
662 of findings from a recently published meta-analysis[13], even after overlapping individuals are
663 removed. In addition, the consistency of our findings from blood DNA with results for DNA
664 isolated from two tissues highly relevant for asthma, eosinophils and nasal respiratory
665 epithelium, provides compelling evidence that our findings are not driven by unmeasured
666 confounding.

667 Identification of differentially methylated regions provides a way to reduce the dimensionality
668 of the epigenome-wide methylation data and can identify associations at the regional level
669 where there are not individually significant CpGs. The two methods that we used for DMR
670 identification, DMRcate and comb-p, are the only two published methods available for use with
671 meta-analysis results[29, 30]. A recent review noted that the various methods published for
672 identifying DMRs employ different assumptions and statistical approaches and thus rarely
673 identify exactly the same regions[62]. Accordingly, to reduce false positives, we reported only
674 DMRs identified as statistically significant by both methods.

675 We measured DNA methylation in whole blood, a mix of cell types. Cell counts were not
676 measured, but we adjusted our models for estimated cell counts using established reference-
677 based methods to address confounding by cell type differences[21]. For childhood, as opposed to
678 newborn, methylation, we used an adult reference panel, because a suitable one is not
679 available for children. Notably, the considerable overlap between our findings in whole blood
680 and smaller studies of two highly asthma-relevant tissues, nasal epithelium, an excellent proxy

for airway epithelium in studies of asthma[63] and purified eosinophils, greatly reduces the concern that our findings are false positives due to failure to fully account for the influence of asthma on white blood cell proportions.

In addition to confirmation of findings in studies of eosinophils and nasal respiratory epithelium, and the high power resulting from meta-analysis, other strengths of the study include our efforts to standardize the definition of asthma across studies, the large sample size provided by meta-analysis, and evaluation of potential biological implications of our findings by detailed examination of functional annotation, pathway analysis, correlating differentially methylated sites with gene expression and consideration of potential druggable targets.

In summary, we identified numerous novel CpGs and regions associated with childhood asthma in relation to DNA methylation measured either at birth, in prospective analyses, or in childhood, in cross-sectional analyses. Many of the genes annotated to these CpGs and regions are significantly enriched for pathways related to immune responses crucial in asthma; several genes are targets for either approved or investigational drugs. Most differentially methylated CpGs or regions correlated with expression at a nearby gene. Many more individual CpGs were differentially methylated in childhood in relation to their current asthma status. There was appreciable overlap with findings in nasal respiratory epithelium and purified eosinophils. The CpGs and regions identified in newborns might be potential biomarkers of later asthma risk; those identified in childhood likely reflect both processes that impact disease risk and effects of having the disease. The novel genes implicated by this study may shed new light on asthma pathogenesis.

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FIGURE LEGENDS

Figure 1: Meta-analysis of asthma in relation to newborn methylation: (A) Manhattan plot and (B) volcano plot. Model adjusted for covariates and cell-types.

Figure 2: Meta-analysis of asthma in relation to childhood methylation: (A) Manhattan plot and (B) volcano plot. Model adjusted for covariates and cell-types. CpGs corresponding to genes with more than one FDR<0.05 significant CpG are highlighted in red.

Figure 3: A network is shown for four categories of disease and biological functions overlapping between analyses of asthma in relation to either newborn or childhood methylation - immunological disease, cell-mediated immune response, inflammatory disease and tissue morphology. A gene is connected to a disease or function if it has been previously shown to be involved in it. All the genes marked in red are implicated from newborn methylation analyses and those in orange are implicated from childhood methylation analyses.

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Table 1: Samples sizes by cohort for epigenome wide association analyses of asthma in relation to DNA methylation in newborns or children. Cohort specific information on covariates is in Supplementary Table E1.

Age Group	Cohort	N	N cases
Newborns	ALSPAC	688	88
	CHS	229	39
	EDEN	150	34
	Generation R	661	37
	GOYA	507	37
	MoBa1	666	149
	MoBa2	458	239
	NEST	213	45
	Meta-analysis	3572	668
Children	BAMSE EpiGene	307	93
	BAMSE MeDALL	214	47
	CHOP	382	19
	GALA II	193	106
	ICAC	194	97
	NFBC 1986	413	17
	PIAMA	197	15
	Raine Study	509	105
	STOPPA	460	137
	Meta-analysis	2869	636

Table 2 *Nine FDR<0.05 significant CpGs from the meta-analysis of asthma in relation to newborn methylation.*

CpG*	chr:pos	UCSC RefGene Name	UCSC Known Gene**	Average Methylation	OR*** (CI)	P-value	Direction****
cg21486411	chr11:77348243	*CLNS1A*	*CLNS1A*	0.089	1.13 (1.08,1.18)	3.43E-07	+?++++++
cg16792002	chr11:95788886	*MAML2*	*Mir_548*	0.840	0.95 (0.93,0.97)	5.59E-07	-------+
ch.11.109687686R	chr11:110182476			0.085	1.08 (1.05,1.11)	7.06E-07	+??+++++
cg13427149	chr1:217804379	*GPATCH2;SPATA17*	*GPATCH2*	0.063	1.19 (1.11,1.27)	8.04E-07	++++++++
cg17333211	chr4:141294016	*SCOC*	*LOC100129858*	0.074	1.13 (1.08,1.19)	8.25E-07	-+-+++++
cg02331902	chr5:90610303		*AK091866*	0.089	1.12 (1.07,1.18)	8.37E-07	--++++++
cg13289553	chr5:32585524	*SUB1*	*SUB1*	0.085	1.14 (1.08,1.20)	8.68E-07	+++++++-
ch.6.1218502R	chr6:51250028			0.054	1.27 (1.15,1.39)	9.32E-07	+??+++++
cg07156990	chr14:102685678	*WDR20*	*WDR20*	0.930	0.87 (0.83,0.92)	9.54E-07	-++-----

* ch probes (ch.11.109687686R and ch.6.1218502R) have been reported to be cross hybridizing and thus UCSC Known Gene is intentionally left blank.

** Annotation based on UCSC Known Gene also fills in nearest gene within 10 MB.

*** Odds ratio of developing asthma for a 1% absolute increase in methylation. Adjusted for covariates and cell type.

**** For each cohort participating in the analysis: + indicates a positive direction of effect, - indicates a negative direction of effect, and ? indicates missing information for that CpG in a given cohort. Cohort Order: ALSPAC, CHS, EDEN, Generation R, GOYA, MoBa1, MoBa2, NEST.

Table 3 Differentially methylated regions (DMRs; N=35) for asthma in relation to newborn methylation identified by both comb-p (P-value<0.01) and DMRcate (FDR<0.01) methods

chr:pos	Gene Name*	N CpGs in region	P-value from comb-p**	FDR from DMRCate***
chr1:59280290-59280842	*LINC01135*	5	1.23E-03	1.01E-03
chr1:220263017-220263699	*BPNT1; RNU5F-1*	11	4.49E-04	7.74E-05
chr1:1296093-1296489	*MXRA8*	2	9.83E-03	3.86E-04
chr2:202097062-202097608	*CASP8*	5	1.14E-03	1.64E-05
chr2:235004843-235005012	*SPP2*	2	6.22E-03	1.15E-03
chr3:194188646-194189444	*ATP13A3*	3	1.06E-03	7.14E-04
chr4:113218385-113218525	*ALPK1*	3	2.00E-03	3.69E-04
chr5:158526108-158526694	*EBF1*	6	9.56E-04	2.16E-05
chr5:81573780-81574461	*RPS23*	11	3.75E-03	1.47E-04
chr5:64777678-64778186	*ADAMTS6*	10	7.09E-03	9.97E-05
chr6:291687-292824	*DUSP22*	9	6.69E-06	1.18E-05
chr6:32799997-32801050	*TAP2*	13	1.27E-03	6.66E-05
chr6:26234819-26235610	*HIST1H1D*	9	6.12E-03	7.67E-05
chr6:29648161-29649085	*ZFP57*	22	1.82E-08	3.13E-11
chr6:31055396-31055503	*C6orf15*	5	3.61E-04	7.05E-05
chr7:106694832-106695007	*PRKAR2B*	2	6.86E-03	7.92E-04
chr7:87974722-87975316	*STEAP4*	4	2.32E-03	7.44E-05
chr7:158045980-158046359	*PTPRN2*	6	1.98E-03	5.94E-04
chr8:127889010-127889296	*PCAT1*	4	2.68E-05	1.44E-05
chr8:33370172-33371226	*TTI2*	9	1.08E-04	6.40E-06
chr10:71871364-71871634	*H2AFY2*	4	8.06E-03	6.19E-04
chr10:65028929-65029169	*JMJD1C*	5	8.56E-03	6.12E-04
chr11:268923-269469	*NLRP6*	5	3.71E-03	1.42E-03
chr11:107328442-107328915	*CWF19L2*	10	5.10E-03	2.13E-05
chr12:74931289-74932008	*ATXN7L3B*	10	1.03E-03	2.81E-06
chr12:58329764-58330116	*LOC100506844*	5	1.58E-03	5.22E-04
chr13:108953659-108954055	*TNFSF13B*	2	5.19E-03	2.37E-03
chr13:31618695-31618744	*TEX26*	2	4.63E-03	2.09E-04
chr14:69341139-69341739	*ACTN1*	4	1.36E-03	9.96E-04
chr16:20774873-20775353	*ACSM3*	5	3.47E-03	1.58E-03
chr17:74667833-74668253	*LOC105274304*	6	2.13E-03	8.34E-07
chr17:21029189-21029296	*DHRS7B*	2	7.18E-03	5.11E-05
chr18:47813745-47815431	*CXXC1*	10	2.58E-05	1.68E-03
chr21:36421467-36421956	*RUNX1*	6	2.23E-03	1.67E-04
chr22:24372913-24374013	*LOC391322*	12	3.21E-04	1.35E-07

* DMRcate annotates to UCSC RefGene from Illumina annotation file.

** Comb-p uses a one-step Sidak multiple-testing correction on the regional P-value assigned using Stouffer-Liptak method.

*** DMRcate takes the minimum Benjamini-Hochberg False Discovery Rate (FDR) corrected P-value in the region as representative after recalculating P-values using Gaussian kernel smoothing.

Table 4 *34 CpGs annotated to 13 genes with more than one FDR<0.05 significant CpG from the meta-analysis of asthma in relation to childhood methylation*

CpG	chr:pos	UCSC RefGene Name	UCSC Known Gene*	P-value	Average Methylation	OR** (CI)	Direction***
cg13066938	chr1:6341140	*ACOT7*	*ACOT7*	1.67E-05	0.682	0.91 (0.88,0.95)	--+?--+--
cg21220721	chr1:6341230	*ACOT7*	*ACOT7*	1.02E-08	0.763	0.94 (0.92,0.96)	--+------
cg09249800	chr1:6341287	*ACOT7*	*ACOT7*	1.19E-08	0.916	0.88 (0.84,0.92)	???---?--
cg11699125	chr1:6341327	*ACOT7*	*ACOT8*	7.54E-10	0.799	0.90 (0.87,0.93)	--+------
cg00043800	chr2:74612144	*LOC100189589*	*LOC100189589*	1.32E-05	0.585	0.91 (0.87,0.95)	-----++--
cg17988187	chr2:74612222	*LOC100189589*	*LOC100189590*	1.21E-06	0.699	0.90 (0.86,0.94)	--+?--+--
cg01310029	chr3:3152374	*IL5RA*	*IL5RA*	4.18E-06	0.744	0.89 (0.85,0.94)	---?--+--
cg10159529	chr3:3152530	*IL5RA*	*IL5RA*	4.48E-06	0.736	0.90 (0.86,0.94)	---?-----
cg07410597	chr3:66404129	*SLC25A26*	*LRIG1*	2.70E-07	0.773	0.88 (0.84,0.93)	--+---+--
cg04217850	chr3:66428294	*SLC25A26*	*LRIG2*	2.35E-06	0.747	0.88 (0.83,0.93)	--+------
cg15304012	chr6:166876490	*RPS6KA2*	*RPS6KA2*	1.86E-05	0.697	1.08 (1.04,1.13)	+++++++++
cg19851574	chr6:167178233	*RPS6KA2*	*RPS6KA2*	3.42E-06	0.671	0.95 (0.94,0.97)	--+------
cg03329755	chr6:167189272	*RPS6KA2*	*RPS6KA2*	6.14E-06	0.818	0.91 (0.88,0.95)	-++------
cg05184016	chr7:149543136	*ZNF862*	*BC045757*	2.74E-08	0.817	0.85 (0.80,0.90)	--+------
cg07970948	chr7:149543165	*ZNF862*	*BC045757*	6.39E-08	0.771	0.91 (0.88,0.94)	---+--+--
cg06558622	chr7:149543177	*ZNF862*	*BC045757*	3.39E-09	0.818	0.88 (0.85,0.92)	---------
cg24576940	chr7:150648283	*KCNH2*	*KCNH2*	1.83E-05	0.848	0.87 (0.81,0.93)	---------
cg23147443	chr7:150649655	*KCNH2*	*KCNH2*	1.83E-06	0.842	0.89 (0.85,0.93)	???---?--
cg18666454	chr7:150651937	*KCNH2*	*KCNH2*	1.46E-07	0.761	0.89 (0.86,0.93)	---------
cg13850063	chr9:138362321		*AK096249*	5.49E-08	0.819	0.78 (0.71,0.85)	--+?-----
cg14011077	chr9:138362327		*AK096249*	7.02E-09	0.797	0.86 (0.82,0.90)	---?-----
cg15700636	chr11:57156050	*PRG2*	*PRG2*	2.35E-07	0.746	0.89 (0.85,0.93)	--+------
cg08773180	chr11:57157607	*PRG2*	*PRG2*	1.77E-07	0.741	0.89 (0.85,0.93)	--+---+--
cg12819873	chr11:57157632	*PRG2*	*PRG2*	9.55E-06	0.760	0.90 (0.86,0.94)	------+--
cg16409452	chr14:100610186	*EVL*	*AX747103*	4.89E-07	0.770	0.91 (0.87,0.94)	--+------
cg14084609	chr14:100610407	*EVL*	*AX747103*	2.96E-09	0.780	0.89 (0.85,0.92)	---------
cg18550847	chr14:100610570	*EVL*	*AX747103*	7.10E-07	0.730	0.91 (0.88,0.94)	--+?-----
cg08640475	chr16:85551478		*KIAA0182*	2.36E-06	0.815	0.92 (0.89,0.95)	--+------
cg10099827	chr16:85551514		*KIAA0182*	1.32E-06	0.808	0.92 (0.89,0.95)	---------
cg08940169	chr16:88540241	*ZFPM1*	*ZFPM1*	2.93E-07	0.778	0.91 (0.87,0.94)	------+--
cg04983687	chr16:88558223	*ZFPM1*	*ZFPM1*	1.33E-10	0.744	0.93 (0.90,0.95)	---------
cg25173129	chr17:56269410	*EPX*	*EPX*	8.09E-07	0.753	0.88 (0.84,0.93)	--+---+--
cg02970679	chr17:56269818	*EPX*	*EPX*	9.99E-07	0.776	0.88 (0.83,0.92)	------+--
cg17374802	chr17:56270828	*EPX*	*EPX*	2.06E-06	0.713	0.90 (0.86,0.94)	---?--+--

* Annotation based on UCSC Known Gene also fills in nearest gene within 10 MB.

** Odds ratio of developing asthma for a 1% absolute increase in methylation. Adjusted for covariates and cell type.

*** For each cohort: + indicates a positive direction of effect, - indicates a negative direction of effect, and ? indicates missing information for that CpG. Cohort Order: BAMSE EpiGene, BAMSE MeDALL, CHOP, GALAII, ICAC, NFBC1986, PIAMA, RAINE, STOPPA

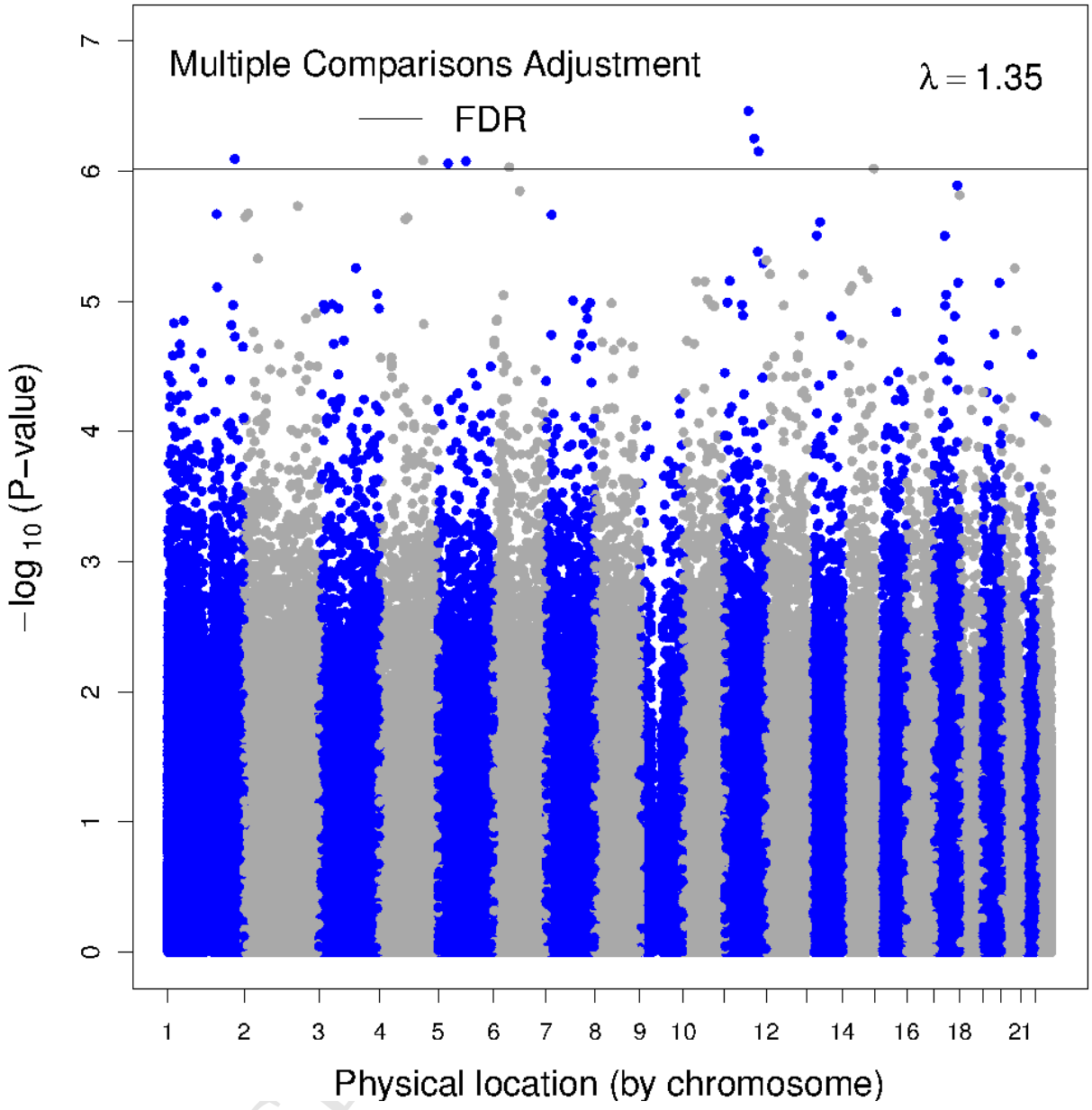
Table 5 Differentially methylated regions for asthma in relation to childhood methylation with adjustment for covariates and cell type identified by both comb-p (P-value<0.01) and DMRcate (FDR<0.01) methods

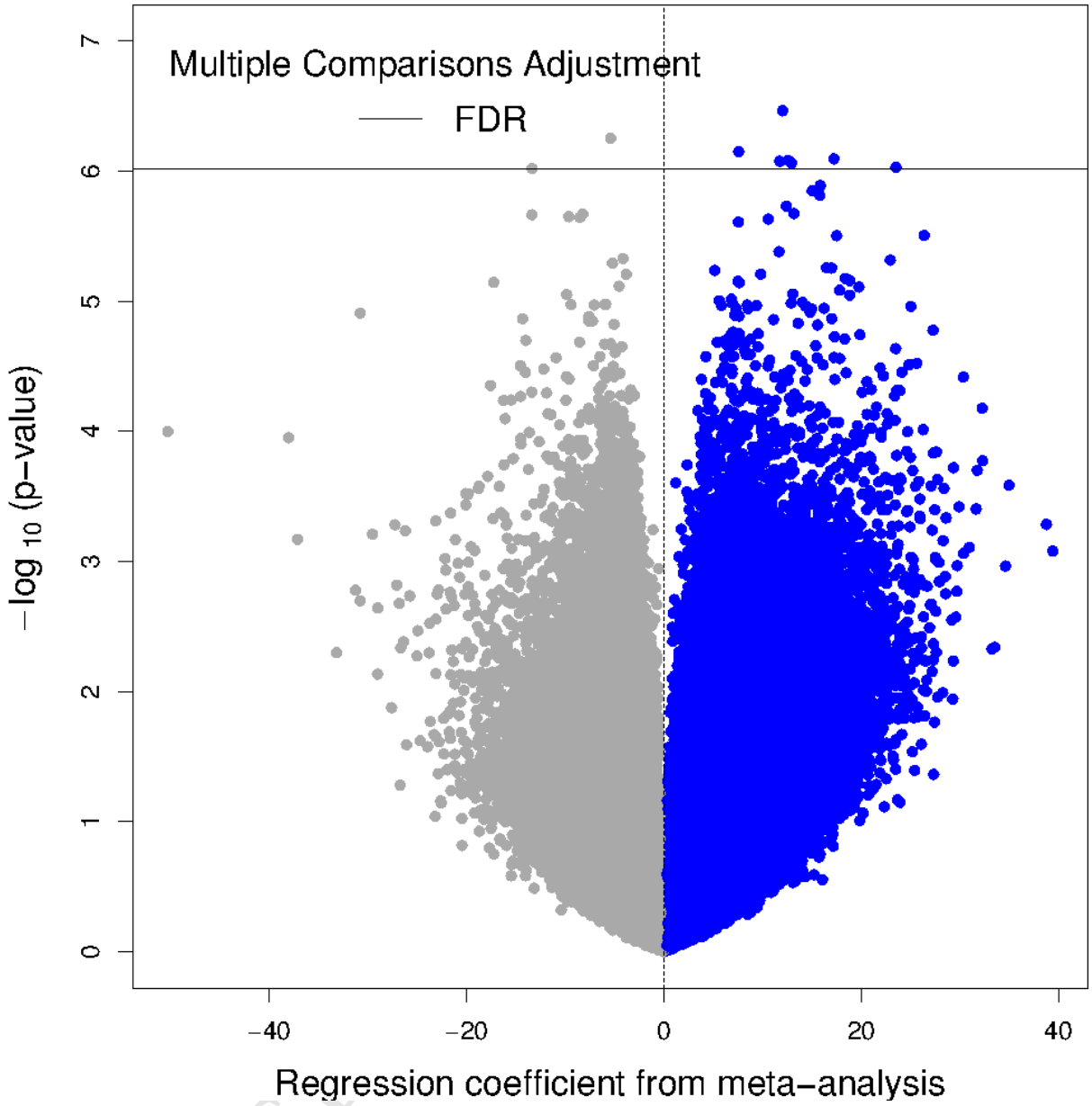
chr:pos	Gene Name*	N CpGs in region	P-value from comb-p**	FDR from DMRCate***
chr1:161575716-161576323	*HSPA7*	4	8.61E-03	1.24E-03
chr1:209979111-209979780	*IRF6*	13	4.62E-04	1.90E-04
chr1:2036283-2036644	*PRKCZ*	4	2.00E-04	3.14E-05
chr1:87596820-87596935	*LINC01140*	3	1.58E-03	2.79E-05
chr2:149639612-149640260	*KIF5C*	4	3.50E-03	1.14E-05
chr2:11917490-11917788	*LPIN1*	3	4.81E-03	6.25E-04
chr3:195974258-195974330	*PCYT1A*	3	5.07E-05	2.00E-05
chr3:3151795-3152917	*IL5RA*	6	1.35E-08	2.12E-09
chr5:38445220-38446193	*EGFLAM*	9	5.11E-06	1.28E-05
chr5:132008525-132009631	*IL4*	4	5.36E-07	3.11E-05
chr6:112688010-112688931	*RFPL4B*	4	4.89E-05	5.19E-04
chr6:166876490-166877039	*RPS6KA2;RPS6KA2-IT1*	8	3.08E-05	1.74E-06
chr7:156735383-156735657	*NOM1*	3	7.11E-03	2.82E-03
chr7:149543136-149543178	*ZNF862*	3	3.85E-16	1.43E-16
chr7:65419185-65419289	*VKORC1L1*	7	2.82E-03	1.04E-03
chr8:832917-833049	*ERICH1-AS1;DLGAP2*	3	6.15E-03	6.44E-03
chr8:141046436-141046853	*TRAPPC9*	5	8.93E-07	3.45E-09
chr9:138362321-138362505	*PPP1R26-AS1*	3	2.72E-05	1.44E-09
chr9:130859454-130859607	*SLC25A25*	2	2.69E-08	5.84E-08
chr11:65545808-65547173	*AP5B1*	8	1.31E-10	9.73E-12
chr11:69291998-69292065	*LINC01488*	3	4.55E-04	1.65E-04
chr11:59856225-59856359	*MS4A2*	2	1.50E-03	3.25E-04
chr12:15125458-15126021	*PDE6H*	4	6.93E-03	7.65E-06
chr14:100610071-100610668	*EVL*	6	7.79E-16	1.24E-19
chr15:64275810-64275854	*DAPK2*	2	4.91E-04	2.04E-04
chr15:99443213-99443667	*IGF1R*	4	6.57E-05	2.41E-04
chr16:875257-875627	*PRR25*	4	3.34E-03	3.21E-03
chr16:88539861-88540397	*ZFPM1*	5	1.09E-04	1.13E-05
chr16:615709-616221	*PRR35*	5	1.62E-04	2.70E-07
chr16:85551478-85551749	*GSE1*	3	5.27E-07	2.37E-07
chr17:56269410-56270829	*EPX*	5	6.20E-11	1.41E-08
chr17:78682785-78683458	*RPTOR*	5	1.18E-04	4.03E-04
chr19:51961666-51961938	*SIGLEC8*	3	2.37E-04	5.07E-04
chr19:50553682-50554511	*LOC400710*	10	1.78E-07	3.81E-06
chr20:35503832-35504554	*TLDC2*	8	1.23E-03	5.90E-08
chr21:42520365-42520903	*LINC00323*	3	1.41E-04	2.64E-05

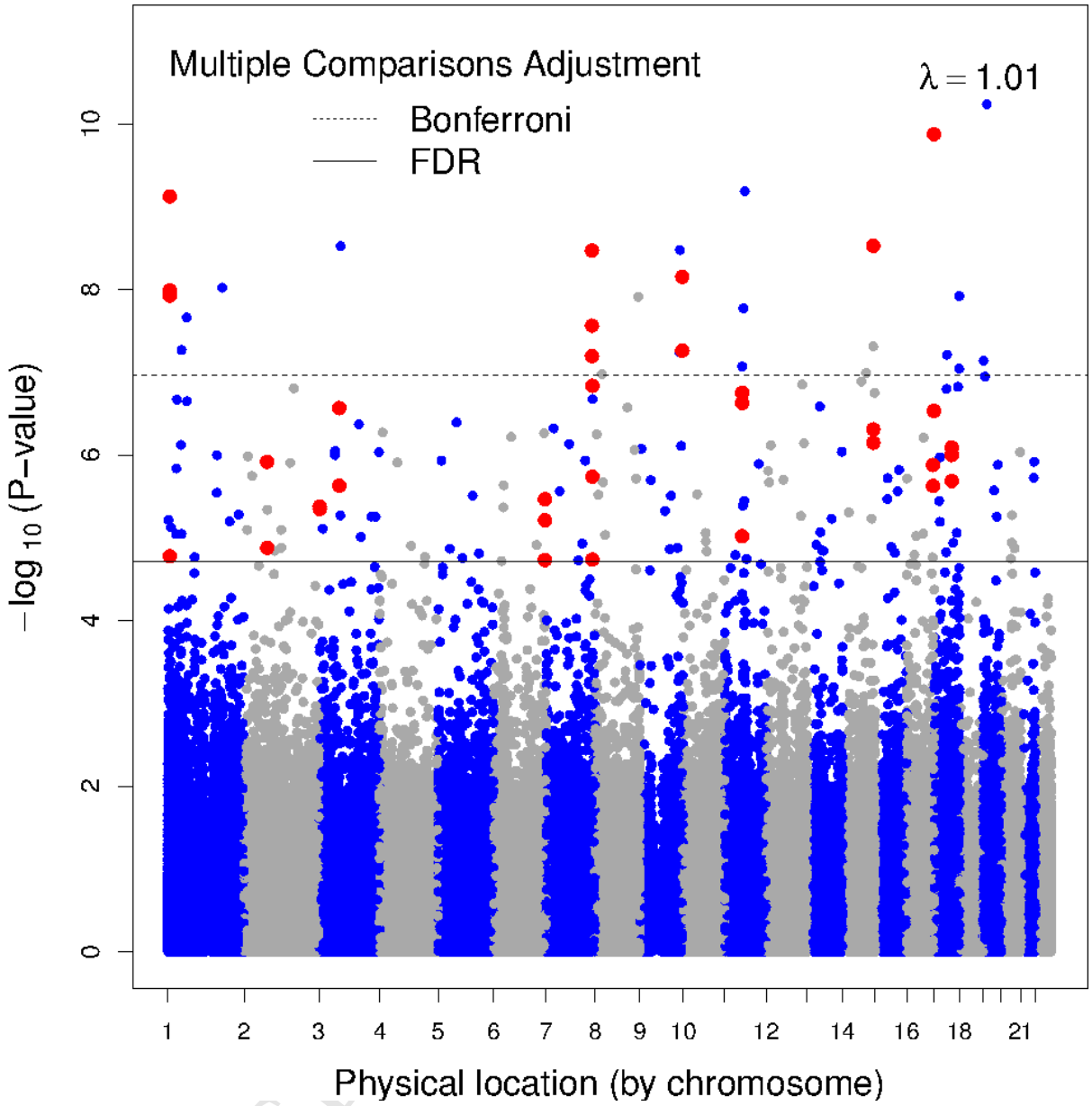
* DMRcate annotates to UCSC RefGene from Illumina annotation file. First listed gene shown.

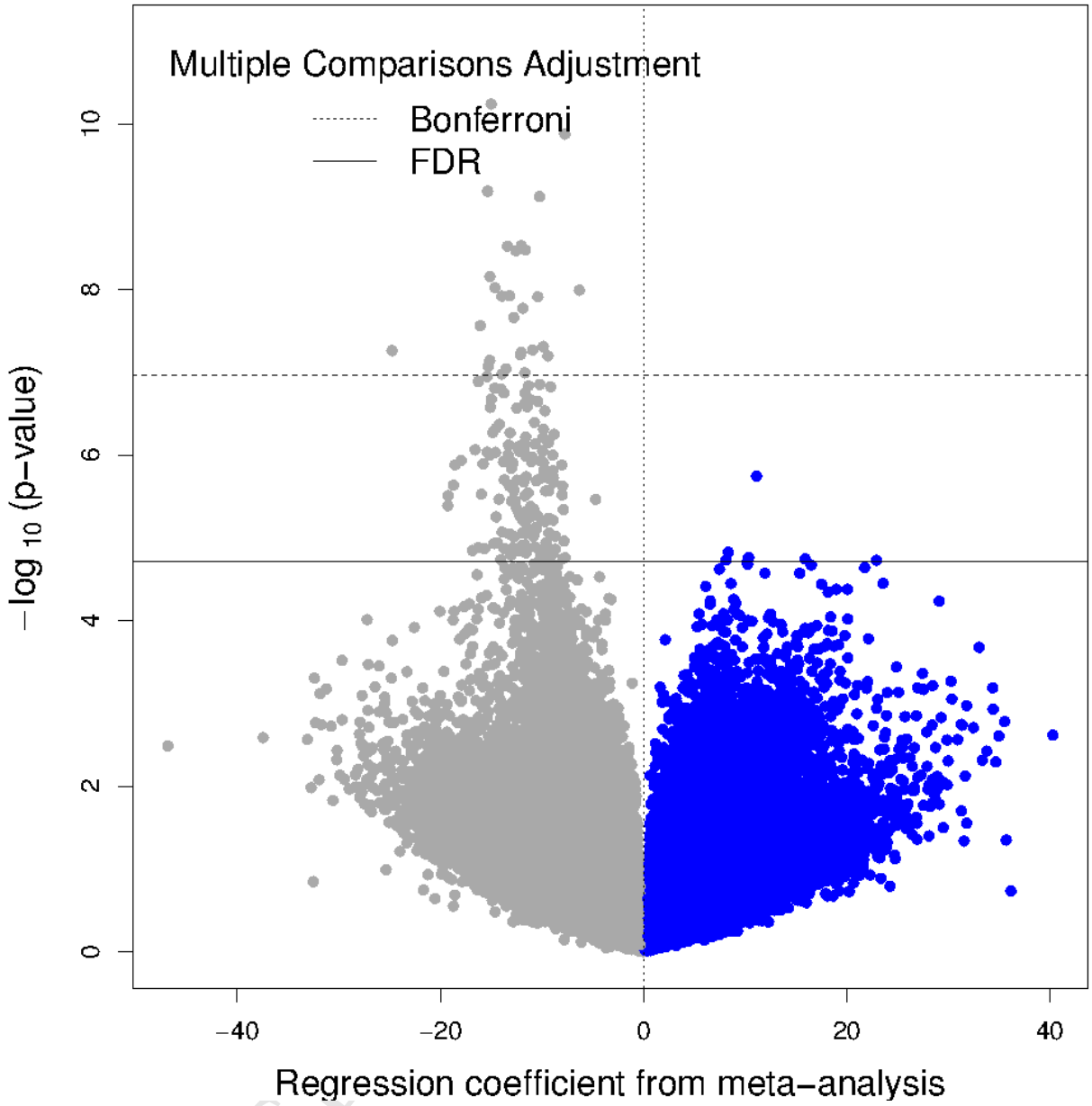
** Comb-p uses a one-step Sidak multiple-testing correction on the regional P-value assigned using Stouffer-Liptak method.

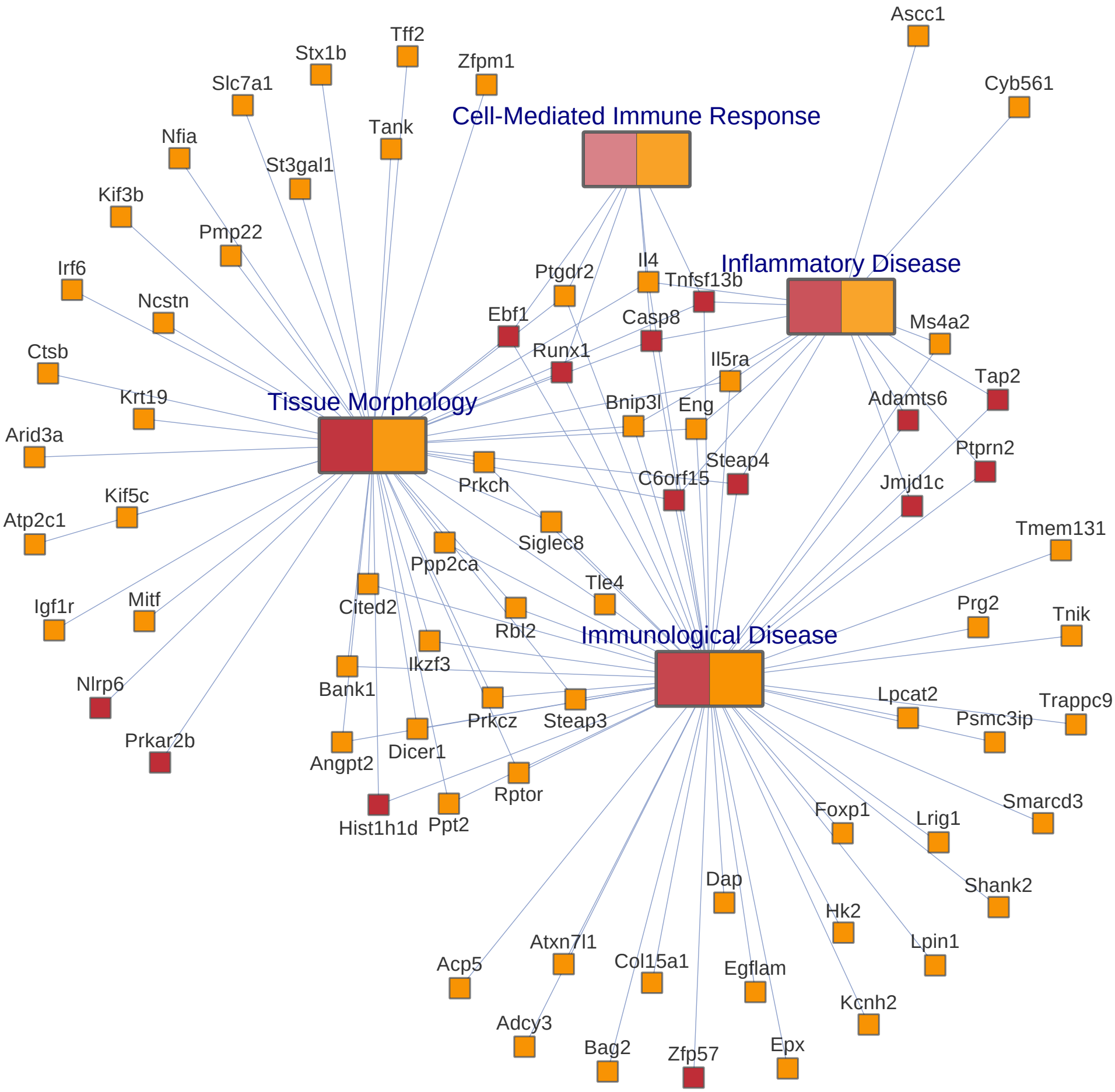
*** DMRcate takes the minimum Benjamini-Hochberg False Discovery Rate (FDR) corrected P-value in the region as representative after recalculating P-values using Gaussian kernel smoothing.


Multiple Comparisons Adjustment
FDR
λ = 1.35
−log 10 (P−value)
0
1
2
3
4
5
6
7
1
2
3
4
5
6
7
8
9
10
12
14
16
18
21
Physical location (by chromosome)








Cell-Mediated Immune Response
Inflammatory Disease
Tissue Morphology
Immunological Disease
Ascc1
Cyb561
Tff2
Stx1b
Zfpm1
Slc7a1
Tank
Nfia
St3gal1
Kif3b
Pmp22
Irf6
Ncstn
Ctsb
Krt19
Arid3a
Kif5c
Atp2c1
Igf1r
Mitf
Nlrp6
Prkar2b
Il4
Ptgdr2
Tnfsf13b
Ebf1
Casp8
Runx1
Ms4a2
Il5ra
Tap2
Bnip3l
Eng
Adamts6
Ptprn2
Steap4
C6orf15
Jmjd1c
Prkch
Siglec8
Ppp2ca
Tle4
Tmem131
Cited2
Rbl2
Prg2
Tnik
Ikzf3
Bank1
Prkcz
Steap3
Lpcat2
Psmc3ip
Trappc9
Angpt2
Dicer1
Rptor
Hist1h1d
Ppt2
Foxp1
Lrig1
Smarcd3
Dap
Shank2
Hk2
Lpin1
Atxn7l1
Acp5
Col15a1
Egflam
Kcnh2
Adcy3
Bag2
Zfp57
Epx

ONLINE REPOSITORY

EPIGENOME-WIDE CONSORTIUM META-ANALYSIS OF DNA METHYLATION AND CHILDHOOD ASTHMA

Supplementary Methods

1. COHORT SPECIFIC DESCRIPTIONS OF STUDY POPULATION, PHENOTYPE DATA, DNA METHYLATION DATA AND SUPPLEMENTAL ACKNOWLEDGEMENTS

ALSPAC

Study population

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a large, prospective cohort study based in the South West of England. In total, 14,541 pregnant women residents in Avon, UK with expected delivery dates between 1st April 1991 and 31st December 1992 were initially enrolled; 13,988 children were alive at 1 year[1, 2]. Please note that the study website contains details of all the data that are available through a fully searchable data dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/). The study has been approved by the ALSPAC Ethics & Law Committee (ALEC) and written consent was obtained from participating parents of their children.

Phenotype data

Questionnaires were sent to parents when the study children were around the age of 91 months. School age children (7 ½ years) were classified as having current asthma if the mother responded "yes" to the question "has a doctor ever actually said that your study child has asthma?" and in addition, responded "yes" to either of the following questions: "has he/she had any of the following in the past 12 months? [Asthma]" or "children often have accidents or illnesses that need treatment. Please indicate which of the following has been given to your child in the past 12 months. [Asthma medication]".

Covariates

Maternal age at delivery was derived from the mother's report of her own and child's dates of birth. Maternal social class was recorded and derived from self-report questionnaire data of occupation according to the Registrar General's Social Classes based upon SOC 2000 codes. Data were collapsed to low (classifications IV & V), middle (classifications of III (non-manual) & III (manual)) and high (classifications of I & II). Maternal smoking status was derived from self-report questionnaire data completed by the mother. Smoking status was recorded at 18 weeks and 32 weeks gestation and was defined as no smoking during pregnancy, smoked during early pregnancy and smoked throughout pregnancy. Maternal asthma was reported by questionnaire completed by the mothers at 12 weeks gestation. Child's sex was recorded as dichotomous variable.

DNA Methylation Data

Cord blood (whole blood or buffy coats) was collected according to standard procedures, spun and frozen at -80˚C. DNA-methylation data pre-processing was conducted as part of the Accessible Resource for Integrated Epigenomic Studies (ARIES) project [ariesepigenomics.org.uk] at the University of Bristol[3]. Briefly, DNA was bisulfite converted using Zymo EZ DNA MethylationTM kit (Zymo, Irvine, CA). The Illumina Infinium® HumanMethylation450k BeadChip assay was used to measure genome-wide methylation status. Assay arrays were scanned using the Illumina iScan and initial quality review was assessed using GenomeStudio (version 2011.1). Samples were distributed across slides using a semi-random approach. Samples with >20% probes with a detection p-value ≥0.01 failed quality control and were repeated. Genotype probes on the array were compared between samples of the same individuals and against genome wide SNP chip data to assess and remove any sample mismatches. The methylation data were pre-processed using the WateRmelon package in R (version 3.0.1) according to the subset quantile normalization approach as described by Touleimat and Tost[4]. After assaying, repeat assays, pre-processing QC and normalization, 485,577 probes were available. Probes with a detection p-value of >0.05 for >5% of samples (N=3,033), probes residing on the X and Y chromosome and SNPs (N=11,713) were removed. This resulted in 471,193 probes available for association analysis.

Technical batch was included in all analyses by adding several surrogate variables generated using the sva() function in the SVA R package. Surrogate variables (SVs) were generated separately for every model and for each exposure. Ten SVs were generated and only those that were not associated with the outcome measure were included as covariates within each model.

Acknowledgements

We are extremely grateful to all the families who took part in the ALSPAC study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses. The UK Medical Research Council and the Wellcome Trust (Grant ref: 102215/2/13/2) and the University of Bristol provide core support for ALSPAC. The Accessible Resource for Integrated Epigenomics Studies (ARIES) was funded by the UK Biotechnology and Biological Sciences Research Council (BB/I025751/1 and BB/I025263/1). This work was supported by the Medical Research Council Integrative Epidemiology Unit and the University of Bristol (MC_UU_12013_2). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

BAMSE

Study population

The Children's Allergy Environment Stockholm Epidemiology study is a population-based birth cohort from Stockholm, Sweden. In short, 4,089 children born between 1994 and 1996 in four municipalities of Stockholm County were enrolled[5]. At baseline, when the infant was approximately 2 months of age, parents completed a questionnaire that assessed residential characteristics, as well as socioeconomic and lifestyle factors. When children were 1, 2, 4, 8, 12 and 16 years, the parents completed questionnaires focusing on children's symptoms related to wheezing and allergic diseases, as well as various exposures. The survey response rates

were 96%, 94%, 91%, 84%, 82% and 78%, respectively. Furthermore, blood was obtained at ages 4, 8 and 16 years from 2,605 (63.7%), 2,470 (60.4%) and 2,547 (62.2%) children, respectively. The baseline and follow-up studies were approved by the Regional Ethical Review Board, Karolinska Institutet, Stockholm, Sweden, and the parents of all participating children provided informed consent. BAMSE-MeDALL and BAMSE-EpiGene represent two sub-studies within BAMSE.

Phenotype Data

Asthma

In BAMSE, asthma is defined based on parental reports of doctor's diagnosis of asthma ("Has your child been diagnosed with asthma by a doctor up to eight years?") AND positive answer to one of the following questions at eight years:

"Has your child had trouble with wheezing or raspy breathing in the last 12 months? OR "Has your child received treatment for breathing difficulties in the last 12 months with short-acting bronchodilation treatment, cortisone inhalation, so "called combination inhalers" and/or long-acting bronchodilation treatment?"

Covariates

The current analyses include the children who had DNA methylation measurements, asthma or and covariate data (N=214 from BAMSE-MeDALL; N=214 from BAMSE- EpiGene), and each dataset was analysed independently. For both datasets, information on maternal age, smoking during pregnancy, maternal asthma, maternal socioeconomic status, and child's sex was collected via questionnaires completed by the parents[5]. Maternal age was included as a continuous variable. Maternal smoking status during pregnancy was classified into three groups: non-smoker, stopped smoking in early pregnancy, and smoked throughout pregnancy. Maternal asthma was included as a dichotomous variable. Maternal socioeconomic status was categorized into two groups: blue collar worker and white-collar worker, the latter including liberal professional patrician with university graduate jobs. Child's sex was included as a dichotomous variable.

DNA Methylation Data

The DNA methylation data were generated as part of MeDALL. For BAMSE-MeDALL Illumina450K methylation data were generated in Groningen, The Netherlands and Mutation Analysis Facility and for BAMSE-EpiGene, the data were generated at the Karolinska Institutet, Stockholm, Sweden[6]. Protocols for data generation and quality control were identical at the two sites. DNA from peripheral and cord blood samples was extracted using the QIAamp blood kit (Qiagen or equivalent protocols), followed by precipitation-based concentration using GlycoBlue (Ambion). DNA concentration was determined by Nanodrop measurement and Picogreen quantification. 500 ng of DNA was bisulphite-converted using the EZ 96-DNA methylation kit (Zymo Research), following the manufacturer's standard protocol. After verification of the bisulphite conversion step using Sanger Sequencing, DNA concentration was normalized and the samples were randomized to avoid batch effects. All paired samples were hybridized on the same chip. Standard male and female DNA samples were included in this step for quality control. In the BAMSE EpiGene study, epigenome-wide DNA methylation was measured in DNA extracted from blood samples collected at the age of 8 years. An aliquot (500 ng) of DNA per sample underwent bisulfite conversion using the EZ-96 DNA Methylation kit (Zymo Research Corporation, Irvine, USA). Samples were plated onto 96-well plates in randomized order. The same standard female DNA control sample that was also used in the MeDALL study was again included for quality control.

Acknowledgements

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CHOP

Study population

The CHOP study (European Childhood Obesity Project) is an ongoing European multicenter randomized prospective nutritional intervention study in 1678 healthy term newborns recruited between October 1, 2002 and July 31, 2004. Currently, infants are followed up until the age of 11 years. Main objective of the CHOP study is to assess the effect of early and later nutrition on children's weight development, growth, body composition and risk of obesity and the role epigenetic and metabolic programming plays in this context. A detailed description of the study design and the comprehensive prospective measurements can be found in recent publications[7-10]. The local ethics committees of each study center approved all study procedures: Belgium (Comitè d'Ethique de L'Hopital Universitaire des Enfants Reine Fabiola; no. CEH 14/02), Germany (Bayerische Landesärztekammer Ethik-Kommission; no. 02070), Italy (Azienda Ospedaliera San Paolo Comitato Etico; no. 14/2002), Poland (Instytut Pomnik–Centrum Zdrowia Dziecka Komitet Etyczny; no 243/KE/2001), and Spain (Comité ético de investigación clinica del Hospital Universitario de Tarragona Joan XXIII). Written informed parental consent was obtained for each participating infant and from children of age 8 years onwards.

Phenotype Data

Asthma

In the CHOP study, asthma was defined based on the following questions asked on questionnaire completed by the mother when the child was 7 to 8 years of age (mean age (sd; range) = 7.1(0.29; 1.57)) and an evaluation of named asthma related medication by an experienced paediatrician. Children were classified as having asthma if the mother responded "YES" to the following questions: "Has your child ever been diagnosed by a physician/ paediatrician of asthma (NO/YES)" and named any asthma medication in response to the question "Is your child currently taking any medication? (>14 days) (NO/YES) Which? _____".

Covariates

Information on maternal age, smoking during pregnancy, asthma, education, and child's sex was collected via questionnaire completed by the mother within the first 8 weeks after delivery. Maternal age was included as a continuous variable. Maternal smoking status during pregnancy was classified into three groups: non-smoker, stopped smoking in early pregnancy, and smoked throughout pregnancy. Reported doctor diagnosed maternal asthma was included as a dichotomous variable. Maternal educational level was categorized into three groups based on years of education: low = basic schooling only or less than 10 yrs.; medium = secondary schooling of

10 to less than 12 yrs; high = completion of college, university or at least 12 years of secondary schooling. Child's sex was included as a dichotomous variable.

The current analyses include the children who had DNA methylation measurements, school-age asthma and covariate data (n=382). Batch effects were accounted for by including categorized variable plate in the analyses.

DNA Methylation Data

In the CHOP study, epigenome-wide DNA methylation was measured with the Illumina Infinium HumanMethylation450K Bead Chip (HM450K) array in 384 children of age 5.5 years (Illumina Inc., San Diego, USA). Briefly, genomic DNA was extracted from peripheral blood cells from buffy coats, bisulfite converted (800 ng) with the EZ-96 DNA Methylation Kit (Zymo Research, Irvine, Ca; USA) and finally hybridized on the HM450K arrays at the Genome Analysis Center of Helmholtz Zentrum Muenchen, Munich, Germany. Details on pre-processing, normalization and quality control were previously described[9]. In brief, raw methylation data were pre-processed and normalized according to the approach of Touleimat and Tost[4] with the modification of a beta-mixture quantile normalization (BMIQ) step[11]. Quality control was conducted according to standard criteria: Retaining only probes with signals from ≥3 beads, detection *p*-values≤0.01 and samples with ≥80% significant probe methylation signals per sample. In addition, color bias correction and background adjustment were conducted with R-package lumi. However, except for identified cross-binding probes[12], no probe filtering according to proximity of CpG site with SNPs of minor allele frequency ≥5% within 50bp or probes on the X and Y chromosomes were conducted. In total, 431 313 CpG methylation values for n= 384 children of age 5.5 years were available for EWAS analysis before potential trimming of calculated beta-values and 429948 after trimming. The final sample for the CHOP study in the school-age asthma EWAS analyses comprised 429948 CpG methylation values for n=382 children after removing any missing in phenotype and covariates (described below). In the CHOP analysis sample mean age (sd; range) of DNA-methylation measurement was 5.5 (0.07; 0.82) years.

Acknowledgements

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CHS

Study population

The Children's Health Study (CHS) is a population-based prospective cohort study from age 5 onwards in Southern California, which has been described in detail elsewhere[13]. The study protocol was approved by the University of Southern California Institutional Review Board and informed, written consent and assent were provided by the parents and children respectively. A total of 5341 children were recruited, all of whom were born between 1995 and 1997 and are currently being followed until age 18.

Based on the availability of newborn bloodspots archived by the state of California, a subset of 273 children was selected for a sub-study in which epigenome-wide DNA methylation was assessed in newborn bloodspots. Multiple births were excluded from analyses (7 subjects).

Phenotype data

Asthma

We classified asthma based on responses to the following questions completed by the parents when the child was 5-10 years of age (if multiple, the year close to age 6-7 window was chosen). Children were classified as having asthma if the parent responded "yes" to the following question – "Has a doctor ever diagnosed this child as having asthma?". Further, the child was classified as asthmatic only if the parent also responded YES to either of the three following questions – "Has your child had wheezing or whistling in the chest in the last 12 months?" OR "In the last 12 months, has your child required medication for asthma or wheezing?" OR "In the last 12 months, has your child taken any other medication for asthma or wheezing except for controller and rescue medication?". The control group was NEVER asthma.

Covariates

Information on maternal smoking during pregnancy, asthma and education were obtained from parent-completed questionnaires at study entry when the subjects were around 6 years old. Child's sex and maternal age at delivery were obtained from California birth certificates. Maternal age was included as a continuous variable. Maternal smoking status during pregnancy and maternal asthma were both included as dichotomous variables. Maternal educational level was categorized into three groups based on years of education: less than or finished high school, some college or completed college, and some graduate training. Child's sex was included as a dichotomous variable. Ancestry was assessed from CHS genome-wide genotypic data using the program STRUCTURE from a set of ancestral informative markers that were scaled to represent the proportion of African American, Asian, Native American and white admixture[14]. We additionally corrected the analyses for batch effect by including the Illumina Infinium HumanMethylation450 BeadChip plate number (n=3).

The current analyses include the children who had DNA methylation measurements, school-age asthma and covariate data (N=229).

DNA Methylation Data

Methylation was measured using the Infinium HumanMethylation450 BeadChip (HM450). Laboratory personnel performing DNA methylation analysis were blinded to study subject information. DNA was extracted from whole blood cells using the QiaAmp DNA blood kit (Qiagen Inc, Valencia, CA) and stored at -80 degrees Celcius. 700-1000ng of genomic DNA from each sample was treated with bisulfite using the EZ-96 DNA Methylation Kit™ (Zymo Research, Irvine, CA, USA), according to the manufacturer's recommended protocol and eluted in 18 μl. The results of the Infinium HumanMethylation450 BeadChip (HM450) were compiled for each locus as previously described and were reported as beta (β) values[15]. A normal-exponential background correction with dye bias correction was applied to the raw intensities at the array level to reduce background noise[16]. We then normalized each sample's methylation values to have the same quantiles to address sample to sample variability[4]. CpG loci on the HM450 array were removed from analyses if they were on the X and Y chromosomes, or if they contained SNPs, deletions, repeats, or if they have more than 10% missing values, leaving a total of 384,310 probes for analysis. Beta values were considered as outliers and were removed if they fall below Quartile 1-3×IQR or above Quartile 3+3×IQR.

Acknowledgements

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Study population

The EDEN (Etude des Déterminants pré et post natals du développement et de la santé de l'Enfant) study is a prospective Birth Cohort Study (https://eden.vjf.inserm.fr/), which has been described in detail elsewhere[17]. Pregnant women seen for a prenatal visit at the departments of Obstetrics and Gynecology of the University Hospital of Nancy and Poitiers before their twenty-fourth week of amenorrhea were invited to participate. Enrollment started in February 2003 in Poitiers and September 2003 in Nancy; it lasted 27 months in each centre. Among eligible women, 55% (2002 women) accepted to participate. The study has been approved by the ethical committees « Comité Consultatif pour la Protection des Personnes dans la Recherche Biomédicale », Le Kremlin-Bicêtre University hospital, and « Commission Nationale de l'Informatique et des Libertés ».

Phenotype Data

Asthma

Asthma was defined based on responses to a questionnaire completed by the mother when the child was five years of age. Children were classified as having asthma if the mother responded "yes" to the following questions – "Has your child ever been diagnosed by a doctor as having asthma". Further, the child was classified as asthmatic only if the mother also responded YES to either of the three following questions: 1) Has your child had asthma in the past 12 months? 2) Has your child had medication for asthma in the past 12 months? 3) Wheezing in the last 12 months.

DNA Methylation Data

DNA was extracted from 150 cord blood samples. Amplified and genomic DNA samples are now stored in 96-well plates at -80°C. More than 40 single nucleotide polymorphisms (SNPs) have been genotyped either from genomic or from amplified DNA. The samples underwent bisulfite treatment using the EZ-96 DNA Methylation kit (Zymo Research Corporation, Irvine, USA), and were subsequently processed with the Illumina Infinium Human Methylation 450 BeadChip (Illumina Inc., San Diego, USA). In total, 439,306 CpGs are available in children with DNA measurements.

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GALA II

Study Population

The Genes-environments and Admixture in Latino Americans (GALA II) study is a case-control study initiated in 2008 designed to investigate genetic, behavioral, social, and environmental determinants of asthma risk and morbidity among children aged 8-21 years, as previously described in detail[18-20]. The study used identical protocols to recruit nearly 5000 Latinos (age 8-21) from 5 recruitment centers across the US (San Francisco Bay area; Houston, TX; Chicago, IL; New York, NY; and Puerto Rico). The study was approved by each of the five sites' institutional review boards, and all subjects provided informed consent/assent. Trained interviewers' bilingual in English and Spanish administered questionnaires to participants' parents/caretakers to obtain basic socio-demographic information, medical histories, and environmental exposures, such as exposure to tobacco smoke at various time points.

Phenotype Data

Asthma

In GALA II, childhood asthma is defined as having reported physician-diagnosed asthma plus at least two symptoms of coughing, wheezing, or shortness of breath in the 2 years preceding recruitment. Outcomes for all subjects were assessed at time of recruitment (baseline assessment). Eligible control subjects must not have had a reported history of asthma, lung disease, or chronic illness, and no reported symptoms of coughing, wheezing, or shortness of breath in the 2 years prior to enrollment. Exclusion criteria for asthma cases and controls included subjects who were in the third trimester of pregnancy, current smokers, or had at least a 10 pack-year smoking history. All subjects were aged 8-21 years at time of recruitment. Therefore, age of asthma onset and current asthma status were both asked at ages 8-21. Selection of subjects was limited to participants who were aged 8 to 10 years old. The current analyses include 193 children who had whole blood DNA methylation measurements and data on school-age asthma.

Covariates

The age of the participant and the participant's mother were both treated as continuous variables. Categorical variables included the child's ethnicity (Mexican, Puerto Rican, and Other Latino), sex (male/female), mother's asthma status (ever/never) and maternal educational achievement (less than high school, high school or equivalent, some college, college graduate or higher). Maternal smoking during pregnancy was classified into one of three categories: non-smoker, stopped smoking in early pregnancy, and smoked throughout pregnancy. Lastly, we also included measures of Native American and African genetic ancestry using ADMIXTURE[21] to account for the mixed ancestry of Latinos.

DNA Methylation Data

After examining DNA for complete bisulfite conversion of DNA (Zymo Research, Irvine, CA), we randomized the samples onto the Illumina Infinium HumanMethylation450 BeadChip (Illumina Inc., San Diego, USA). Raw genome-wide methylation data were loaded in the R package minfi and assessed for basic quality control metrics, including determination of poorly performing probes with insignificant detection p-values above

background control probes (i.e., detection p-value >0.01). Probes with a single nucleotide polymorphism in the single base extension site were excluded. Since our study population included males and females, we also removed the X and Y chromosomes from the raw methylation values. A total of 321,509 methylation loci were included for analysis. We corrected for batch (microarray chip) effect using the ComBat function in the R package SVA (surrogate variable analysis) and performed SWAN normalization to correct for intra-array differences between Illumina Type I and Type II probes[22, 23].

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Generation R

Study Population

The Generation R Study is a population-based prospective cohort study from fetal life onwards in Rotterdam, the Netherlands[24, 25]. Assessments in pregnant women and children consisted of physical examinations, fetal ultrasounds, biological samples, and questionnaires. All children were born between April 2002 and January 2006. The study has been approved by the Medical Ethical Committee of the Erasmus University Medical Center and written consent was obtained from participating parents of their children.

DNA methylation

DNA was extracted from cord blood samples of 979 Caucasian children. Using the EZ-96 DNA-methylation kit (Shallow-well) (Zymo Research Corporation, Irvine, USA), 500 ng DNA per sample underwent bisulfite conversion. Samples were transferred onto 96-well plates in a random order. Samples were processed with Illumina's Infinium HumanMethylation450 BeadChip (Illumina Inc., San Diego, USA). Quality control of analyzed samples was performed using standardized criteria. Samples were excluded due to sample call rate <99% (n=7) or poor bisulfite conversion (n=1). In addition, 2 samples were excluded because of a gender mismatch and 1 sample because of a retracted informed consent, leaving a total of 969 samples in the statistical analysis. Probes with a single nucleotide polymorphism in the single base extension site with a frequency of >1% in the GoNLv4 reference panel were excluded, as were probes with non-optimal binding (non-mapping or mapping multiple times to either the normal or the bisulphite-converted genome), resulting in the exclusion of 49,564 probes, leaving a total of 436,013 probes in the analysis. Data were normalized with DASES normalization using a pipeline adapted from that developed by Touleimat and Tost[4]. DASES normalization includes background adjustment, between-array normalization applied to type I and type II probes separately, and dye bias correction applied to type I and type II probes separately. DASES is based on the DASEN method, but adds the dye bias correction, which is not included in DASEN[26]. Beta-values were calculated for all CpG sites.

Phenotype Data

Asthma

Information about asthma (no; yes) was collected by questionnaires at the ages 4 and 6 years. Response rates for these questionnaires were 73% and 68%, respectively. Asthma was defined by a "yes" response to the following two questions on the questionnaire at age 6 years: 'Was your child ever diagnosed with asthma by a doctor? AND 'Did your child ever suffer from chest wheezing? [never, 1-3 times, >4 times]. Non-cases were children without report of asthma at either follow-up time.

Covariates

Information on maternal age, parity, asthma, maternal education and maternal smoking during pregnancy was collected by questionnaires at enrollment. Maternal age was used as a continuous covariate. Parity was categorized into nulli- and multiparity. Maternal education was categorized into lower or normal (none, primary or secondary education) and higher (more than secondary education). Maternal smoking during pregnancy was assessed by questionnaires in early (<18 weeks gestational age), mid (18-25 weeks gestational age) and late (>25 weeks gestational age) pregnancy. In each trimester, pregnant women were asked whether they had smoked and if so, how much. Maternal smoking during pregnancy was categorized into no smoking during pregnancy, smoking during first trimester only, and continued smoking during pregnancy. Analyses were additionally adjusted for batch effects by adding plate number (11 categories) as a covariate.

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GOYA

Study Population

The Genome-Wide Population-based Association Study of Extremely Overweight Young Adults (GOYA) study has been described previously by Paternoster et al.[27, 28]. It is based on the Danish National Birth Cohort (DNBC) that included 92,000 pregnant women and their pregnancies during 1996-2002. Of 67,853 women who had given birth to a live born infant, 67,853 had provided a blood sample during pregnancy and had BMI information available, 3.6% of these women with the largest residuals from the regression of BMI on age and parity (all entered as continuous variables) were selected for GOYA. The BMI for these 2451 women ranged from 32.6 to 64.4. From the remaining cohort, a random sample of similar size (2,450) was also selected. DNA methylation data were generated for the offspring of 1000 mothers in the GOYA study. Study "cases" had mothers with a BMI>32 and "controls" were sampled from the normal BMI distribution (can include mothers with a BMI>32). All participants in the DNBC gave written informed consent and the collection and use of their data has ethics approval.

Phenotype data

Asthma

Information on asthma was obtained from a questionnaire completed by the mothers at 7 years after birth and defined as asthma ever (diagnosed by a doctor).

Covariates

Data on maternal parity, socio-economic status, smoking and pre-pregnancy body mass index were collected via a telephone interview at around 16 weeks' gestation. Maternal age was derived from the mother's report of her own date of birth. Newborn sex and gestational age at birth were extracted from birth records. Socioeconomic status was defined using maternal education or occupation: 1) manager/long or medium education, 2) work requiring a short training period, or skilled manual labor, 3) unskilled or public service. Parity was categorized for this study as nulliparous or parous. Maternal smoking in pregnancy was defined as any smoking in pregnancy or no smoking in pregnancy. We restricted the analysis to GOYA controls, i.e. mothers sampled from the normal BMI distribution.

DNA Methylation measurements

Cord blood was collected according to standard procedures, spun and frozen at -80˚C. DNA methylation analysis and data pre-processing were performed at the University of Bristol. Following extraction, DNA was bisulfite converted using the Zymo EZ DNA MethylationTM kit (Zymo, Irvine, CA). Following conversion, the genome-wide methylation status of over 485,000 CpG sites was measured using the Illumina Infinium® HumanMethylation450k BeadChip assay according to the standard protocol. The arrays were scanned using an

Illumina iScan and initial quality review was assessed using GenomeStudio (version 2011.1). The level of methylation is expressed as a "Beta" value (β-value), ranging from 0 (no cytosine methylation) to 1 (complete cytosine methylation). Samples were distributed across slides using a semi-random approach to minimize the possibility of confounding by batch effects. Samples failing quality control (average probe detection p-value ≥ 0.01) were repeated. As an additional quality control step genotype probes on the HumanMethylation450k were compared between samples from the same individual and against SNP-chip data to identify and remove any sample mismatches. Data were normalized using the functional normalization approach in the Minfi R package. We removed probes that had a detection p-value >0.05 for >5% of samples, probes on the X or Y chromosomes and SNPs (rs probes). 473864 probes remained. Batch correction was done using 10 surrogate variables generated using the sva package in R and included these in models.

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ICAC

Study Population

The Inner-City Asthma Consortium EPIGEN population consisted of inner-city children aged 6-12 years with atopy and persistent asthma (cases) and without atopy or asthma (healthy controls). The cases and controls were recruited by six sites of the Inner-City Asthma Consortium (Boston; Washington, DC; Denver; New York; Dallas; and Detroit) from census tracts that contain at least 20% of households below the U.S. government poverty level[29].

Phenotype data

Asthma

Cases of asthma were required to meet the following criteria: 1) a physician diagnosis of asthma; 2) persistent or uncontrolled disease as defined by the National Asthma Education and Prevention Program[30]; 3) physiologic evidence of asthma (FEV_1 < 85% predicted, or FEV_1/FVC ratio < 85% and bronchodilator responsiveness (≥ 12%), or PC_{20} < 8 mg/ml of methacholine); and 4) positive prick skin-test to as least one of a panel of indoor aeroallergens (i.e. dust mite, cockroach, mold, cat, dog, rat, or mouse). Controls were required to have: 1) no medical history of asthma, rhinitis, sinusitis, and atopic dermatitis; 2) an FEV_1 > 85% predicted; and 3) no positive prick skin-tests.

DNA Methylation

Peripheral blood mononuclear cells (PBMCs) were isolated from whole blood using the Ficoll density gradient separation. DNA was isolated from the PBMCs using the AllPrep DNA/RNA kit (Qiagen, Germantown, MD), and purity was assessed using a NanoDrop spectrophotometer (Thermo Scientific, Wilmington, DE). We used Illumina's Infinium Human Methylation 450k BeadChip on bisulfite-treated samples. 0.85-1.00 µg DNA were bisulfite converted using the Zymo EZ DNA Methylation kit (Zymo Research, Orange, CA). Each conversion assay included a commercially available positive and negative control sample. Bisulfite converted samples formed the input for the Illumina Infinium Methylation assay using the Human Methylation 450k BeadChips (Illumina Inc, San Diego, CA). The labeling, hybridization, and scanning procedures were performed on the iScan system. All samples were assayed once (no technical replicates) with 194 arrays performed in 3 batches.

INMA –contributed analysis of gene expression in relation to methylation

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Study population

The INMA—INfancia y Medio Ambiente— (Environment and Childhood) Project is a network of birth cohorts in Spain that aims to study the role of environmental pollutants in air, water and diet during pregnancy and early childhood in relation to child growth and development[31]. Mothers were enrolled at week 12 of pregnancy from 1997 to 2008 in seven regions of Spain (Flix, Granada, Menorca, Asturias, Gipuzkoa, Sabadell and Valencia). The cohort consisted of 3,768 children at birth. During the follow-up visits information on environmental exposures and health outcomes (reproductive, growth and obesity, lung function, allergies and neurodevelopment) were assessed through questionnaires, biomarker measurements, clinical data, and physical exploration. The study website contains details of the design and data available in INMA project (http://www.proyectoinma.org/). The study was approved by the Ethical Committees of each participating center and written consent was obtained from parents. The present study uses data only from the Sabadell birth subcohort.

DNA Methylation Data

Cord blood and whole blood collected at age 4y was extracted using the Chemagen kit (Perkin Elmer). DNA concentration was determined by a NanoDrop spectrophotometer (Thermo Scientific) and with the Quant-iT PicoGreen dsDNA Assay Kit (Life Technologies).

Blood methylation data were produced in two laboratories: the Genome Analysis Facility of the University Medical Center Groningen (UMCG) in Holland as part of the MeDALL project (0y and 4y), and the Bellvitge Biomedical Research Institute (IDIBELL) in Barcelona as part of the BREATHE project (0y). Both laboratories randomized the samples in batches and followed the Illumina protocol for the Infinium HumanMethylation450 BeadChip. Briefly, 500 ng of DNA was bisulfite-converted using the EZ 96-DNA methylation kit, and DNA methylation was measured through hybridization on the BeadChips. BeadChips were scanned with an Illumina iScan and image data were uploaded into the Methylation Module of Illumina's analysis software GenomeStudio and converted in β-values.

Two blood samples with overall low quality (MethylAid package[32]), and three blood samples discordant for sex (shinyMethyl package[33]) were removed during the quality control. After applying a stringent detection p-value[34] of $1.10x10^{-16}$, 18 blood samples with a call rate <98% were excluded. Data were normalized with the functional normalization method implemented in the minfi package[35]. 7,136 probes with a call rate <95%, control probes and probes designed to detect genetic polymorphisms were removed. ComBat was applied to eliminate laboratory batch effects, without removing age differences by keeping age in the statistical model (Johnson, Li, and Rabinovic 2007). Finally, one of the 12 duplicated samples was excluded. The final dataset consisted of 476,946 probes and 616 samples (391 at age 0y and 209 at age 4y, 185 of them paired 0-4y).

Gene expression data

At age 4 years, whole blood was collected in PAXGene tubes and extracted using the kit recommended by the company. All samples had an RNA Integrity Number higher (RIN) than 7.

Gene expression data were obtained using the Affymetrix HTA 2.0 array at the European Institute for Systems Biology and Medicine in Lyon, France. Gene expression was normalized using the Expression Console Software from Affymetrix and probes were clustered to the transcript level using the version 35 of Affymetrix annotation. In addition, Affymetrix transcript clusters were mapped to gene symbols. Four samples were excluded because there were sex discrepancies (N=4). The final sample size was 124 (113 of them have DNA methylation at 0y and 112 at 4y).

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A full roster of the INMA Project Investigators can be found at http://www.proyectoinma.org/presentacion-inma/listado-investigadores/en_listado-investigadores.html.

IoW – analysis of gene expression and methylation data

Study population

This is the Isle of Wight (IoW) 3rd Generation Study[36]. The recruitment of newborns started from April 2010. Data used in the analyses were from infants born between April 2010 to May 2014. In total, 200 newborns were recruited such that at least one of their parents is in the IoW birth cohort (IoW F1) and the recruitment is ongoing.

DNA Methylation Data

We measured epigenome-wide DNA methylation of 192 newborns using DNA extracted from cord blood. One thousand ng DNA per sample underwent bisulfite conversion using the EZ-96 DNA Methylation kit (Shallow) (Zymo Research Corporation, Irvine, USA). Samples were processed with the Illumina Infinium HumanMethylation450 BeadChip (n = 129) and Illumina MethylationEPIC Beadchips (n = 63). "CPACOR" method by Lehne, et al. [34] has been used in normalization of the beta values. The 65 single nucleotide polymorphism (SNP) markers were removed. Illumina Background Correction was applied to the intensity values. The CpGs with set intensity values with detection p-value $\geq 10^{-16}$ was set as missing and removed in the further analysis. Samples exhibiting call rate <98% were excluded. Quantile normalization on intensity values was applied by incorporating control probe adjustment and reduction of global correlation. Also, DNA methylation from the 192 subjects were measured in seven batches. The R function ComBat (package sva)[37] built upon an empirical Bayes framework was used to remove batch effects. Beta-values were calculated for all CpG sites. After pre-processing a total 399, 383 CpG sites were remained for subsequent studies.

Gene expression data

We analyzed data from 157 matching cord blood samples between methylation data and gene expression (Agilent one-color microarray, Agilent Technologies, Santa Clara, CA). The pre-processing was performed with Limma [38] in the R statistical computing environment [39]. Raw idat files are read into R with the read.miamages function with the source set to Agilent. Background correction was performed with the function backgroundCorrect using the method “normexp” [40]. This method fits a convolution of normal and exponential distributions to the foreground intensities with the background probe intensities set as a covariate. The expected signal, given the foreground observed, is then set as the corrected intensity measures. Normalization is then performed with the normalizeBetweenArrays function and the method is set to “quantile”. Data is then converted to log2 transformed data for further analysis. Filtering is performed to remove lowly expressed probes that are close to the background level. Negative control probes are also removed from the data.

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MoBa1 & MoBa2

Study Population

Participants represent two subsets of mother-offspring pairs from the national Norwegian Mother and Child Cohort Study (MoBa)[41-43]. The years of birth for MoBa participants ranged from 1999-2009. MoBa mothers provided written informed consent. Each subset is referred to here as MoBa1 and MoBa2. MoBa1 is a subset of

a larger study within MoBa that included a cohort random sample and cases of asthma at age three years[44]. We previously reported an association between maternal smoking during pregnancy and differential DNA methylation in MoBa1 newborns[45]. We subsequently measured DNA methylation in additional newborns (MoBa2) in the same laboratory (Illumina, San Diego, CA)[46]. MoBa2 included a cohort random sample plus cases of asthma at age seven years and non-asthmatic controls. Years of birth were 2002-2004 for children in MoBa1 and 2000-2005 for MoBa2. Both studies were approved by the Regional Committee for Ethics in Medical Research, Norway and were approved by the Institutional Review Board of the National Institute of Environmental Health Sciences, USA.

Phenotype data

Asthma

MoBa1 participants were originally selected for analysis of methylation based on asthma status at age 3 years (current asthma with use of inhaled asthma medications) along with a cohort random sample. Individuals whose parent responded to the follow-up questionnaire at age 7 years were included in the current study. Asthma was defined at age 7 according to the ideal definition, i.e. as doctor diagnosed asthma and one of current asthma, asthma symptoms in the past year, or medication for asthma in the past year. The reference group excluded children whose mother had reported asthma at age 3 but not at age 7.

MoBa2 was selected on asthma case/noncase status based on the questionnaire at age 7 years, therefore school-age asthma is defined by this selection variable. There were additional approximately 200 subjects selected because they had measurement of plasma folate available and these are excluded from the analysis. Asthma was previously defined as current asthma (symptoms in the last year) AND medication for asthma in the past year. The control group is NEVER asthma.

Covariates

For both datasets, information on maternal age, smoking during pregnancy, asthma, education, and child's sex was collected via questionnaires completed by the mother or from birth registry records as previously described [44]. Maternal age was included as a continuous variable. Maternal smoking status during pregnancy was classified into three groups: non-smoker, stopped smoking in early pregnancy, and smoked throughout pregnancy. Maternal asthma was included as a dichotomous variable. Maternal educational level was categorized into four groups based on years of education: less than high school/secondary school, high school/secondary school completion, some college or university, or 4 years of college/university or more. Child's sex was included as a dichotomous variable.

DNA Methylation Data

Details of the DNA methylation measurements and quality control for the MoBa1 participants were previously described[45] and the same protocol was implemented for the MoBa2 participants. Briefly, umbilical cord blood samples were collected and frozen at birth at -80**°**C. All biological material was obtained from the Biobank of the MoBa study[43]. Bisulfite conversion was performed using the EZ-96 DNA Methylation kit (Zymo Research Corporation, Irvine, CA) and DNA methylation was measured at 485,577 CpGs in cord blood using Illumina's Infinium HumanMethylation450 BeadChip[47]. Raw intensity (.idat) files were handled in R using the *minfi* package to calculate the methylation level at each CpG as the beta-value (β=intensity of the methylated allele (M)/(intensity of the unmethylated allele (U) + intensity of the methylated allele (M) + 100)) and the data were

exported for quality control and processing. Probe and sample-specific quality control was performed in the MoBa1 and MoBa2 datasets separately. Similar protocols were applied to MoBa1 and Moba2, as follows: Control probes (N=65) and probes on X (N=11 230) and Y (N=416) chromosomes were excluded in both datasets. Remaining CpGs missing > 10% of methylation data were also removed (N=20 in MoBa1, none in MoBa2). Samples indicated by Illumina to have failed or have an average detection p-value across all probes < 0.05 (N=49 MoBa1, N=35 MoBa2) and samples with gender mismatch (N=13 MoBa1, N=8 MoBa2) were also removed. For MoBa1 and MoBa2, we accounted for the two different probe designs by applying the intra-array normalization strategy Beta Mixture Quantile dilation (BMIQ)[11]. The Empirical Bayes method via *ComBat* was applied separately in each dataset for batch correction using the *sva* package in *R*[37].

The following number of samples passed the above quality control: 1,068 for MoBa1 and 685 for MoBa2. Samples determined to be ancestry outliers based on principal components analysis of Illumina HumanCore genotype data were excluded from analyses (12 in MoBa1; 5 in MoBa2). The current analyses include the children who had cord blood DNA methylation measurements, school-age asthma and covariate data (N=661 from MoBa1; N=456 from MoBa2), and each dataset was analysed independently.

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NEST

Study Population

NEST is a multiethnic birth cohort designed to identify the effects of early exposures on epigenetic profiles and phenotypic outcomes. Pregnant women were recruited from prenatal clinics serving Duke University Hospital and Durham Regional Hospital Obstetrics facilities in Durham, North Carolina from April 2005 to July 2009. Gestational age at enrollment ranged from 6 to 42 weeks (median 30 weeks). Eligibility criteria were women aged 18 years or older, English speaking, pregnant, and an intention to use one of the two obstetrics facilities. Among these, women infected with HIV or intending to give up custody of the offspring of index pregnancy were excluded. Current smokers were targeted for the first ~200 participants. Of the 1101 women who met eligibility criteria and were approached, 895 (81%) were enrolled and umbilical cord blood was collected from 741 infants. This study was approved by the Duke Institutional Review Board. Additional details about NEST may be found in previous publications[48, 49].

Phenotype Data

Asthma

Asthma was defined based on a combination of medical records and survey responses. The survey included the following two questions which were used to identify asthma diagnoses: 1) "What was the outcome of your child's doctor visits? Normal or concerns. If there were Concerns, what were they?" and 2) "Was your child diagnosed with any condition by his/her doctor? Yes or No. If Yes, please specify". Parental reports of asthma in these questions were classified as asthma cases, otherwise if the parent said there were no diagnoses or concerns they were classified as not having asthma. Medical records were further used to refine and supplement survey data. Medical billing codes related to asthma (i.e. ICD 9 493.XX codes) and the number of encounters were used to identify children with asthma among those with recent visits. This was checked against a review of the child's full medical records to ensure accuracy. The age at which the asthma diagnosis was reported varies; however, it ranges from five to nine years.

Covariates

The sex of the child was collected from medical records following delivery. Maternal smoking status, socioeconomic status (education), age, asthma, and race were reported by the mother on a questionnaire completed during pregnancy. Maternal age was included as a continuous variable. Maternal smoking status during pregnancy was classified into three groups: non-smoker, stopped smoking in early pregnancy, and smoked throughout pregnancy. Maternal asthma was included as a dichotomous variable. Maternal educational level was categorized into 3 groups: high school education/GED or less, some college, or college degree or higher.

DNA Methylation Data

Genomic DNA from buffy coat specimens was extracted from umbilical cord blood using Puregene Reagents (Qiagen, Valencia, CA). Bisulfite conversion was performed using the EZ-96 DNA Methylation Kit (Zymo Research Corporation) and DNA methylation was measured at 485577 CpGs using Illumina Infinium HumanMethylation450 BeadChip (Illumina Inc., San Diego, USA). Illumina's GenomeStudio Methylation module version 1.0 (Illumina Inc.) was used to calculate the methylation level at each CpG as the beta value. Probe and sample-specific quality control was performed in the NEST cohort using a similar approach to MoBa1 and MoBa2 cohorts. Specifically, control probes (N=65) and probes on X (N=11 230) and Y (N=416) chromosomes were excluded as well as CpGs missing > 10% of methylation data. Samples indicated by Illumina to have failed or have an average detection p-value across all probes < 0.05 and samples with gender mismatch were also removed. The two different probe designs by applying the intra-array normalization strategy Beta Mixture Quantile dilation (BMIQ)[11]. The Empirical Bayes method via ComBat was applied for batch correction using the sva package in R[37]. The current analyses include the children who had cord blood DNA methylation measurements, school-age asthma and covariate data (N= 213 from NEST).

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NFBC 1986

Study Population

The Northern Finland Birth Cohort 1986 (NFBC 1986) is a prospective population-based birth cohort which consists of 99% of all children who were born in the provinces of Oulu and Lapland in Northern Finland between 1 July 1985 and 30 June 1986. 9,203 live-born individuals entered the study[50]. At the age of 16, the subjects living in the original target area or in the capital area (n=9,215) were invited to participate in a follow-up study including a clinical examination. 7344 participants attend the study in year 2001/2002, of which 5654 completed the postal questionnaire, the clinical examination and provided a blood sample.

Ethical approval was obtained from the ethical committee of the Northern Ostrobothnia Hospital District and all participants gave written informed consent. The Finnish Ministry of Social Affairs and Health has granted permission to use register data and patient records. Participants' interviews and postal questionnaires were completed/returned from the 24th gestational week onwards with data since 12-16th gestational week. Both the course of pregnancy and delivery, and also complications, were confirmed from patient records, as was the neonatal outcome. Follow-ups of children have been conducted at the age of 6-12 months, 7-8 years and 14-16 years. DNA methylation was measured on 566 randomly selected subjects.

Phenotype Data

Asthma

In the Northern Finland Birth Cohort 1986, asthma was defined based on the following questions asked on questionnaire completed by the child at an age of 16 years. Children were classified as having asthma if they responded "yes" to both of the following questions – "Have you ever had any of the following respiratory and/or allergic symptoms or illnesses? - Asthma (Diagnosed or treated by a doctor)". Further, the child was classified as asthmatic only if the child also responded with occasionally or regularly to the following question "How often do you take the following medicines at the present? - Asthma medication".

Covariates

SES was defined based on the question asked on questionnaire completed by the mother during pregnancy. "Your own school attendance: 1= less than 6 years primary school, 2=7-8 years primary school,3= 9-10 years primary school, 4 =vocational school or college 6-12 months, 5 =vocational school or college > 1 years, 6 =matriculation, no vocational schooling, 7=matriculation + college, 8=matriculation, university studies not finished, 9=university degree". This was recoded according to the leaving age of school education: 1= before 16 years, 2= 16 to 19 years old, 3 = older than 19 years.

DNA Methylation Data

Methylation of genomic DNA was quantified using the Illumina HumanMethylation450 array according to manufacturer's instructions. Bisulfite conversion of genomic DNA was performed using the EZ DNA methylation kit according to manufacturer's instructions (Zymo Research, Orange, CA). DNA methylation was recoded on Illumina HumanMethlation450K array for 566 randomly selected subjects. To account for batch effects in the

data, beta values underwent a functional normalization approach described by Fortin *et al*.[51] using the first 10 PCs of the Illumina 450K array control probes. This approach includes subset quantile normalization of the data and normal-exponential out-of-band background correction.

24 technical replicates were excluded. 18 samples did not reach a call rate of >95% applying a detection p-value filter of $1x10^{-16}$. We excluded 7 samples with gender inconsistency, no sample was outlying from the overall data structure (1st PC score of the DNA methylation values outside mean +/- 4SD). DNA methylation data of 517 samples with 466290 autosomal probes (call rate filter 95%) each were available for analysis.

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PIAMA

Study Population

PIAMA (Prevention and Incidence of Asthma and Mite Allergy) is a birth cohort study of children born in 1996-1997 in the Netherlands. Details of the study design have been published previously[51]. In brief, 10,232 pregnant women completed a validated screening questionnaire at their prenatal health care clinic (n=52). Based on this screening, 7,862 women were invited to participate, of whom 4,146 women agreed and gave informed consent. The study started with 3,963 newborns. Questionnaire based follow-up of the children took place at 3 months of age, yearly from 1 to 8 years of age, and at 11, 14, and 16 years of age, with clinical investigations at ages 4, 8, 12 and 16 years. Whole blood DNA was extracted of children who provided a blood sample at ages 4, 8 and 16 years.

At the age of 16 years, nasal epithelial cells were collected in two study centers (Groningen and Utrecht) by brushing the lateral area underneath the right inferior turbinate. Brushes were placed in screw-cap Eppendorf tubes and stored at -80oC until further processing. DNA was extracted from nasal brushes using DNA investigator kits (Qiagen, Benelux BV, Venlo, the Netherlands), followed by precipitation-based concentration using GlycoBlue (Ambion). DNA (500ng) was bisulphite-converted using EZ 96-DNA methylation kits (Zymo Research), following manufacturer's standard protocols. After verification of bisulphite conversion using Sanger

Sequencing, DNA concentration was normalized and samples were randomized to avoid batch effects. One standard DNA sample per chip was included in this step for quality control.

The Medical Ethical Committees of the participating institutes approved the study, and the parents and legal guardians of all participants as well as the participants themselves gave written informed consent.

Phenotype Data

Asthma

Asthma was defined based on the questionnaire completed by the mother when the child was eight years of age.

Children were classified as having asthma if the mother responded "yes" to the question – "Has your child ever been diagnosed by a doctor as having asthma". Further, the child was classified as asthmatic only if the mother also responded YES to either of the three following questions: 1) "whether a child had asthma in the past 12 months?", 2) "Has your child had medication for respiratory or lung problems?", or 3) Wheezing in the last 12 months

Covariates

Information on maternal age, smoking during pregnancy, asthma, education, and child's sex was collected via questionnaires completed by the mother. Maternal age was included as a continuous variable. Maternal smoking status during pregnancy was classified into three groups: non-smoker, stopped smoking in early pregnancy, and smoked throughout pregnancy. Maternal asthma was included as a dichotomous variable. Maternal educational level was categorized into three groups based on years of education: 1=primary school, lower vocational or lower secondary education; 2=intermediate vocational education or intermediate/higher secondary; 3=higher vocational education and university (high). Child's sex was included as a dichotomous variable.

DNA Methylation Data

Details of the DNA methylation measurements and quality control for the PIAMA participants were previously described[52]. Briefly, peripheral blood samples were collected from all consenting cohort participants and DNA was extracted using the QIAamp blood kit (Qiagen or equivalent protocols), followed by precipitation-based concentration using GlycoBlue (Ambion). DNA concentration was determined by Nanodrop measurement and Picogreen quantification. 500 ng of DNA was bisulphite-converted using the EZ 96-DNA methylation kit (Zymo Research), following the manufacturer's standard protocol. After verification of the bisulphite conversion step using Sanger Sequencing, genome-wide DNA methylation was measured using the Illumina Infinium HumanMethylation450 BeadChip. After normalization of the concentration, the samples were randomized to avoid batch effects. Standard male and female DNA samples were included in this step as control samples. DNA methylation data were pre-processed in R with the Bioconductor package Minfi[35], using the original IDAT files extracted from the HiScanSQ scanner. Samples that did not provide significant methylation signals in more than 10% of probes (detection P=0.01) were excluded from further analysis. Samples were also excluded in cases of low staining efficiency, low single base extension efficiency, low stripping efficiency of DNA from probes after single base extension, poor hybridization performance, poor bisulphite conversion and high negative control probe staining. Further, we used the 65 SNP probes to check for concordances between paired DNA samples

from the sample individual and assessed the methylation distribution of the X-chromosome to verify gender. Paired samples with Pearson correlation coefficients <0.9 were regarded as sample mix-ups and were excluded from the study. In probe filtering[12], we excluded probes on sex chromosomes, probes that mapped on multi-loci, the 65 random SNPs assay and probes that contained SNPs at the target CpG sites with a minor allele frequency >10%. Finally, we implemented "DASEN"[26] to perform signal correction and normalization. After quality control, 226 samples and 439,306 autosomal probes remained for further analysis.

For nasal epithelium, in total 479 nasal epithelium DNA samples were hybridized to the Infinium HumanMethylation450 BeadChip array (Illumina, San Diego, CA). DNA methylation data were pre-processed with Bioconductor package Minfi3, using the original IDAT files from the HiScanSQ scanner. Samples with call rate <99% were removed. We used 65 SNP probes to check for concordance between paired DNA samples (nasal and blood DNA samples from the same subjects were hybridized in the same experiments); paired samples with Pearson correlation coefficient <0.9 were excluded, as were probes on sex chromosomes, probes that mapped to multiple loci, 65 SNP-probes, and probes containing SNPs at the target CpG sites with a MAF>5%. "DASEN" was used to perform signal correction and normalization. After QC, 455 samples and 436,824 probes remained.

Acknowledgements

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Raine Study

Study Population

The Western Australian Pregnancy Cohort (Raine) Study (http://www.rainestudy.org.au) is a longitudinal Australian birth cohort that has serially assessed the offspring of 2900 pregnant women from 18 weeks' gestation in utero. Follow-up of the offspring has been undertaken at 1, 2, 3, 5, 8, 10, 14, 17, and 24 years[53, 54]. DNA was extracted from whole blood samples (n=1137) obtained at 17-year-old follow up.

Asthma

Asthma was ascertained at 6- and 17-year-old follow up time-points, by questionnaire answered by the primary care-giver. At the 6-year-old follow up, asthma was defined as a prior doctor diagnosis or prior wheeze or asthma medication in last 12 months. At 17 years it was defined by presence of wheeze in last 12 months. For the current analysis, asthma was defined as asthma diagnosis by age 17 years plus wheeze in the past 12 months reported at that same time point. Children with report of asthma at age 6, but not at age 17 were excluded from the comparison group.

DNA Methylation Data

Bisulphite conversion was prepared from whole blood cells by standard phenol:chloroform extraction and ethanol precipitation. Processing of the Illumina Infinium HumanMethylation450 BeadChips was carried out by the Centre for Molecular Medicine and Therapeutics (CMMT) http://www.cmmt.ubc.ca. The raw IDAT files were imported into R using the rnb.run.import() function available in the *RnBeads* package. Two packages were used to perform quality control checks of the samples; *shinyMethyl*[33] and *MethylAid*[32]. Three samples were evident as outliers based on the output from *shinyMethyl* and *MethylAid*. Gender was inferred using the rnb.execute.gender.prediction() function available in the *RnBeads* package[55]. When predicted gender was compared to known gender there was a single discrepancy. 58 of the samples were run in duplicate or triplicate and the 65 SNP probes present on the BeadChip were used to assess genetic similarity between these individuals as a check for sample mix-ups. The rnb.plot.snp.heatmap() function available in the *RnBeads* package was used to produce a heatmap of β values. One contaminated sample was excluded based on this plot. Intentional SNP probes (n=65), sex chromosome probes (n=11,648) and probes with a detection *p*-value greater than 0.05 in any sample (n=10,777) were removed. A further 160 probes with low bead counts (bead counts less than 3 in more than 5% of samples) were removed.

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SLSJ – Analysis of asthma in relation to methylation in purified eosinophils

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Study Population

The families (1394 individuals distributed in 271 families) included in the Saguenay-Lac-Saint-Jean asthma familial cohort[56] were recruited through probands with documented allergic asthma. To be included in the study, a family needs to fulfill these criteria: the two parents must be available for clinical assessment, one parent must be unaffected and all grand-parents must be of French-Canadian origin. Clinical evaluation (measures of lung function: forced expiratory volume in 1 s (FEV_1) and methacholine challenge (PC_{20})), white blood cell counts, skin prick test for allergy and a standardized questionnaire were completed for all individuals.

Acknowledgements

The Saguenay-Lac-Saint-Jean asthma familial cohort was supported by Laprise grants from the Canadian Institute of Health Research (CIHR).

STOPPA

Study Population

The Swedish Twin study On Prediction and Prevention of Asthma (STOPPA) is a twin cohort study including n=752 individuals[57]. Study participants were selected from an on-going data collection within the Child and Adolescent Twin study in Sweden (CATSS)[58] based on the pair's asthma status. Approximately one third each of asthma concordant (ACC), asthma discordant (ADC) and healthy concordant (HCC) pairs took part in clinical examinations including questionnaires, lung function testing (spirometry with reversibility test and fractional exhaled nitric oxide, FeNO) and collection of biosamples. The twins were 9-14 years old at the time of invitation to the study.

The study population has been linked to the Swedish population-based Medical Birth Register for information on pregnancy and delivery outcomes, the National Patient Register for all in- and outpatient diagnoses and the Swedish Prescribed Drug Register for data on prescribed drugs since 2005. Biosamples include whole blood (collected in 4 ml EDTA tubes and stored at -80°C) from n=708 twins. Further details regarding STOPPA have been provided in a separate publication[57].

Phenotype Data

Asthma

In STOPPA, childhood asthma is defined based on the following sources;

1) Questionnaires to parents and children distributed at the clinical examinations within STOPPA.
2) A telephone interview with the study participants' parents when the children were 9 years of age (within the Child and Adolescent Twin Study in Sweden, CATSS)
3) Population-based register data covering asthma diagnoses in in- and outpatient care (National Patient Register, NPR) and dispensed asthma medication (Swedish Prescribed Drug Register, SPDR).
   a) The presence of an asthma diagnosis prior to the clinical examination, from either the STOPPA questionnaires (parent -reported), the CATSS telephone interview (parent-reported), or that had been recorded in the NPR.

and

   b) At least one of the following:
      i) Yes to *"Does your child have asthma?"* (STOPPA parent questionnaire) or *"Do you have asthma?"* (STOPPA twin questionnaire)

ii) Yes to "Has your child had wheezing or whistled breathing at some point during the last 12 months?" (STOPPA parent questionnaire) or "Have you had wheezing or whistled breathing at some point during the last 12 months?" (STOPPA twin questionnaire)
iii) Yes to "Does your child currently take any asthma medication? (STOPPA parent questionnaire)
iv) During the year prior to the clinical examination in STOPPA, the child fulfilled either of the following validated[59] asthma medication combinations in the SPDR:
    (1) Two or more dispenses of inhaled corticosteroids (ICS, ATC code R03BA), fixed combinations of selective beta-2-agonists and ICS (β2-ICS, ATC code R03AK), or Leukotriene Receptor Antagonists (LTRA, ATC code R03DC).
    (2) Three or more dispenses of selective beta-2-agonists (β2, ATC code R03AC), ICS, β2 + ICS or LTRA, within one year.

The **reference group** for school age asthma were those who answered No to *"Has your child ever had wheezing or whistled breathing?"* (STOPPA parent questionnaire). There was no question regarding asthma ever in STOPPA.

DNA Methylation Data

DNA was extracted from whole blood using the Chemagic Star 400 kit (PerkinElmer chemagen, Baesweiler, Aachen, Germany) according to a standardized protocol. Samples allocation was performed by complete randomization of samples between analysis plates and chips, with the exception that samples from twin pairs were kept within the same chip to allow for within-pair comparisons free of batch effects. Laboratory analyses took place at the Mutation Analysis Facility (MAF), Karolinska Institutet, Stockholm, Sweden, using the Infinium HumanMethylation450 Beadchip Kit (Illumina, Inc., San Diego, California, USA).

Quality control, sample and probe filtering were performed using RnBeads[55]. Predicted gender and phenotype-based sex were compared and matched for all samples. Probes were filtered out due to overlap with single nucleotide polymorphisms or specific nucleotide contexts, unreliable measurements (defined as detection p-values > $5x10^{-8}$), or location on sex chromosomes, leaving approximately 455,000 CpG probes for final analyses when using the full data set. The methylation data were normalized using the dasen method, which includes background adjustment and separate between-array normalization of Type I and Type II probes[26]. Methylation at each CpG site was expressed as beta values.

To allow for all twins to be retained within the sample, generalized estimating equation (GEE) models are generally used in analyses using STOPPA data. By specifying twin pairs as clusters, the GEE method produces robust standard errors and corrects for within-cluster (i.e. within-pair) correlations. The parameter estimates themselves are not affected. For these analyses the R package drgee is used[60].

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2. META-ANALYSIS DETAILS

2.1. PACE CONSORTIUM

The Pregnancy and Childhood Epigenetics (PACE) Consortium is an international consortium of cohorts with Illumina Infinium HumanMethylation450 BeadChip (450K) data measured at birth (ie: in newborns) or in childhood[61].

The studies participating in the prospective analysis of newborn DNA methylation data in relation to the development of asthma are: the Avon Longitudinal Study of Parents and Children (ALSPAC), the Children's Health Study (CHS), Etudes des Déterminants pré et postnatals précoces du développement et de la santé de l'Enfant (EDEN, the Generation R Study, the Genome-Wide Population-based Association Study of Extremely Overweight Young Adults (GOYA) study (part of the Danish National Birth Cohort), Infancia y Medio Ambiente (INMA), the Isle of Wight (IoW) study, two independent datasets from the Norwegian Mother and Child Cohort Study (MoBa1 and MoBa2), and the Newborn Epigenetics Study (NEST).

The studies participating in the cross-sectional analyses of asthma in relation to DNA methylation measured in childhood are two independent cohorts from the Children's Allergy Environment Stockholm Epidemiology study (BAMSE; BAMSE-EpiGene and BAMSE-MeDALL), the European Childhood Obesity Project (CHOP) Study, the Genes-environments and Admixture in Latino Americans (GALA II) study, the Inner City Asthma Consortium (ICAC), the Northern Finish Birth Cohort (NFBC 1986), the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study, the Western Australian Pregnancy Cohort (Raine) Study, and the Swedish Twin Study on Prediction and Prevention of Asthma (STOPPA).

2.2. HARMONIZATION OF CHILDHOOD ASTHMA AND WHEEZE OUTCOMES

We developed a common definition of asthma to be generated from questionnaire data by each cohort. Asthma cases were children with doctor diagnosis of asthma and report of at least one of the following: (a) current asthma, (b) asthma (or asthma symptoms such as wheeze) in the past year, or (c) asthma medication use in the last year. The time point for the assessment of asthma was school age – defined as at least 5 years of age. Controls were children that had never had asthma. Details of cohort specific definitions are provided in the previous section.

2.3 Methylation Data Measurements and Quality Control

DNA methylation was measured either in newborns or older children using the Illumina 450K platform. All cohorts analyzed untransformed beta values. Cohorts performed their preferred quality control and normalization methods (see previous section). We had previously found that different pre-processing or normalization methods do not have an effect on meta-analysis results[46]. Cohorts corrected for batch effects in their data using ComBat[62] or by including a batch covariate in their models. To reduce the impact of severe outliers in the methylation data on the meta-analysis, all cohorts trimmed the methylation beta values by removing, for each CpG, observations more than three times the interquartile range below the 25th percentile or above the 75th percentile (outer fences)[63].

Cohorts retained all CpGs that passed quality control and did not remove CpGs that were included on lists of polymorphic, SNP, or non-specific probes such as in Chen, et al. [12]. Instead these were evaluated post-hoc in the

meta-analysis results. The distribution of all individual significant CpGs that appear on these lists were visually assessed for multi-modality in three of the larger cohorts (MoBa1, Generation R, and STOPPA).

2.3. Cohort Specific Statistical Analyses

The association of methylation and asthma was assessed using logistic regression. Covariates included in the adjusted models were maternal age (continuous), maternal smoking status (did not smoke during pregnancy, smoked early then quit, smoked throughout pregnancy), maternal asthma (yes or no), child's sex, and maternal socioeconomic status (generally categorical maternal education). As noted above, Cohorts corrected for batch effects in their data using ComBat[62] or by including a batch covariate in their models. Cohorts that have oversampled or selected on a phenotype included this selection variable in the analysis. We also adjusted for potential confounding by cell type using estimated cell type proportions calculated using the Houseman method[64] from either the cord blood cell type reference panel[65] for newborn cohorts (CD8T, CD4T, NK, Bcell, Mono, Gran, and nRBC) or the adult blood cell type reference panel[66] for cohorts with older children (CD8T, CD4T, NK, Bcell, Mono, Eos, and Neu). A crude model with adjustment only for optional batch, ancestry, and selection covariates was also done. The primary models presented include adjustment for covariates as well as cell type.

2.4. Meta-analyses Methods

We performed inverse variance-weighted fixed effects meta-analysis with METAL[67] and accounted for multiple testing by controlling for the false discovery rate (FDR) at 0.05[68]. As a sensitivity analysis, we also performed random effects meta-analysis using the METASOFT tool[69].

2.5. Enhanced CpG Annotation

The official gene name was noted for each CpG via Illumina's genome coordinate 40. As in Joubert, et al. [46], we enhanced the annotation provided by Illumina by using the UCSC Genome Browser (including data the RefSeq and Ensembl databases) to identify the UCSC Known Gene. UCSC genes occasionally differ from the Illumina annotation file RefSeq genes. All of the annotations use the human February 2009 (GRCh37/hg19) assembly. UCSC Known Gene annotations include nearest genes within 10 Mb of each CpG and thus fill in gene names missing in the Illumina annotation file.

2.6. Analysis of Differentially Methylated Regions

Differentially methylated regions (DMRs) were assessed via two methods, comb-p[70] and DMRcate[71]. Among the available methods, these two accept p-values as input, and thus can be used in the context of meta-analysis. Comb-p and DMRcate use different algorithms to identify significantly differentially methylated regions. Comb-p uses a one-step Šidák correction method for multiple comparisons[72], while DMRcate uses an FDR method[68]. Each method requires the input of parameters to be used in selecting the regions and these were chosen such that they were most similar to each other as detailed below. To reduce false positives, we only considered a DMR to be statistically significant if it was statistically significant in both packages, according to the definition used in each. DMRcate annotates CpGs using the UCSC Refgene in the Illumina annotation file.

For Comb-p, the input parameters found in Online Repository Methods Table 1 were used. For DMRcate, the input parameters found in Online Repository Methods Table 2 were used.

2.7. Lookup of significant DNA methylation findings in previous literature

We performed a literature review of all DNA methylation and asthma association studies to identify genes reported as differentially methylated in relation to asthma or wheeze. The literature review was performed using the below PubMed search terms (originally on June 3, 2016 and updated 1/12/2018): ((((((("Asthma"[Majr])))) OR (((((airways hyper responsiveness[Title/Abstract]) OR airway reactivity[Title/Abstract]) OR bronchodilator response[Title/Abstract]) OR asthma[Title/Abstract]) OR wheez*[Title/Abstract] OR FENO[Title/Abstract])))) AND ((((("Methylation"[Majr]) OR "DNA Methylation"[Majr])) OR ((methylation[Title/Abstract]) OR DNA methylation[Title/Abstract])))

We additionally identified genes related to asthma in genome-wide association study (GWAS) results in the GWAS catalog[73](p-value<$5x10^{-8}$; downloaded 6/29/2016) and updated subsequently using the Genome-Wide Repository of Associations Between SNPs and Phenotypes (GRASP) database[74](p-value<$1x10^{-8}$; downloaded 3/7/2017). We updated the literature review on 01/12/2018 to include novel loci identified in the largest GWAS meta-analysis of asthma to date[75].

2.8. Functional follow-up of significant DNA methylation findings

2.8.1. Analysis of DNA Methylation in relation to Expression of Nearby Genes

To identify associations between methylation levels and the expression levels of nearby genes (cis-eQTMs) we analyzed methylation and blood gene expression available in the same subjects from several sources. The association of gene expression with methylation was assessed within a 500kb window for each individual CpG (+/-250kb from the CpG). For differential methylated regions, we used a window 250kb up- and down-stream of the end and start site of each region.

There were five datasets available with expression and methylation measured in the blood from the same subjects at different periods of the life course. The largest dataset was adults with 3,096 samples from four cohorts in the Netherlands (Biobank-Based Integrative Omics Studies (BIOS) consortium) in which gene expression was assessed by RNA-Seq[76, 77]). The BAMSE study consisted of 248 samples from older children (16 years) in which gene expression was assessed using the Affymetrix Human Transcriptome Array (HTA 2.0)[78]. From the INMA study we analyzed 112 samples with methylation in cord blood and 113 samples with methylation at age 4 years, both compared to gene expression measured at age four also using the Affymetrix Human Transcriptome Array (HTA 2.0) (Affymetrix, Inc, Santa Clara, CA) (ref). From the IoW cohort we analyzed paired methylation and gene expression data from cord blood samples from 158 newborns where gene expression was measured using the Agilent one-color microarray (Agilent Technologies, Santa Clara, C). In all of these studies, linear regression analysis took into account cohort specific joint sources of variability (age, gender, differential cell counts, batch effects for both methylation and gene expression). Additionally, we assessed correlation between gene expression and methylation in 38 cord blood samples from Mexican newborns deposited in Gene Expression Omnibus (GEO) [GSE62924 for methylation[79], GSE48354 for gene expression measured using the Affymetrix HTA 2.0 Array[80]]. For this study, Pearson correlation coefficients were calculated because covariates were not available for linear regression analysis. Given the modest size of the studies of newborns or children, we report association based on nominal significant (P<0.05). For the much larger BIOS study of adults, the FDR was used to account for multiple testing. In all studies, methylation was measured using the Ilumina450K array.

2.8.2. Functional Annotation

Functional annotation was done using tracks customized to DNA methylation in the UCSC Genome Browser. See Online Repository Methods Table 3 for detail on specific tracks. We examined regions to which the genome-wide significant individual CpGs annotated as well as the significant differentially methylated regions (DMRs).

2.8.3. Search for Druggable Targets

We matched the list of genes to which our asthma-associated CpGs and DMRs annotated against the ChEMBL database (v22.1, updated on November 15, 2016)[81] to identify genes as targets of approved drugs or drugs in development. In addition, we used the Ingenuity Pathway Analysis[82] (IPA, www.ingenuity.com, content of 2017-06-22) to identify drug targets and upstream regulators of the gene lists. We reported the upstream regulators in the following categories, biologic drug, chemical - endogenous mammalian, chemical - kinase inhibitor, chemical – other, chemical drug, chemical reagent, and chemical toxicant.

2.8.4. Identification of tissue and cell specific signals using eFORGE

To identify tissue or cell type specific signals in EWAS results, we used eFORGE software[83]. Input for eFORGE was a list of FDR significant CpGs: 9 CpGs for newborn analysis and 179 for older kids analysis. We examined enrichments for DNase I hypersensitive sites (DHSs) or histone marks. The software provides DHS data from the Roadmap Epigenomics, ENCODE, and BLUEPRINT projects; five separate histone marks (H3K27me3, H3K36me3, H3K4me3, H3K9me3, and H3K4me1) from the Roadmap Epigenomics project. We used default options (proximity distance to filter out nearby CpGs = 1 kb, the number of background CpG sets = 1000) to run the analyses.

2.8.5. Pathway Analysis

We performed pathway and network analyses using Ingenuity Pathway Analysis (IPA) ((QIAGEN Inc., https://www.qiagenbioinformatics.com/products/ingenuity-pathway-analysis)[82].

3. Online Repository Methods Tables

Online Repository Methods Table 1: Input parameters used in the comb-p algorithm

Parameter	Value	Description
dist	1000	Maximum distance to search for adjacent peaks.
seed	0.05	A value must be at least this large/small in order to seed a region.
region-filter-p	0.01	Maximum adjusted region-level p-value to be reported in final output.
region-filter-n	2	Require at least this number of probes for a region to be reported in final output.

Online Repository Methods Table 2: Input parameters used in the DMRcate

Parameter	Value	Description
lambda	1000	Gaussian kernel bandwidth for smoothed-function estimation. Gaps ≥ lambda between significant CpG sites will be in separate DMRs.
C	2	Scaling factor for bandwidth. Gaussian kernel is calculated where lambda/C = sigma. Empirical testing shows that, for 450k data when lambda = 1000, near-optimal prediction of sequencing-derived DMRs is obtained when C is approximately 2.
pcutoff	0.01	p-value cutoff to determine DMRs.
min.cpgs	2	Minimum number of consecutive CpGs constituting a DMR.

Supplementary Methods Table 3: UCSC Genome Browser customized track details.

Category	Label	Description
Our EWAS results	CpGs	CpGs included in the meta-analysis: red – p-value < FDR; light blue – FDR ≤ p-value < 0.001; royal blue – 0.001 ≤ p-value < 0.05; black – p-value ≥ 0.05
	DMRs	Significant DMRs
UCSC Genes	Gene Name	UCSC Genes (RefSeq, GenBank, CCDS, Rfam, tRNAs & Comparative Genomics)
Human mRNAs	Human mRNAs	Human mRNAs from GenBank
CpG Islands	CpG Islands	Islands<300 bases are light green

SNP	Common SNPs	Simple Nucleotide Polymorphisms (dbSNP 147) found in ≥ 1% of samples (https://genome.ucsc.edu/cgi-bin/hgTrackUi?g=snp147Common&hgsid=560497663_3Vf9tNVA6AoTDdnAgU0NTbvVGlc8&db=hg19) - SNP feature for color specification Unknown and intron: black; Coding-synonymous: green; Coding – non-synonymous: red; untranslated: blue, Splice site: red
	SNPs	Sequences in scientific articles (https://genome.ucsc.edu/cgi-bin/hgTrackUi?hgsid=560497663_3Vf9tNVA6AoTDdnAgU0NTbvVGlc8&g=pubs) - Filter articles by keywords in abstract, title or authors: 'lung'
DNaseI Hypersensitivity Site	Master DNaseI HS	DNaseI Hypersensitive Site Master List (125 cell types) from ENCODE/Analysis
DNaseI Hypersensitivity Site Open chromatin	FL DNase 76 46, FL DNase 27 17, FL DNase 48 07, FL DNase 90 85, FL DNase 47 66, FL DNase 66 24, FL DNase 66 51, FL DNase 84 09, FL DNase 84 20, FL DNase 65 27, FL DNase 99 61, FL DNase 19 73	DNase Hypersensitivity Raw Signal from REMC/UW: Fetal Lung
	H1-hESC Syn PK	H1-hESC DNaseI/FAIRE/ChIP Synthesis from ENCODE/OpenChrom.

		- Open Chromatin (OC) code (detection assay) and color (level of validation determined by its OC Code and its statistical significance) are below. Validated, OC Code=1, Black; Open Chromatin, OC Code = 2 or 3, Blue; DNase, OC Code = 2, Blue (high significance), Green (low significance); FAIRE, OC Code = 3, Blue (high significance), Dark Red (low significance); ChIP-seq, OC Code = 4, Pink
Chromatin State Segmentation	NHLF ChromHMM	NHLF Chromatin State Segmentation by HMM from ENCODE/Broad. The fifteen states of the HMM, associated segment color, and annotations are below. State 1 - Bright Red - Active Promoter State 2 - Light Red -Weak Promoter State 3 - Purple - Inactive/poised Promoter State 4 - Orange - Strong enhancer State 5 - Orange - Strong enhancer State 6 - Yellow - Weak/poised enhancer State 7 - Yellow - Weak/poised enhancer State 8 - Blue - Insulator State 9 - Dark Green - Transcriptional transition State 10 - Dark Green - Transcriptional elongation State 11 - Light Green - Weak transcribed State 12 - Gray - Polycomb-repressed State 13 - Light Gray - Heterochromatin; low signal State 14 - Light Gray - Repetitive/Copy Number Variation State 15 - Light Gray - Repetitive/Copy Number Variation

Chromatin State Segmentation Histone Modification	LNG	Chromatin State Segmentations from the cell types used by Roadmap Consortium. The HMM states, associated color, and annotations are below. State 1 - Red - TssA (Active_TSS) State 2 - OrangeRed - TssAFlnk (Flanking_Active_TSS) State 3 - LimeGreen - TxFlnk (Transcr_at_gene_5_and_3primer) State 4 - Green - Tx (Strong_transcription) State 5 - DarkGreen - TxWk (Weak_transcription) State 6 - GreenYellow - EnhG (Genic_enhancers) State 7 - Yellow - Enh (Enhancers) State 8 - MediumAquamarine - ZNF/Rpts (ZNF_genes&repeats) State 9 - PaleTurquoise - Het (Heterochromatin) State 10 - IndianRed - TssBiv (Bivalent/Poised_TSS) State 11 - DarkSalmon - BivFlnk (Flanking_Bivalent_TSS/Enh) State 12 - DarkKhaki - EnhBiv (Bivalent_Enhancer) State 13 - Silver - ReprPC (Repressed_PolyComb) State 14 - Gainsboro - ReprPCWk (Weak_Repressed_PolyComb) State 15 - White - Quies (Quiescent/Low)
	Lung H3K27ac 01 61, Lung H3K27ac 02 48, Lung H3K36me3 01 64, Lung H3K36me3 02 14,	Histone Modification by ChIP-seq from REMC/UCSD: Lung

	Lung H3K4me1 01 66, Lung H3K4me1 02 98, Lung H3K4me3 02 33, Lung H3K9me3 01 84, Lung H3K9me3 02 49, Lung Input 01 53, Lung Input 02 61, Lung Input 02 96	
Genomic Footprinting	FL DGF 66 24	Digital Genomic Footprinting (HOTSPOT_SCORE=0.5004 Pcnt=20): Fetal Lung
Gene expression	GTEx	Gene Expression in 53 tissues from GTEx RNA-seq of 8555 samples (570 donors) – subset of 4 tissues: Whole Blood, Lung, Cells – EBV-transformed lymphocytes, and Cells – Transformed fibroblasts
	Lung F YFC4	GTEx RNA-seq read coverage for female donor sample YFC4 (20-49 years): Lung
	wholBlood F YFC4	GTEx RNA-seq read coverage for female donor sample YFC4 (20-49 years): Whole Blood
	Lung M ZPU1	GTEx RNA-seq read coverage for male donor sample ZPU1 (20-49 years): Lung
	wholBlood M ZPU1	GTEx RNA-seq read coverage for male donor sample ZPU1 (20-49 years): Whole Blood
	Lung mRNA	RNA-seq signal from REMC: Lung
Transcription Factor Binding Sites (TFBS)		Transcription Factor ChIP-seq (161 factors) from ENCODE with Factorbook Motifs – subset of asthma-related TFBS: ATF1, ATF2, BCLAF1, CREB1, E2F1, EBF1, ELK1, EP300, ETS1, FOS, GABPA, GATA1, GATA3, GTF2B, HDAC1, HDAC6, HMGN3, HSF1, IRF4, JUN, KDM5A, MAFF, MYBL2, MYC, NFATC1, NFYB, NR3C1, RAD21, RELA, RUNX3, RXRA, SIN3A, SP1, SP2, SPI1, SRF, STAT1, STAT3, STAT5A, TBP, TFAP2A, UBTF, USF1, USF2, YY1

4. Online Repository Figure Legends

Figure E1: Forest plots of 9 significant CpGs from the meta-analysis of asthma in relation to newborn methylation with adjustment for covariates and cell type. These plots show the number of cases and non-cases and odds ratios (OR) and 95% confidence intervals (95% CI) for a one percent change in methylation for each cohort along with the meta-analysis results.

Figure E2: Leave out one plots for the 9 significant CpGs from the meta-analysis of asthma in relation to newborn methylation with adjustment for covariates and cell type. These plots show the untransformed regression coefficients and 95% confidence intervals for the meta-analysis of all studies and then for the meta-analysis repeated leaving each labelled cohort out, one at a time.

Figure E3. Forest plots of 179 significant CpGs from the meta-analysis of asthma in relation to methylation in children with adjustment for covariates and cell type. These plots show the number of cases and noncases and odds ratios (OR) and 95% confidence intervals (95% CI) for a one percent change in methylation for each cohort along with the meta-analysis results.

Figure E4. Leave out one plots for the 179 significant CpGs from the meta-analysis of asthma in relation to childhood methylation with adjustment for covariates and cell type. These plots show the untransformed regression coefficients and 95% confidence intervals for the meta-analysis of all studies and then for the meta-analysis repeated leaving each labelled cohort out, one at a time.

Figure E5: Functional annotation plots of 7 significant CpGs (A-I) from the meta-analysis of asthma in relation to newborn methylation with adjustment for covariates and cell type. Custom track titled "CpGs (Newborns)" show the location of the significant CpG (red) in relation to other nearby CpGs (red – p-value < FDR; light blue – FDR ≤ p-value < 0.001; royal blue – 0.001 ≤ p-value < 0.05; black – p-value ≥ 0.05).

(A) cg21486411 – CLNS1A
(B) cg16792002 – MAML2
(C) cg13427149 – GPATCH2; SPATA17
(D) cg17333211 – SCOC; LOC100129858
(E) cg02331902 – RP11-213H15.3; AK091866 (near LUCAT1)
(F) cg13289553 – SUB1
(G) cg07156990 – WDR20

Figure E6: Functional annotation plots of 34 CpGs non-singleton significant CpGs corresponding to 13 genes from the meta-analysis of asthma in relation to childhood methylation with adjustment for covariates and cell type. Custom track titled "CpGs (Older Kids)" show the location of the significant CpG (red) in relation to other nearby CpGs (red – p-value < FDR; light blue – FDR ≤ p-value < 0.001; royal blue – 0.001 ≤ p-value < 0.05; black – p-value ≥ 0.05). Custom track titled "DMRs (Older Kids)" indicates the location of the significant differentially methylated region.

Figure E7: Tissue and cell type specific enrichment pattern of CpGs significantly associated (FDR < 0.05) with asthma in relation to childhood methylation.

(A) DNase1 sites (probably transcription factor binding sites) in cell lines for H3K4me1 on Roadmap Epigenomics Project (Consolidated data)
(B) DNase1 sites (probably transcription factor binding sites) in cell lines for H3K36me3 on Roadmap Epigenomics Project (Consolidated data)

Figure E8: A heatmap is drawn using the categories of disease and biological functions, significant at p-value cutoff of 0.05 in at either newborns or children. All the categories as well as the genes are hierarchically clustered. The genes involved in newborns are colored as red and those in children as orange.

Figure E9: Density distributions of 9 significant CpGs in 2 cohorts, (A) MoBa1 and (B) Generation R from the meta-analysis of asthma in relation to newborn methylation with adjustment for covariates and cell type.

(A) MoBa1
(B) Generation R

Figure E10: Density distributions of 34 non-singleton CpGs in STOPPA from the meta-analysis of asthma in relation to childhood methylation with adjustment for covariates and cell type. Distributions of all 179 CpGs were checked (not shown).

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Table E1 *Descriptive statistics of covariates for each cohort*

Methylation Age Group	Cohort	Ancestry*	Total N	N cases	N controls	Age at Asthma Phenotyping (SD)	Mean maternal age (SD)	N any smoking in pregnancy	N no smoking in pregnancy	N smoking in early pregnancy	N smoking throughout pregnancy	N maternal asthma	N boys	N girls	N SES group1 ** (low)	N SES group2 **	N SES group3 **	N SES group4 ** (high)
Newborns	ALSPAC	EU	688	88	600	7.63 (0.11)	30.30 (4.23)	75	613	19	56	81	337	351	62	296	330	
	CHS	M	229	39	190	6.40 (0.58)	29.50 (5.72)	17	212			21	91	138	75	121	33	
	EDEN	EU	150	34	116	5.65 (0.12)	30.80 (5.00)	36	114	13	23	14	87	63	8	94	48	
	Generation R	EU	661	37	624	6.20 (0.50)	31.80 (4.00)	162	499	64	98	46	344	317	239	422		
	GOYA	EU	507	37	470	7.20 (0.12)	29.50 (4.00)	112	395	44	68		250	257	50	169	288	
	MoBa1	EU	666	149	517	7.14 (0.14)	29.99 (4.28)	175	491	88	87	68	347	319	44	223	296	103
	MoBa2	EU	458	239	219	7.20 (0.28)	30.20 (4.61)	103	355	68	35	59	264	194	40	156	171	91
	NEST	M	213	45	168	7.00 (1.13)	28.78 (6.41)	73	140	24	49	38	109	104	78	62	73	
Children	BAMSE EpiGene	EU	307	93	214	8.33 (0.52)	30.94 (4.32)	31	276	3	28	34	160	147	45	262		
	BAMSE MeDALL	EU	214	47	167	8.37 (0.37)	31.32 (4.48)	25	189	5	20	20	120	94	37	177		
	CHOP	EU	382	19	363	7.10 (0.29)	32.01 (4.24)	76	306	18	58	11	183	199	68	200	114	
	GALA II	M	193	106	87	9.31 (0.83)	35.03 (6.72)	19	174	12	7	31	108	85	88	43	41	21
	ICAC	AA	187	92	95	9.19 (1.92)						8	96	91	147	40		
	NFBC 1986	EU	413	17	396	16.00 (0.38)	29.05 (5.03)	96	317	57	39	24	191	222	30	252	131	
	PIAMA	EU	197	15	182	8.06 (0.28)	30.51 (3.60)	35	162	17	18	161	99	98	37	90	70	
	Raine Study	EU	509	105	404	17.01 (0.23)	29.66(5.73)	130	379	51	79	69	248	261	51	109	140	209
	STOPPA	EU	460	137	323	12.54 (1.47)	31.21 (4.68)	37	423			65	244	216	21	119	105	215

* EU = European Ancestry; M = Mixed Ancestry; AA = African American Ancestry

** SES = Socioeconomic Status; each cohort used their best estimate for SES, often maternal education level.

Table E2 All CpGs within the significant differentially methylated regions in analysis of asthma in relation to newborn methylation. Sorted by chromosomal position

DMR chr:pos	N CpGs (N nominal*)	CpG	CpG Position	p-value
chr1:1296093-1296489	2 (2)	cg13354934	1296093	3.68E-05
		cg14375163	1296488	1.39E-02
chr1:59280290-59280842	5 (5)	cg17826530	59280290	9.13E-03
		cg20593826	59280370	1.01E-02
		cg08731696	59280489	6.71E-03
		cg02951357	59280619	8.05E-03
		cg16037711	59280841	2.64E-02
chr1:220263017-220263699	11 (8)	cg17009631	220263017	2.00E-02
		cg06854438	220263111	6.35E-02
		cg07017209	220263177	3.77E-02
		cg10818272	220263189	1.14E-01
		cg23274377	220263237	3.69E-02
		cg00578530	220263239	7.47E-03
		cg04168050	220263278	1.36E-03
		cg00784308	220263509	7.05E-03
		cg20243626	220263520	5.86E-01
		cg11379360	220263525	4.77E-02
		cg00719685	220263698	1.19E-02
chr2:202097062-202097608	5 (3)	cg04048517	202097062	2.34E-01
		cg02878216	202097093	3.99E-05
		cg19448993	202097129	7.28E-03
		cg24410214	202097173	9.46E-05
		cg20608990	202097607	2.44E-01
chr2:235004843-235005012	2 (2)	cg03259207	235004843	8.92E-04
		cg27534679	235005011	1.70E-04
chr3:194188646-194189444	3 (3)	cg08059402	194188646	1.66E-03
		cg13959207	194188988	5.29E-04
		cg15977148	194189443	2.24E-02
chr4:113218385-113218525	3 (3)	cg17445830	113218385	5.05E-03
		cg15299279	113218437	9.35E-05
		cg16292983	113218524	3.83E-03
chr5:64777678-64778186	10 (6)	cg02577849	64777678	1.03E-01
		cg24184449	64777750	3.14E-02
		cg24166172	64777777	5.49E-02
		cg10642820	64777786	3.16E-02
		cg14700821	64777802	3.89E-02
		cg10944144	64777807	8.20E-01
		cg19927028	64777838	1.15E-02
		cg14793753	64778097	8.76E-02
		cg18140645	64778147	4.28E-02
		cg26688155	64778185	5.08E-05
chr5:81573780-81574461	11 (7)	cg08341821	81573780	2.60E-02
		cg07833035	81573845	3.44E-01
		cg27310251	81574067	4.83E-02
		cg04645034	81574156	1.14E-03
		cg01556715	81574292	2.30E-03
		cg14916917	81574294	9.71E-03
		cg26986558	81574325	2.46E-01
		cg17724054	81574408	1.90E-02
		cg05002974	81574439	5.25E-01
		cg10681725	81574453	1.71E-01
		cg10425506	81574460	1.26E-02
chr5:158526108-158526694	6 (4)	cg27347265	158526108	3.41E-01
		cg07256113	158526263	1.11E-01
		cg17036833	158526332	1.17E-03
		cg05530568	158526614	8.00E-03
		cg17009297	158526642	2.41E-03
		cg04217450	158526693	1.36E-03
chr6:291687-292824	9 (6)	cg07332563	291687	5.62E-02
		cg21548813	291882	4.10E-03
		cg03395511	291903	3.20E-03
		cg15383120	291909	2.50E-03
		cg18110333	292329	1.45E-02
		cg05064044	292385	1.96E-03
		cg11235426	292522	5.30E-02
		cg01516881	292596	2.73E-02

		cg26668828	292823	2.24E-01
chr6:26234819-26235610	9 (4)	cg24036126	26234819	5.76E-01
		cg23705973	26235061	7.83E-04
		cg24855943	26235224	4.05E-04
		cg21085190	26235254	4.47E-01
		cg15689967	26235287	5.50E-02
		cg25267285	26235290	1.08E-01
		cg03761746	26235311	3.46E-02
		cg25091056	26235462	9.14E-04
		cg10638657	26235609	1.49E-01
chr6:29648161-29649085	22 (19)	cg25978138	29648161	2.28E-01
		cg11747594	29648225	1.20E-02
		cg15708526	29648271	1.02E-03
		cg04071440	29648275	8.85E-02
		cg08022281	29648345	4.94E-02
		cg10648573	29648348	2.82E-02
		cg12644888	29648360	2.14E-02
		cg22494932	29648379	5.72E-04
		cg25699073	29648381	1.91E-03
		cg07134666	29648400	2.28E-02
		cg00588198	29648452	1.67E-02
		cg16885113	29648507	9.60E-03
		cg20228636	29648525	2.17E-02
		cg11383134	29648590	9.34E-03
		cg03198009	29648604	3.17E-02
		cg03449857	29648623	2.62E-02
		cg15570656	29648628	4.84E-02
		cg02157626	29648736	1.57E-02
		cg13835168	29648756	1.70E-01
		cg08041448	29648901	4.61E-02
		cg24100841	29649024	3.15E-02
		cg19636627	29649084	1.12E-02
chr6:31055396-31055503	5 (5)	cg15583958	31055396	1.17E-03
		cg09470958	31055471	2.45E-03
		cg15625467	31055486	2.15E-03
		cg17077639	31055492	1.28E-02
		cg26138460	31055502	1.11E-02
chr6:32799997-32801050	13 (9)	cg01283574	32799997	4.94E-02
		cg11752893	32800103	3.97E-02
		cg12121080	32800427	4.22E-01
		cg13600652	32800429	4.20E-01
		cg12644497	32800444	3.24E-02
		cg00720839	32800486	3.65E-03
		cg16026549	32800519	1.16E-02
		cg12761728	32800523	6.14E-03
		cg07015256	32800541	4.81E-03
		cg24813704	32800549	1.45E-02
		cg21359558	32800563	1.76E-02
		cg09187413	32800591	1.99E-01
		cg24469596	32801049	5.08E-01
chr7:87974722-87975316	4 (3)	cg27221053	87974722	9.90E-06
		cg03673737	87974733	1.02E-02
		cg10649525	87974756	2.58E-03
		cg23857078	87975315	3.80E-01
chr7:106694832-106695007	2 (2)	cg22214581	106694832	2.16E-05
		cg15154519	106695006	5.00E-03
chr7:158045980-158046359	6 (5)	cg27200869	158045980	2.98E-02
		cg16571642	158045996	1.01E-02
		cg06715136	158046025	1.37E-03
		cg02770061	158046166	6.25E-03
		cg06400119	158046222	3.70E-02
		cg10473311	158046358	6.17E-02
chr8:33370172-33371226	9 (7)	cg26948599	33370172	2.41E-01
		cg04340421	33370637	1.06E-02
		cg13529074	33370659	5.59E-03
		cg11008718	33370666	9.01E-03
		cg19906737	33370681	2.21E-02
		cg22610784	33370693	5.02E-04
		cg08328324	33370759	2.07E-02

		cg18030007	33370902	3.70E-03
		cg07516225	33371225	5.06E-01
chr8:127889010-127889296	4 (4)	cg22056468	127889010	3.38E-05
		cg02411950	127889025	1.93E-03
		cg26726325	127889050	1.86E-03
		cg21238284	127889295	8.78E-03
chr10:65028929-65029169	5 (4)	cg22492966	65028929	2.66E-04
		cg14534336	65028980	1.67E-01
		cg09254098	65029020	2.07E-03
		cg16951385	65029115	2.10E-02
		cg27596707	65029168	2.86E-02
chr10:71871364-71871634	4 (3)	cg17523282	71871364	1.13E-03
		cg03096811	71871388	3.52E-04
		cg02735204	71871463	1.08E-02
		cg09777856	71871633	1.58E-01
chr11:268923-269469	5 (4)	cg02443306	268923	1.29E-02
		cg13185005	268950	8.48E-03
		cg10308673	268976	8.30E-04
		cg11546385	269375	9.60E-02
		cg02563407	269468	4.39E-02
chr11:107328442-107328915	10 (5)	cg20965478	107328442	1.25E-01
		cg25435332	107328525	9.88E-02
		cg12301744	107328559	1.20E-01
		cg02558537	107328586	5.82E-01
		cg25102621	107328605	4.11E-02
		cg19998148	107328636	3.96E-02
		cg07444288	107328657	6.96E-04
		cg23880829	107328671	1.98E-01
		cg10872513	107328690	1.04E-03
		cg12578959	107328914	1.80E-04
chr12:58329764-58330116	5 (4)	cg14878686	58329764	8.22E-04
		cg09932636	58329862	7.64E-02
		cg02175503	58329896	1.14E-02
		cg22764591	58329936	2.25E-02
		cg06537201	58330115	1.41E-03
chr12:74931289-74932008	10 (8)	cg15612392	74931289	6.83E-04
		cg04707531	74931420	1.34E-02
		cg20100969	74931493	1.20E-03
		cg21144006	74931510	1.79E-02
		cg16403677	74931512	9.90E-04
		cg17824173	74931535	1.14E-02
		cg01865610	74931554	4.38E-02
		cg22232397	74931695	4.11E-01
		cg23311950	74931760	4.46E-02
		cg23798332	74932007	9.00E-01
chr13:31618695-31618744	2 (2)	cg07321753	31618695	4.11E-03
		cg10670748	31618743	3.12E-06
chr13:108953659-108954055	2 (2)	cg11726530	108953659	3.67E-04
		cg16929959	108954054	1.40E-03
chr14:69341139-69341739	4 (4)	cg00000289	69341139	2.40E-02
		cg11072851	69341430	7.39E-03
		cg27036347	69341603	8.09E-04
		cg01707795	69341738	7.18E-03
chr16:20774873-20775353	5 (4)	cg06478823	20774873	8.35E-02
		cg10060338	20774960	6.01E-03
		cg10078415	20775011	4.98E-03
		cg00394823	20775166	4.45E-03
		cg21644826	20775352	2.13E-02
chr17:21029189-21029296	2 (2)	cg19360316	21029189	1.87E-04
		cg06582708	21029295	5.92E-04
chr17:74667833-74668253	6 (4)	cg04684864	74667833	1.12E-03
		cg03874568	74667923	9.02E-01
		cg09326547	74667999	1.70E-03
		cg05121093	74668089	3.13E-04
		cg09509528	74668195	1.29E-06
		cg17177017	74668252	4.56E-01
chr18:47813745-47815431	11 (8)	cg27250841	47813745	2.22E-02
		cg22433261	47813856	1.25E-02
		cg00418882	47814150	1.31E-03

		cg13423076	47814178	3.38E-02
		cg07675399	47814227	3.78E-01
		cg20016845	47814312	3.63E-01
		cg02159718	47814464	5.65E-02
		cg27419474	47814612	1.63E-02
		cg21134610	47815407	1.42E-02
		cg15632775	47815417	7.91E-03
		cg11871295	47815430	2.30E-02
chr21:36421467-36421956	6 (3)	cg01519261	36421467	5.67E-02
		cg04915566	36421472	3.92E-04
		cg13030790	36421503	4.93E-01
		cg15242225	36421857	5.48E-04
		cg19836199	36421941	1.48E-03
		cg08443845	36421955	1.19E-01
chr22:24372913-24374013	12 (7)	cg20007245	24372913	1.61E-02
		cg04824771	24372921	1.86E-01
		cg24565820	24372926	3.84E-02
		cg10150615	24372951	5.24E-01
		cg18538332	24372958	7.44E-01
		cg23131131	24373011	8.83E-02
		cg25703541	24373054	7.83E-03
		cg02953382	24373134	2.88E-03
		cg04234412	24373322	5.03E-03
		cg12419862	24373484	8.06E-05
		cg09033563	24373618	3.54E-04
		cg21256200	24374012	4.33E-01

* p-value<0.05

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Table E3 *Nine significant (FDR<0.05) CpGs from the meta-analysis of asthma in relation to newborn methylation with adjustment for covariates and cell type, and look up of results for same CpGs without cell type adjustment and without any adjustment*

CpG	chr:pos	UCSC RefGene Name	UCSC Known Gene*	Covariates + Cell Type					Covariates		Crude	
				OR** (CI)	P-value	HetPVal	RE OR** (CI)	RE p-value	OR** (CI)	P-value	OR** (CI)	P-value
cg21486411	chr11:77348243	*CLNS1A*	*CLNS1A*	1.13 (1.08,1.18)	3.43E-07	0.3090			1.11 (1.06,1.15)	1.97E-06	1.10 (1.05,1.14)	8.35E-06
cg16792002	chr11:95788886	*MAML2*	*Mir_548*	0.95 (0.93,0.97)	5.59E-07	0.7276			0.95 (0.94,0.97)	2.67E-06	0.96 (0.94,0.98)	5.05E-05
ch.11.109687686R	chr11:110182476			1.08 (1.05,1.11)	7.06E-07	0.3949			1.05 (1.03,1.08)	5.29E-05	1.05 (1.02,1.07)	2.50E-04
cg13427149	chr1:217804379	*GPATCH2;SPATA17*	*GPATCH2*	1.19 (1.11,1.27)	8.04E-07	0.8095			1.17 (1.10,1.25)	4.51E-07	1.15 (1.08,1.22)	8.26E-06
cg17333211	chr4:141294016	*SCOC*	*LOC100129858*	1.13 (1.08,1.19)	8.25E-07	0.4246			1.10 (1.05,1.15)	5.24E-05	1.08 (1.04,1.13)	1.52E-04
cg02331902	chr5:90610303		*AK091866*	1.12 (1.07,1.18)	8.37E-07	0.9151			1.10 (1.05,1.14)	5.27E-05	1.09 (1.05,1.13)	4.03E-05
cg13289553	chr5:32585524	*SUB1*	*SUB1*	1.14 (1.08,1.20)	8.68E-07	0.0392	1.13 (1.04,1.23)	4.00E-03	1.10 (1.04,1.15)	8.80E-05	1.10 (1.05,1.15)	1.02E-04
ch.6.1218502R	chr6:51250028			1.27 (1.15,1.39)	9.32E-07	0.7301			1.16 (1.06,1.26)	1.06E-03	1.13 (1.04,1.23)	3.55E-03
cg07156990	chr14:102685678	*WDR20*	*WDR20*	0.87 (0.83,0.92)	9.54E-07	0.2642			0.89 (0.85,0.94)	6.02E-06	0.89 (0.85,0.94)	7.18E-06

* Annotation based on UCSC Known Gene also fills in nearest gene within 10 MB.

** Odds ratio of developing asthma for a 1% absolute increase in methylation.

Table E4 *Genes previously associated with childhood asthma identified from literature review in either methylation or GWAS of asthma.*

ADAM17	FCER2	IL2RA	LOC105373951	NOTCH4	SLC38A6
ADRB2	FLJ41481	IL2RB	LOC105374811	NPSR1	SMAD3
AHR	FOXP2	IL33	LOC105375647	NRG1	SNTB1
AK5	FOXP3	IL4	LOC105375922	NTF3	STAC2
AKAP6	GATA3	IL4R	LOC105375976	OR51A7	STARD3
ALOX12	GC	IL5	LOC105376400	ORMDL1	STAT6
ARG1	GSDMA	IL6	LOC105376583	ORMDL3	SYNM
ARG2	GSDMB	IL6R	LOC105376673	PAPLN	TBCD
ARMC10	GTF3AP1	INPP4B	LOC105376928	PBX2	TBX21
BRD2	HCG23	KCNH1	LOC105377623	PDE4D	TBX5
BTNL2	HERC2	KCNQ4	LOC105377670	PGAP3	TCAP
C11orf30	HGC6.3	KIAA1244	LOC105377671	PNMT	TENM3
C1orf53	HLA-DOA	KIAA1598	LOC105378906	PPP3CA	TET1
C6orf10	HLA-DPA1	LCE5A	LOC105378907	PSMD3	TGFB1
CCDC40	HLA-DQA1	LEP	LOC105379121	PYHIN1	TLR1
CCL5	HLA-DQA2	LIF	LOC105379200	PYY2	TNFa
CDC14B	HLA-DQB1	LINC01565	LOC284661	RAD50	TNXB
CDH17	HLA-DRA	LOC100130207	LOC727896	RAM19A4	TOP2A
CDHR3	HLA-DRB1	LOC100131635	LOC727896;LPIN2	RANBP6	TSLP
CDK2	HLA-DRB5	LOC100216346	LOC90246	RAP2B	TUSC3
CHI3L1	HNMT	LOC100996770	LPIN2	RBP1	TYRP1
CLEC16A	HPSE2	LOC101927335	LRRC3C	RNA5SP299	USP38
COL12A1	HTATIP2	LOC101928813	MAX	RNA5SP508	WDR36
CRB1	HTR5A	LOC101928947	ME1	RORA	ZFPM1
CRNN	IKZF3	LOC101929163	MED24	RPL21P96	ZNF432
CTD-2350J17.1	IKZF4	LOC101929497	MIR8084	RPS3AP21	ZNF614
CUX1	IL13	LOC102725019	MLLT3	RTP2	ZNF616
DDIT4L	IL18R1	LOC102725082	MMP13	SCARB1	ZNF680
DENND1B	IL18RAP	LOC105369165	MNAT1	SEC22B	ZNF841
ERBB2	IL1R2	LOC105369563	MTUS1	SH2B3	ZNF90P3
ETS1	IL1RL1	LOC105371272	NCRNA00250	SIX4	ZPBP2
FAM110B	IL1RL2	LOC105371273	NEK6	SLC26A5	
FBXL7	IL2 site 1	LOC105373949	NHEJ1	SLC30A8	

Table E5 The 179 CpGs significantly differentially methylated in childhood in relation to asthma (FDR<0.05) along with the look-up of their associations with newborn methylation.

CpG	chr:pos	UCSC RefGene Name	UCSC Known Gene*	Childhood Methylation							Newborn Methylation				
				Coef	SE	OR** (CI)	p-value	HetPVal	RE OR** (CI)	RE P-value	Coef	SE	OR** (CI)	P-value	
cg06315149	chr1:2036398	*PRKCZ*	*PRKCZ*	-11.88	2.63	0.89 (0.84,0.93)	6.08E-06	0.2363			-0.04	1.44	1.00 (0.97,1.03)	0.9791	
cg13066938	chr1:6341140	*ACOT7*	*ACOT7*	-9.14	2.12	0.91 (0.88,0.95)	1.67E-05	0.0457	0.92 (0.86,0.98)	1.21E-02	-0.17	0.70	1.00 (0.98,1.01)	0.8084	
cg21220721	chr1:6341230	*ACOT7*	*ACOT7*	-6.32	1.10	0.94 (0.92,0.96)	1.02E-08	0.0049	0.94 (0.90,0.98)	1.73E-03	-1.99	1.68	0.98 (0.95,1.01)	0.2363	
cg09249800	chr1:6341287	*ACOT7*	*ACOT7*	-13.20	2.31	0.88 (0.84,0.92)	1.19E-08	0.2057			-0.28	1.65	1.00 (0.97,1.03)	0.8653	
cg11699125	chr1:6341327	*ACOT7*	*ACOT7*	-10.23	1.66	0.90 (0.87,0.93)	7.54E-10	0.1397			-0.65	1.25	0.99 (0.97,1.02)	0.6033	
cg18783781	chr1:9599067	*SLC25A33*	*SLC25A33*	-10.56	2.36	0.90 (0.86,0.94)	7.45E-06	0.0424	0.91 (0.85,0.98)	1.39E-02	0.37	0.84	1.00 (0.99,1.02)	0.6572	
cg02171825	chr1:26517586	*CATSPER4*	*CATSPER4*	-13.19	2.97	0.88 (0.83,0.93)	9.01E-06	0.5951			-0.44	2.27	1.00 (0.95,1.04)	0.8476	
cg01942646	chr1:27240694	*NR0B2*	*NR0B2*	-13.02	2.70	0.88 (0.83,0.93)	1.45E-06	0.4145			-1.43	1.69	0.99 (0.95,1.02)	0.3966	
cg16263722	chr1:29523841	*MECR*	*MECR*	-11.15	2.15	0.89 (0.86,0.93)	2.14E-07	0.4042			-1.31	1.29	0.99 (0.96,1.01)	0.3117	
cg11987455	chr1:43290834	*ERMAP*	*ERMAP*	-11.98	2.42	0.89 (0.85,0.93)	7.55E-07	0.5742			0.74	1.45	1.01 (0.98,1.04)	0.6099	
cg11683482	chr1:44678623	*DMAP1*	*DMAP1*	-10.92	2.01	0.90 (0.86,0.93)	5.39E-08	0.0067	0.88 (0.82,0.95)	5.26E-04	0.55	1.03	1.01 (0.99,1.03)	0.5965	
cg12643917	chr1:44715958	*ERI3*	*ERI3*	-11.13	2.51	0.89 (0.85,0.94)	8.98E-06	0.5525			-0.51	1.38	0.99 (0.97,1.02)	0.7101	
cg26252077	chr1:61607055	*NFIA*	*NFIA*	-12.78	2.28	0.88 (0.84,0.92)	2.18E-08	0.0388	0.88 (0.82,0.95)	9.20E-04	-1.20	1.49	0.99 (0.96,1.02)	0.4204	
cg10704177	chr1:62209607	*INADL*	*INADL*	-10.42	2.01	0.90 (0.87,0.94)	2.25E-07	0.0135	0.90 (0.84,0.96)	2.12E-03	0.44	1.25	1.00 (0.98,1.03)	0.7225	
cg01445399	chr1:87596934	*LOC339524*	*LOC339524*	-9.37	2.18	0.91 (0.87,0.95)	1.72E-05	0.3217			-0.91	1.12	0.99 (0.97,1.01)	0.4179	
cg19805160	chr1:159870731	*CCDC19*	*CCDC19*	-11.37	2.43	0.89 (0.85,0.94)	2.85E-06	0.0611			2.62	1.32	1.03 (1.00,1.05)	0.0477	***
cg09332506	chr1:160309220	*COPA*	*NCSTN*	-15.15	3.10	0.86 (0.81,0.91)	1.00E-06	0.5562			-2.36	2.82	0.98 (0.92,1.03)	0.4040	
cg17971251	chr1:177907297	*SEC16B*	*SEC16B*	-14.63	2.55	0.86 (0.82,0.91)	9.52E-09	0.1650			1.55	1.94	1.02 (0.98,1.05)	0.4245	
cg26033504	chr1:201458737	*CSRP1*	*CSRP1*	-9.70	2.15	0.91 (0.87,0.95)	6.35E-06	0.0006	0.91 (0.83,0.99)	3.21E-02	1.69	1.46	1.02 (0.99,1.05)	0.2466	
cg04895895	chr1:231005895	*C1orf198*	*C1orf198*	-12.21	2.68	0.89 (0.84,0.93)	5.26E-06	0.0314	0.91 (0.83,0.99)	2.35E-02	0.07	1.38	1.00 (0.97,1.03)	0.9581	
cg02473287	chr2:9752386	*YWHAQ*	*YWHAQ*	-10.99	2.46	0.90 (0.85,0.94)	8.00E-06	0.0334	0.90 (0.83,0.97)	5.96E-03	-0.80	1.41	0.99 (0.97,1.02)	0.5700	
cg10142874	chr2:11917623	*LPIN1*	*LPIN1*	-11.55	2.36	0.89 (0.85,0.93)	1.04E-06	0.0355	0.89 (0.82,0.95)	1.10E-03	0.67	1.91	1.01 (0.97,1.05)	0.7262	
cg26752663	chr2:25142016	*ADCY3*	*ADCY3*	11.13	2.33	1.12 (1.07,1.17)	1.79E-06	0.0551			1.44	1.01	1.01 (0.99,1.03)	0.1525	
cg00043800	chr2:74612144	*LOC100189589*	*LOC100189589*	-9.47	2.17	0.91 (0.87,0.95)	1.32E-05	0.6044			-1.68	1.23	0.98 (0.96,1.01)	0.1715	
cg17988187	chr2:74612222	*LOC100189589*	*LOC100189589*	-11.04	2.27	0.90 (0.86,0.94)	1.21E-06	0.0403	0.89 (0.83,0.96)	2.28E-03	-1.90	1.51	0.98 (0.95,1.01)	0.2068	
cg12077754	chr2:75089669	*HK2*	*HK2*	-7.90	1.72	0.92 (0.89,0.96)	4.56E-06	0.3634			0.55	1.13	1.01 (0.98,1.03)	0.6295	
cg22674082	chr2:98585733	*TMEM131*	*TMEM131*	-12.20	2.81	0.89 (0.84,0.94)	1.44E-05	0.1191			-0.54	1.51	0.99 (0.97,1.02)	0.7220	
cg00327263	chr2:120019111	*STEAP3*	*STEAP3*	-10.70	2.40	0.90 (0.86,0.94)	8.00E-06	0.1989			-0.25	1.17	1.00 (0.97,1.02)	0.8333	
cg25950520	chr2:121036760	*RALB*	*RALB*	-16.28	3.74	0.85 (0.79,0.91)	1.31E-05	0.4625			-2.66	2.64	0.97 (0.92,1.03)	0.3140	
cg00213281	chr2:149639822	*KIF5C;MIR1978*	*JA429504*	-12.85	2.65	0.88 (0.83,0.93)	1.24E-06	0.1106			2.13	1.43	1.02 (0.99,1.05)	0.1365	
cg02494549	chr2:161798364		*TANK*	-14.66	2.80	0.86 (0.82,0.91)	1.56E-07	0.0096	0.88 (0.80,0.98)	1.52E-02	-1.16	1.93	0.99 (0.95,1.03)	0.5488	
cg01310029	chr3:3152374	*IL5RA*	*IL5RA*	-11.12	2.42	0.89 (0.85,0.94)	4.18E-06	0.3101			0.94	1.52	1.01 (0.98,1.04)	0.5358	
cg10159529	chr3:3152530	*IL5RA*	*IL5RA*	-10.82	2.36	0.90 (0.86,0.94)	4.48E-06	0.1419			0.44	1.49	1.00 (0.98,1.03)	0.7688	
cg25224369	chr3:12918528		*DQ581328*	-10.53	2.36	0.90 (0.86,0.94)	7.75E-06	0.0265	0.89 (0.83,0.96)	3.58E-03	-2.38	1.25	0.98 (0.95,1.00)	0.0564	

cg07386061	chr3:52492874	*NISCH*	*NISCH*	-8.93	1.83	0.91 (0.88,0.95)	1.00E-06	0.3566			0.70	1.21	1.01 (0.98,1.03)	0.5622	
cg17890764	chr3:52864816	*ITIH4*	*ITIH4*	-9.95	2.03	0.91 (0.87,0.94)	8.95E-07	0.0503			0.99	1.08	1.01 (0.99,1.03)	0.3571	
cg07410597	chr3:66404129	*SLC25A26*	*LRIG1*	-12.48	2.43	0.88 (0.84,0.93)	2.70E-07	0.1875			0.69	1.78	1.01 (0.97,1.04)	0.6968	
cg04217850	chr3:66428294	*SLC25A26*	*LRIG1*	-13.23	2.80	0.88 (0.83,0.93)	2.35E-06	0.0001	0.85 (0.76,0.96)	8.68E-03	-0.50	1.95	0.99 (0.96,1.03)	0.7967	
cg06070625	chr3:69812798	*MITF*	*MITF*	-10.54	2.32	0.90 (0.86,0.94)	5.36E-06	0.0079	0.91 (0.84,0.99)	3.24E-02	-0.15	1.74	1.00 (0.97,1.03)	0.9327	
cg06391412	chr3:71295684	*FOXP1*	*FOXP1*	-13.39	2.26	0.87 (0.84,0.91)	3.00E-09	0.2689			1.92	1.40	1.02 (0.99,1.05)	0.1697	
cg20263733	chr3:130616293	*ATP2C1*	*ATP2C1*	-14.20	2.81	0.87 (0.82,0.92)	4.26E-07	0.1056			-2.60	2.57	0.97 (0.93,1.02)	0.3123	
cg09423651	chr3:136618442	*NCK1*	*NCK1*	-12.74	2.88	0.88 (0.83,0.93)	9.72E-06	0.8604			-5.22	1.88	0.95 (0.91,0.98)	0.0056	***
cg08698681	chr3:171091657	*TNIK*	*TNIK*	-12.14	2.67	0.89 (0.84,0.93)	5.52E-06	0.1997			-1.74	1.67	0.98 (0.95,1.02)	0.2978	
cg25636075	chr3:185217761	*TMEM41A*	*TMEM41A*	-14.50	3.19	0.87 (0.81,0.92)	5.59E-06	0.4020			-0.69	1.46	0.99 (0.97,1.02)	0.6350	
cg02803925	chr3:195974300	*PCYT1A*	*PCYT1A*	-14.57	2.97	0.86 (0.82,0.92)	9.27E-07	0.5322			-5.06	3.23	0.95 (0.89,1.01)	0.1179	
cg04077085	chr4:9937674	*SLC2A9*	*SLC2A9*	-14.84	2.96	0.86 (0.81,0.91)	5.34E-07	0.4046			4.07	1.74	1.04 (1.01,1.08)	0.0198	***
cg18912470	chr4:57848125	*POLR2B*	*POLR2B*	-9.85	2.03	0.91 (0.87,0.94)	1.23E-06	0.3294			0.27	1.51	1.00 (0.97,1.03)	0.8575	
cg26396815	chr4:102878132	*BANK1*	*BANK1*	-11.95	2.74	0.89 (0.84,0.94)	1.24E-05	0.3019			0.73	1.85	1.01 (0.97,1.04)	0.6918	
cg20866785	chr4:148733880	*ARHGAP10*	*Metazoa_SRP*	-9.27	2.16	0.91 (0.87,0.95)	1.70E-05	0.1982			0.36	1.65	1.00 (0.97,1.04)	0.8267	
cg16362140	chr5:10708717	*DAP*	*DAP*	-10.14	2.09	0.90 (0.87,0.94)	1.17E-06	0.0078	0.91 (0.85,0.98)	1.57E-02	-2.27	1.33	0.98 (0.95,1.00)	0.0877	
cg22588983	chr5:38783142		*AK126213*	-15.64	3.60	0.86 (0.80,0.92)	1.35E-05	0.7202			1.60	2.44	1.02 (0.97,1.07)	0.5120	
cg00944309	chr5:60142446		*ELOVL7*	-10.74	2.12	0.90 (0.86,0.94)	4.03E-07	0.0674			1.67	1.63	1.02 (0.98,1.05)	0.3032	
cg14978242	chr5:79501131	*SERINC5*	*SERINC5*	-7.74	1.80	0.93 (0.89,0.96)	1.74E-05	0.3326			2.48	1.19	1.03 (1.00,1.05)	0.0374	***
cg09565310	chr5:112541553	*MCC*	*MCC*	-11.68	2.50	0.89 (0.85,0.93)	3.10E-06	0.0920			-2.16	1.55	0.98 (0.95,1.01)	0.1640	
cg08969102	chr5:133563532		*PPP2CA*	-8.91	2.06	0.91 (0.88,0.95)	1.54E-05	0.1870			-0.89	1.20	0.99 (0.97,1.01)	0.4559	
cg21627181	chr6:25754190	*SLC17A4*	*SLC17A4*	-10.14	2.37	0.90 (0.86,0.95)	1.90E-05	0.0424	0.90 (0.84,0.97)	4.22E-03	-0.38	1.80	1.00 (0.96,1.03)	0.8313	
cg09597192	chr6:32141591	*AGPAT1*	*PPT2*	-12.53	2.73	0.88 (0.84,0.93)	4.29E-06	0.0134	0.88 (0.80,0.96)	6.09E-03	0.12	1.48	1.00 (0.97,1.03)	0.9355	
cg06426027	chr6:33232644	*VPS52*	*VPS52*	-18.72	3.96	0.83 (0.77,0.90)	2.32E-06	0.6621			-1.25	1.99	0.99 (0.95,1.03)	0.5316	
cg18460809	chr6:57048049	*BAG2*	*BAG2*	-11.60	2.32	0.89 (0.85,0.93)	6.05E-07	0.0535			-2.84	1.53	0.97 (0.94,1.00)	0.0631	
cg15961693	chr6:139689053		*CITED2*	-11.72	2.68	0.89 (0.84,0.94)	1.22E-05	0.1694			-1.77	1.79	0.98 (0.95,1.02)	0.3237	
cg26774971	chr6:158994407	*TMEM181*	*TMEM181*	-10.23	2.39	0.90 (0.86,0.95)	1.88E-05	0.0615			0.46	1.83	1.00 (0.97,1.04)	0.8032	
cg05477517	chr6:164531576		*AK093114*	-13.14	2.62	0.88 (0.83,0.92)	5.42E-07	0.0055	0.87 (0.79,0.96)	5.86E-03	-2.04	1.51	0.98 (0.95,1.01)	0.1771	
cg15304012	chr6:166876490	*RPS6KA2*	*RPS6KA2*	8.11	1.89	1.08 (1.04,1.13)	1.86E-05	0.1151			-0.23	1.05	1.00 (0.98,1.02)	0.8266	
cg19851574	chr6:167178233	*RPS6KA2*	*RPS6KA2*	-4.71	1.01	0.95 (0.94,0.97)	3.42E-06	0.2116			-0.82	0.64	0.99 (0.98,1.00)	0.1955	
cg03329755	chr6:167189272	*RPS6KA2*	*RPS6KA2*	-8.91	1.97	0.91 (0.88,0.95)	6.14E-06	0.2372			-1.50	1.82	0.99 (0.95,1.02)	0.4102	
cg25270424	chr7:24965657	*OSBPL3*	*OSBPL3*	-14.53	2.88	0.86 (0.82,0.92)	4.75E-07	0.3966			-0.63	2.02	0.99 (0.96,1.03)	0.7538	
cg04321303	chr7:44107504		*PGAM2*	-9.36	2.00	0.91 (0.88,0.95)	2.72E-06	0.0422	0.91 (0.85,0.96)	1.84E-03	-0.16	1.25	1.00 (0.97,1.02)	0.8994	
cg02435538	chr7:75507337	*RHBDD2*	*RHBDD2*	-10.68	2.16	0.90 (0.86,0.94)	7.37E-07	0.1305			-0.70	1.05	0.99 (0.97,1.01)	0.5045	
cg13007207	chr7:105279391	*ATXN7L1*	*ATXN7L1*	22.95	5.36	1.26 (1.13,1.40)	1.87E-05	0.1715			-5.33	2.80	0.95 (0.80,1.00)	0.0566	
cg17947765	chr7:117857964		*ANKRD7*	-14.71	3.36	0.86 (0.81,0.92)	1.17E-05	0.1488			-2.04	2.73	0.98 (0.93,1.03)	0.4551	
cg14678084	chr7:127627251	*SND1*	*SND1-IT1*	-17.96	3.69	0.84 (0.78,0.90)	1.17E-06	0.0463	0.82 (0.73,0.92)	7.30E-04	-1.00	2.06	0.99 (0.95,1.03)	0.6291	

cg05184016	chr7:149543136	*ZNF862*	*BC045757*	-16.07	2.89	0.85 (0.80,0.90)	2.74E-08	0.0470	0.85 (0.78,0.93)	2.28E-04	-1.86	2.10	0.98 (0.94,1.02)	0.3759
cg07970948	chr7:149543165	*ZNF862*	*BC045757*	-9.41	1.74	0.91 (0.88,0.94)	6.39E-08	0.0567			-0.74	1.23	0.99 (0.97,1.02)	0.5436
cg06558622	chr7:149543177	*ZNF862*	*BC045757*	-12.58	2.13	0.88 (0.85,0.92)	3.39E-09	0.6337			-1.04	1.36	0.99 (0.96,1.02)	0.4429
cg24576940	chr7:150648283	*KCNH2*	*KCNH2*	-14.05	3.28	0.87 (0.81,0.93)	1.83E-05	0.3610			-0.30	1.26	1.00 (0.97,1.02)	0.8088
cg23147443	chr7:150649655	*KCNH2*	*KCNH2*	-11.54	2.42	0.89 (0.85,0.93)	1.83E-06	0.6492			-0.59	0.65	0.99 (0.98,1.01)	0.3585
cg18666454	chr7:150651937	*KCNH2*	*KCNH2*	-11.32	2.15	0.89 (0.86,0.93)	1.46E-07	0.5027			-0.93	0.87	0.99 (0.97,1.01)	0.2858
cg02596233	chr7:150970209	*SMARCD3*	*SMARCD3*	-14.99	2.89	0.86 (0.81,0.91)	2.11E-07	0.0041	0.89 (0.79,0.99)	3.75E-02	0.72	2.35	1.01 (0.96,1.05)	0.7604
cg23706836	chr8:6407997	*ANGPT2;MCPH1*	*ANGPT2*	-8.80	1.76	0.92 (0.88,0.95)	5.63E-07	0.0080	0.92 (0.86,0.98)	6.91E-03	-1.69	1.26	0.98 (0.96,1.01)	0.1795
cg21919729	chr8:11719367	*CTSB*	*CTSB*	-8.01	1.71	0.92 (0.89,0.95)	3.03E-06	0.1753			-0.26	1.32	1.00 (0.97,1.02)	0.8422
cg03437605	chr8:22847209	*RHOBTB2*	*RHOBTB2*	-13.92	2.62	0.87 (0.83,0.92)	1.05E-07	0.3078			1.54	1.83	1.02 (0.98,1.05)	0.4002
cg22816343	chr8:26243601	*BNIP3L*	*BNIP3L*	-11.80	2.49	0.89 (0.85,0.93)	2.12E-06	0.0804			0.13	1.57	1.00 (0.97,1.03)	0.9339
cg23205629	chr8:33421410	*RNF122*	*RNF122*	-9.10	2.05	0.91 (0.88,0.95)	9.28E-06	0.1432			1.40	1.31	1.01 (0.99,1.04)	0.2863
cg10815420	chr8:105599835	*LRP12*	*LRP12*	-15.10	2.93	0.86 (0.81,0.91)	2.66E-07	0.9000			0.33	2.03	1.00 (0.96,1.04)	0.8719
cg02133716	chr8:128981622	*PVT1*	*MIR1205*	-16.57	3.37	0.85 (0.79,0.91)	8.64E-07	0.3547			0.91	1.72	1.01 (0.98,1.04)	0.5991
cg00736681	chr8:134546052	*ST3GAL1*	*ST3GAL1*	-10.18	2.14	0.90 (0.87,0.94)	1.93E-06	0.1431			0.29	1.87	1.00 (0.97,1.04)	0.8753
cg09377531	chr8:141046469	*TRAPPC9*	*AX748239*	-10.41	1.83	0.90 (0.87,0.93)	1.23E-08	0.0578			1.38	1.25	1.01 (0.99,1.04)	0.2705
cg14025883	chr9:5436224	*C9orf46*	*C9orf46*	-11.76	2.39	0.89 (0.85,0.93)	8.42E-07	0.1487			0.88	1.28	1.01 (0.98,1.03)	0.4934
cg01499988	chr9:35755346	*MSMP*	*MSMP*	-12.47	2.62	0.88 (0.84,0.93)	2.01E-06	0.5397			0.04	1.50	1.00 (0.97,1.03)	0.9794
cg13482814	chr9:82183332		*TLE4*	-12.32	2.69	0.88 (0.84,0.93)	4.74E-06	0.0662			-1.36	2.02	0.99 (0.95,1.03)	0.5015
cg13576859	chr9:97403129	*FBP1*	*FBP1*	-8.69	2.00	0.92 (0.88,0.95)	1.37E-05	0.0438	0.91 (0.86,0.97)	3.67E-03	-0.82	1.20	0.99 (0.97,1.02)	0.4951
cg20503329	chr9:101705792	*COL15A1*	*COL15A1*	-19.24	4.13	0.82 (0.76,0.89)	3.10E-06	0.0285	0.83 (0.73,0.96)	8.80E-03	-4.73	2.76	0.95 (0.80,1.01)	0.0861
cg00045753	chr9:123630545	*PHF19*	*PHF19*	-12.84	2.95	0.88 (0.83,0.93)	1.32E-05	0.0388	0.88 (0.80,0.97)	7.24E-03	-2.38	1.24	0.98 (0.95,1.00)	0.0548
cg13458609	chr9:130608923	*ENG*	*ENG*	-12.05	2.22	0.89 (0.85,0.93)	5.74E-08	0.2476			0.37	1.41	1.00 (0.98,1.03)	0.7930
cg13835688	chr9:130859454	*SLC25A25*	*SLC25A25*	-11.63	1.97	0.89 (0.86,0.93)	3.33E-09	0.0364	0.89 (0.83,0.95)	2.62E-04	0.05	1.29	1.00 (0.98,1.03)	0.9718
cg13628444	chr9:134883788	*MED27*	*MED27*	-12.04	2.44	0.89 (0.85,0.93)	7.76E-07	0.2127			-1.51	1.69	0.98 (0.95,1.02)	0.3701
cg13850063	chr9:138362321		*AK096249*	-24.77	4.56	0.78 (0.71,0.85)	5.49E-08	0.0736			-1.65	2.28	0.98 (0.94,1.03)	0.4696
cg14011077	chr9:138362327		*AK096249*	-15.12	2.61	0.86 (0.82,0.90)	7.02E-09	0.6429			-0.53	2.10	0.99 (0.95,1.04)	0.7997
cg06958964	chr10:45494806	*C10orf25;ZNF22*	*ZNF22*	-15.96	3.42	0.85 (0.80,0.91)	2.97E-06	0.7645			1.25	2.68	1.01 (0.96,1.07)	0.6400
cg25854298	chr10:73936754	*ASCC1*	*ASCC1*	-11.91	2.68	0.89 (0.84,0.94)	8.74E-06	0.2139			-0.89	1.29	0.99 (0.97,1.02)	0.4901
cg04973995	chr10:74057977		*DDIT4*	-7.83	1.78	0.92 (0.89,0.96)	1.10E-05	0.3720			0.10	2.08	1.00 (0.96,1.04)	0.9632
cg00366037	chr10:76781121	*MYST4*	*KAT6B*	-12.66	2.92	0.88 (0.83,0.93)	1.45E-05	0.9001			0.14	2.10	1.00 (0.96,1.04)	0.9473
cg22235258	chr11:34675402	*EHF*	*EHF*	-13.03	3.02	0.88 (0.83,0.93)	1.61E-05	0.1041			-1.23	2.47	0.99 (0.94,1.04)	0.6194
cg24459209	chr11:57148215	*PRG3*	*PRG3*	-15.30	2.86	0.86 (0.81,0.91)	8.52E-08	0.8292			0.70	1.75	1.01 (0.97,1.04)	0.6907
cg15700636	chr11:57156050	*PRG2*	*PRG2*	-11.65	2.25	0.89 (0.85,0.93)	2.35E-07	0.0146	0.89 (0.83,0.96)	2.61E-03	0.28	1.51	1.00 (0.97,1.03)	0.8533
cg08773180	chr11:57157607	*PRG2*	*PRG2*	-11.66	2.23	0.89 (0.85,0.93)	1.77E-07	0.0409	0.88 (0.83,0.95)	5.02E-04	-1.98	1.66	0.98 (0.95,1.01)	0.2336
cg12819873	chr11:57157632	*PRG2*	*PRG2*	-10.83	2.45	0.90 (0.86,0.94)	9.55E-06	0.2663			-0.42	1.88	1.00 (0.96,1.03)	0.8246
cg27533472	chr11:59856225	*MS4A2*	*MS4A2*	-19.27	4.18	0.82 (0.76,0.90)	4.09E-06	0.3282			-3.27	3.38	0.97 (0.91,1.03)	0.3334

cg25087851	chr11:60623918	*GPR44*	*PTGDR2*	-11.86	2.10	0.89 (0.85,0.93)	1.69E-08	0.2450			-0.76	1.43	0.99 (0.97,1.02)	0.5940	
cg13233042	chr11:63432489	*ATL3*	*ATL3*	-13.01	2.81	0.88 (0.83,0.93)	3.59E-06	0.1843			1.36	1.76	1.01 (0.98,1.05)	0.4387	
cg05300717	chr11:65546210	*DKFZp761E198*	*DKFZp761E198*	-15.35	2.48	0.86 (0.82,0.90)	6.51E-10	0.1399			-0.94	2.38	0.99 (0.95,1.04)	0.6930	
cg15219163	chr11:70842128	*SHANK2*	*SHANK2*	15.93	3.71	1.17 (1.09,1.26)	1.80E-05	0.4823			1.13	1.53	1.01 (0.98,1.04)	0.4600	
cg24368962	chr11:111570978	*SIK2*	*DQ599327*	-15.79	3.26	0.85 (0.80,0.91)	1.28E-06	0.0010	0.86 (0.75,0.99)	3.43E-02	-0.90	4.14	0.99 (0.91,1.07)	0.8277	
cg19434937	chr12:7104184	*LPCAT3*	*EMG1*	-8.95	1.86	0.91 (0.88,0.95)	1.55E-06	0.0382	0.92 (0.86,0.97)	3.25E-03	-1.33	1.28	0.99 (0.96,1.01)	0.2976	
cg03014680	chr12:10122522	*CLEC12A*	*CLEC12A*	-8.84	1.86	0.92 (0.88,0.95)	2.14E-06	0.2674			-1.85	1.28	0.98 (0.96,1.01)	0.1477	
cg09447105	chr12:15126020	*PDE6H*	*PDE6H*	-13.27	2.68	0.88 (0.83,0.92)	7.60E-07	0.0074	0.89 (0.81,0.97)	1.22E-02	0.89	1.51	1.01 (0.98,1.04)	0.5557	
cg24028828	chr12:56694932	*CS*	*CS*	-13.71	2.88	0.87 (0.82,0.92)	1.99E-06	0.5495			1.11	1.44	1.01 (0.98,1.04)	0.4374	
cg21498475	chr12:113737469	*SLC24A6*	*SLC24A6*	-10.40	2.29	0.90 (0.86,0.94)	5.44E-06	0.0297	0.90 (0.84,0.97)	6.21E-03	-0.75	1.52	0.99 (0.96,1.02)	0.6193	
cg10065736	chr12:117440120	*FBXW8*	*AK055849*	-10.22	1.94	0.90 (0.87,0.94)	1.41E-07	0.1856			-1.02	1.16	0.99 (0.97,1.01)	0.3790	
cg03131767	chr12:123446272	*ABCB9*	*ABCB9*	-11.72	2.36	0.89 (0.85,0.93)	7.21E-07	0.1245			0.15	1.41	1.00 (0.97,1.03)	0.9145	
cg19928703	chr13:30143971	*SLC7A1*	*SLC7A1*	-11.71	2.68	0.89 (0.84,0.94)	1.21E-05	0.4460			1.26	1.97	1.01 (0.97,1.05)	0.5223	
cg07908654	chr13:41631052		*TRNA_Glu*	-11.47	2.23	0.89 (0.85,0.93)	2.60E-07	0.1662			-0.55	1.50	0.99 (0.97,1.02)	0.7142	
cg24818699	chr13:43355514	*C13orf30*	*C13orf30*	-13.92	3.13	0.87 (0.82,0.93)	8.53E-06	0.2994			2.02	2.31	1.02 (0.98,1.07)	0.3828	
cg08770358	chr13:48876684	*RB1*	*BC039553*	-16.86	3.88	0.84 (0.78,0.91)	1.42E-05	0.9019			1.35	2.03	1.01 (0.97,1.05)	0.5072	
cg00222125	chr13:53226144	*SUGT1*	*SUGT1*	-10.12	2.33	0.90 (0.86,0.95)	1.43E-05	0.8730			2.93	1.19	1.03 (1.01,1.05)	0.0138	***
cg11770323	chr13:80066032	*NDFIP2*	*NDFIP2*	-9.41	2.08	0.91 (0.87,0.95)	5.86E-06	0.0916			-0.23	1.35	1.00 (0.97,1.02)	0.8630	
cg25479097	chr13:113305704	*C13orf35*	*C13orf35*	-12.19	2.48	0.89 (0.84,0.93)	9.11E-07	0.1731			1.36	1.57	1.01 (0.98,1.05)	0.3861	
cg18368116	chr14:21436271		*RNASE2*	-11.80	2.58	0.89 (0.84,0.93)	4.93E-06	0.2402			0.58	2.10	1.01 (0.97,1.05)	0.7820	
cg08077807	chr14:62001072	*PRKCH*	*PRKCH*	-16.27	3.08	0.85 (0.80,0.90)	1.29E-07	0.6743			-2.93	2.14	0.97 (0.93,1.01)	0.1708	
cg04933530	chr14:77419754		*IRF2BPL*	-11.70	2.20	0.89 (0.85,0.93)	1.02E-07	0.4659			-0.12	1.47	1.00 (0.97,1.03)	0.9368	
cg01901579	chr14:95615731	*DICER1*	*DICER1*	-9.29	2.05	0.91 (0.88,0.95)	5.86E-06	0.0257	0.91 (0.85,0.97)	5.84E-03	0.10	1.44	1.00 (0.97,1.03)	0.9473	
cg16409452	chr14:100610186	*EVL*	*AX747103*	-9.84	1.96	0.91 (0.87,0.94)	4.89E-07	0.2881			-2.62	0.75	0.97 (0.96,0.99)	0.0005	***
cg14084609	chr14:100610407	*EVL*	*AX747103*	-12.03	2.03	0.89 (0.85,0.92)	2.96E-09	0.3931			-0.68	0.93	0.99 (0.98,1.01)	0.4653	
cg18550847	chr14:100610570	*EVL*	*AX747103*	-9.38	1.89	0.91 (0.88,0.94)	7.10E-07	0.1220			-0.07	0.55	1.00 (0.99,1.01)	0.8948	
cg01000631	chr14:100610667		*EVL*	-9.86	1.81	0.91 (0.87,0.94)	4.88E-08	0.0153	0.90 (0.84,0.96)	8.40E-04	0.38	0.49	1.00 (0.99,1.01)	0.4364	
cg05875066	chr14:104625249	*KIF26A*	*KIF26A*	-13.75	2.63	0.87 (0.83,0.92)	1.77E-07	0.1313			-0.23	0.58	1.00 (0.99,1.01)	0.6869	
cg18817654	chr15:39485138		*C15orf54*	-14.23	3.06	0.87 (0.82,0.92)	3.41E-06	0.1330			2.59	3.18	1.03 (0.96,1.09)	0.4151	
cg25939647	chr15:40173065	*GPR176*	*GPR176*	-9.35	1.96	0.91 (0.88,0.95)	1.91E-06	0.0607			2.37	1.67	1.02 (0.99,1.06)	0.1553	
cg07177867	chr15:52030746	*LYSMD2*	*LYSMD2*	-10.62	2.44	0.90 (0.86,0.94)	1.29E-05	0.2360			0.44	1.14	1.00 (0.98,1.03)	0.7032	
cg11266582	chr15:64275853	*DAPK2*	*DAPK2*	-11.58	2.68	0.89 (0.85,0.94)	1.52E-05	0.0761			-3.00	2.29	0.97 (0.93,1.02)	0.1904	
cg10387956	chr15:72646210	*HEXA*	*BC034424*	-9.63	2.05	0.91 (0.87,0.95)	2.72E-06	0.0368	0.90 (0.85,0.96)	2.27E-03	-0.44	1.33	1.00 (0.97,1.02)	0.7430	
cg23387863	chr15:77472416	*SGK269*	*AX747193*	-9.78	2.03	0.91 (0.87,0.94)	1.51E-06	0.0407	0.92 (0.86,0.97)	5.65E-03	1.28	1.53	1.01 (0.98,1.04)	0.4017	
cg04497992	chr16:616212	*NHLRC4*	*C16orf11*	-10.13	2.13	0.90 (0.87,0.94)	1.92E-06	0.1859			-1.08	1.82	0.99 (0.95,1.03)	0.5532	
cg08067346	chr16:25011481	*ARHGAP17*	*DQ583809*	-10.13	2.35	0.90 (0.86,0.95)	1.60E-05	0.0093	0.92 (0.85,1.00)	4.91E-02	0.66	1.44	1.01 (0.98,1.04)	0.6467	
cg26134665	chr16:31021544	*STX1B*	*STX1B*	-8.66	1.96	0.92 (0.88,0.95)	9.50E-06	0.3601			-0.73	1.43	0.99 (0.97,1.02)	0.6118	

cg09147843	chr16:53467612	*RBL2*	*RBL2*	-11.57	2.60	0.89 (0.85,0.94)	8.89E-06	0.0427	0.91 (0.84,0.99)	3.27E-02	1.67	1.61	1.02 (0.99,1.05)	0.2982
cg01998785	chr16:55542709	*LPCAT2*	*LPCAT2*	-9.91	1.99	0.91 (0.87,0.94)	6.17E-07	0.0594			-0.74	0.94	0.99 (0.97,1.01)	0.4310
cg27383865	chr16:84075870	*SLC38A8*	*SLC38A8*	10.35	2.41	1.11 (1.06,1.16)	1.73E-05	0.0300	1.12 (1.04,1.21)	4.24E-03	-1.72	1.71	0.98 (0.95,1.02)	0.3171
cg08640475	chr16:85551478		*KIAA0182*	-7.97	1.69	0.92 (0.89,0.95)	2.36E-06	0.0577			-0.63	1.01	0.99 (0.97,1.01)	0.5372
cg10099827	chr16:85551514		*KIAA0182*	-8.05	1.66	0.92 (0.89,0.95)	1.32E-06	0.2595			-0.35	1.10	1.00 (0.98,1.02)	0.7509
cg08940169	chr16:88540241	*ZFPM1*	*ZFPM1*	-9.73	1.90	0.91 (0.87,0.94)	2.93E-07	0.1990			-1.50	1.56	0.99 (0.96,1.02)	0.3346
cg04983687	chr16:88558223	*ZFPM1*	*ZFPM1*	-7.76	1.21	0.93 (0.80,0.95)	1.33E-10	0.1560			-0.54	1.10	0.99 (0.97,1.02)	0.6259
cg20315954	chr17:15137304	*PMP22*	*PMP22*	-12.65	2.73	0.88 (0.84,0.93)	3.58E-06	0.1377			-0.55	1.68	0.99 (0.96,1.03)	0.7436
cg20885063	chr17:17939419	*ATPAF2*	*ATPAF2*	-10.94	2.24	0.90 (0.86,0.94)	1.06E-06	0.1305			-0.30	1.34	1.00 (0.97,1.02)	0.8197
cg14611258	chr17:17946468	*C17orf39*	*C17orf39*	-11.70	2.59	0.89 (0.85,0.94)	6.41E-06	0.0120	0.89 (0.82,0.97)	1.06E-02	2.35	1.53	1.02 (0.99,1.05)	0.1254
cg19468946	chr17:37922297	*IKZF3*	*IKZF3*	8.35	1.93	1.09 (1.05,1.13)	1.50E-05	0.9004			-0.34	0.96	1.00 (0.98,1.02)	0.7268
cg21723861	chr17:39686628		*KRT19*	-14.05	2.68	0.87 (0.82,0.92)	1.59E-07	0.4059			-0.59	1.59	0.99 (0.96,1.03)	0.7077
cg00170714	chr17:40724562	*MLX;PSMC3IP*	*PSMC3IP*	-12.13	2.24	0.89 (0.85,0.93)	6.15E-08	0.1413			0.58	1.50	1.01 (0.98,1.04)	0.6985
cg25173129	chr17:56269410	*EPX*	*EPX*	-12.40	2.51	0.88 (0.84,0.93)	8.09E-07	0.0960			1.23	1.76	1.01 (0.98,1.05)	0.4845
cg02970679	chr17:56269818	*EPX*	*EPX*	-13.35	2.73	0.88 (0.83,0.92)	9.99E-07	0.1576			-3.60	1.90	0.96 (0.93,1.00)	0.0584
cg17374802	chr17:56270828	*EPX*	*EPX*	-10.55	2.22	0.90 (0.86,0.94)	2.06E-06	0.0543			-1.40	1.25	0.99 (0.96,1.01)	0.2630
cg17041511	chr17:61509620		*CYB561*	-9.62	2.19	0.91 (0.87,0.95)	1.15E-05	0.4396			-0.74	1.38	0.99 (0.97,1.02)	0.5905
cg22312249	chr17:72779428	*TMEM104*	*TMEM104*	-9.31	2.09	0.91 (0.87,0.95)	8.73E-06	0.1446			-0.66	1.16	0.99 (0.97,1.02)	0.5724
cg09705784	chr17:76565232	*DNAH17*	*DNAH17*	-9.15	1.74	0.91 (0.88,0.94)	1.50E-07	0.0185	0.87 (0.82,0.93)	3.95E-05	0.94	1.31	1.01 (0.98,1.04)	0.4743
cg06725287	chr17:80533762	*FOXK2*	*FOXK2*	-13.56	2.54	0.87 (0.83,0.92)	9.07E-08	0.3875			-0.26	0.81	1.00 (0.98,1.01)	0.7504
cg13054523	chr17:81055722		*METRNL*	-13.94	2.45	0.87 (0.83,0.91)	1.20E-08	0.1336			-0.60	1.81	0.99 (0.96,1.03)	0.7400
cg18337287	chr19:930871	*ARID3A*	*ARID3A*	-15.13	2.81	0.86 (0.81,0.91)	7.21E-08	0.2100			-0.07	1.36	1.00 (0.97,1.03)	0.9583
cg12104982	chr19:5592815	*SAFB2*	*SAFB2*	-15.43	2.91	0.86 (0.81,0.91)	1.13E-07	0.2578			2.89	3.25	1.03 (0.97,1.10)	0.3750
cg10644885	chr19:11687621	*ACP5*	*ACP5*	-15.00	2.29	0.86 (0.82,0.90)	5.77E-11	0.2290			-0.84	1.17	0.99 (0.97,1.01)	0.4712
cg02359181	chr19:34860339	*GPI*	*GPI*	-12.75	2.72	0.88 (0.83,0.93)	2.68E-06	0.0204	0.89 (0.82,0.97)	1.15E-02	-0.80	1.51	0.99 (0.96,1.02)	0.5938
cg20673965	chr19:44220148	*IRGC*	*IRGC*	-11.06	2.43	0.90 (0.85,0.94)	5.54E-06	0.2895			-0.61	1.57	0.99 (0.96,1.02)	0.6983
cg26979537	chr19:48016860	*NAPA*	*NAPA*	-18.55	3.83	0.83 (0.77,0.90)	1.31E-06	0.5977			1.53	3.53	1.02 (0.95,1.09)	0.6642
cg21073212	chr20:30866501	*KIF3B*	*KIF3B*	-7.94	1.85	0.92 (0.89,0.96)	1.79E-05	0.3531			-0.41	1.15	1.00 (0.97,1.02)	0.7204
cg20226253	chr20:34022914	*GDF5*	*GDF5OS*	-14.37	3.28	0.87 (0.81,0.92)	1.15E-05	0.0008	0.87 (0.77,0.99)	3.62E-02	2.61	1.54	1.03 (1.00,1.06)	0.0901
cg21045547	chr20:35422703	*C20orf117*	*KIAA0889*	-11.71	2.57	0.89 (0.85,0.94)	5.32E-06	0.2887			-0.37	0.62	1.00 (0.98,1.01)	0.5521
cg13792581	chr20:43590115	*TOMM34*	*TOMM34*	-13.71	3.15	0.87 (0.82,0.93)	1.34E-05	0.2441			0.40	1.69	1.00 (0.97,1.04)	0.8132
cg13197551	chr20:60709957	*LSM14B*	*LSM14B*	-15.40	3.14	0.86 (0.81,0.91)	9.23E-07	0.7768			-1.03	2.73	0.99 (0.94,1.04)	0.7063
cg18042632	chr21:42520902	*C21orf130*	*LINC00323*	-8.87	1.86	0.92 (0.88,0.95)	1.87E-06	0.6020			1.36	1.38	1.01 (0.99,1.04)	0.3245
cg18879389	chr21:43771120	*TFF2*	*TFF2*	-13.79	2.84	0.87 (0.82,0.92)	1.21E-06	0.5763			-1.17	1.31	0.99 (0.96,1.01)	0.3730

* Annotation based on UCSC Known Gene also fills in nearest gene within 10 MB.

** Odds ratio of developing asthma for a 1% absolute increase in methylation.

*** Significant nominal (<0.05) p-value

Table E6 *Lookup of 179 CpGs differentially methylated in blood in childhood in two studies of nasal methylation: PIAMA and ICAC*

CpG	chr:position	UCSC RefGene Name	UCSC Known Gene*	PACE Discovery (N=647 cases)		PIAMA Look-Up in Nasal (N= 37 cases)		ICAC Look-Up in Nasal (N=36 cases)	
				OR (CI)	P-value	Direction of Effect Concordant with PACE	P-value	Direction of Effect Concordant with PACE	P-value
cg06315149	chr1:2036398	*PRKCZ*	*PRKCZ*	0.89 (0.84,0.93)	6.08E-06	yes	5.66E-01	yes	3.40E-01
cg13066938	chr1:6341140	*ACOT7*	*ACOT7*	0.91 (0.88,0.95)	1.67E-05	yes	1.88E-01	yes	2.39E-01
cg21220721	chr1:6341230	*ACOT7*	*ACOT7*	0.94 (0.92,0.96)	1.02E-08	yes	1.09E-01	yes	1.14E-05
cg09249800	chr1:6341287	*ACOT7*	*ACOT7*	0.88 (0.84,0.92)	1.19E-08	NA	NA	yes	1.40E-06
cg11699125	chr1:6341327	*ACOT7*	*ACOT7*	0.90 (0.87,0.93)	7.54E-10	yes	5.80E-03	yes	1.19E-04
cg18783781	chr1:9599067	*SLC25A33*	*SLC25A33*	0.90 (0.86,0.94)	7.45E-06	no	3.71E-01	yes	3.33E-02
cg02171825	chr1:26517586	*CATSPER4*	*CATSPER4*	0.88 (0.83,0.93)	9.01E-06	no	9.17E-01	yes	1.82E-03
cg01942646	chr1:27240694	*NR0B2*	*NR0B2*	0.88 (0.83,0.93)	1.45E-06	yes	7.50E-01	yes	6.98E-02
cg16263722	chr1:29523841	*MECR*	*MECR*	0.89 (0.86,0.93)	2.14E-07	yes	4.54E-02	yes	2.92E-03
cg11987455	chr1:43290834	*ERMAP*	*ERMAP*	0.89 (0.85,0.93)	7.55E-07	no	8.81E-01	yes	9.29E-04
cg11683482	chr1:44678623	*DMAP1*	*DMAP1*	0.90 (0.86,0.93)	5.39E-08	yes	4.67E-01	yes	1.39E-01
cg12643917	chr1:44715958	*ERI3*	*ERI3*	0.89 (0.85,0.94)	8.98E-06	yes	1.96E-01	yes	4.28E-04
cg26252077	chr1:61607055	*NFIA*	*NFIA*	0.88 (0.84,0.92)	2.18E-08	yes	2.24E-01	yes	2.89E-02
cg10704177	chr1:62209607	*INADL*	*INADL*	0.90 (0.87,0.94)	2.25E-07	yes	3.16E-01	yes	1.77E-02
cg01445399	chr1:87596934	*LOC339524*	*LOC339524*	0.91 (0.87,0.95)	1.72E-05	yes	1.48E-02	yes	2.15E-03
cg19805160	chr1:159870731	*CCDC19*	*CCDC19*	0.89 (0.85,0.94)	2.85E-06	yes	1.69E-01	yes	1.55E-02
cg09332506	chr1:160309220	*COPA*	*NCSTN*	0.86 (0.81,0.91)	1.00E-06	yes	1.34E-01	yes	2.64E-03
cg17971251	chr1:177907297	*SEC16B*	*SEC16B*	0.86 (0.82,0.91)	9.52E-09	yes	1.33E-01	yes	5.66E-03
cg26033504	chr1:201458737	*CSRP1*	*CSRP1*	0.91 (0.87,0.95)	6.35E-06	no	5.99E-01	yes	3.52E-02
cg04895895	chr1:231005895	*C1orf198*	*C1orf198*	0.89 (0.84,0.93)	5.26E-06	yes	9.29E-01	yes	8.06E-02
cg02473287	chr2:9752386	*YWHAQ*	*YWHAQ*	0.90 (0.85,0.94)	8.00E-06	no	7.98E-01	yes	1.39E-02
cg10142874	chr2:11917623	*LPIN1*	*LPIN1*	0.89 (0.85,0.93)	1.04E-06	yes	6.74E-01	yes	5.26E-04
cg26752663	chr2:25142016	*ADCY3*	*ADCY3*	1.12 (1.07,1.17)	1.79E-06	no	1.51E-01	yes	3.88E-03
cg00043800	chr2:74612144	*LOC100189589*	*LOC100189589*	0.91 (0.87,0.95)	1.32E-05	no	4.21E-01	yes	3.66E-03
cg17988187	chr2:74612222	*LOC100189589*	*LOC100189589*	0.90 (0.86,0.94)	1.21E-06	yes	6.80E-01	yes	3.17E-03
cg12077754	chr2:75089669	*HK2*	*HK2*	0.92 (0.89,0.96)	4.56E-06	yes	6.02E-01	yes	1.08E-04
cg22674082	chr2:98585733	*TMEM131*	*TMEM131*	0.89 (0.84,0.94)	1.44E-05	no	2.89E-01	yes	2.19E-03
cg00327263	chr2:120019111	*STEAP3*	*STEAP3*	0.90 (0.86,0.94)	8.00E-06	no	9.08E-02	yes	5.62E-02
cg25950520	chr2:121036760	*RALB*	*RALB*	0.85 (0.79,0.91)	1.31E-05	yes	2.01E-01	yes	1.58E-01
cg00213281	chr2:149639822	*KIF5C;MIR1978*	*JA429504*	0.88 (0.83,0.93)	1.24E-06	yes	8.98E-03	yes	2.24E-05
cg02494549	chr2:161798364		*TANK*	0.86 (0.82,0.91)	1.56E-07	yes	6.51E-02	yes	2.56E-05
cg01310029	chr3:3152374	*IL5RA*	*IL5RA*	0.89 (0.85,0.94)	4.18E-06	yes	7.91E-02	yes	6.09E-04

cg10159529	chr3:3152530	*IL5RA*	*IL5RA*	0.90 (0.86,0.94)	4.48E-06	yes	1.69E-01	yes	3.77E-02
cg25224369	chr3:12918528		*DQ581328*	0.90 (0.86,0.94)	7.75E-06	yes	8.13E-01	yes	3.03E-03
cg07386061	chr3:52492874	*NISCH*	*NISCH*	0.91 (0.88,0.95)	1.00E-06	yes	5.27E-01	yes	4.22E-02
cg17890764	chr3:52864816	*ITIH4*	*ITIH4*	0.91 (0.87,0.94)	8.95E-07	yes	5.33E-02	yes	1.90E-02
cg07410597	chr3:66404129	*SLC25A26*	*LRIG1*	0.88 (0.84,0.93)	2.70E-07	yes	2.12E-01	yes	8.38E-02
cg04217850	chr3:66428294	*SLC25A26*	*LRIG1*	0.88 (0.83,0.93)	2.35E-06	no	2.70E-01	yes	9.42E-03
cg06070625	chr3:69812798	*MITF*	*MITF*	0.90 (0.86,0.94)	5.36E-06	yes	1.72E-01	yes	2.88E-01
cg06391412	chr3:71295684	*FOXP1*	*FOXP1*	0.87 (0.84,0.91)	3.00E-09	yes	1.03E-01	no	9.59E-01
cg20263733	chr3:130616293	*ATP2C1*	*ATP2C1*	0.87 (0.82,0.92)	4.26E-07	yes	3.63E-02	yes	3.80E-04
cg09423651	chr3:136618442	*NCK1*	*NCK1*	0.88 (0.83,0.93)	9.72E-06	yes	6.47E-02	yes	6.71E-06
cg08698681	chr3:171091657	*TNIK*	*TNIK*	0.89 (0.84,0.93)	5.52E-06	yes	7.36E-01	yes	5.54E-03
cg25636075	chr3:185217761	*TMEM41A*	*TMEM41A*	0.87 (0.81,0.92)	5.59E-06	yes	5.90E-01	yes	1.15E-01
cg02803925	chr3:195974300	*PCYT1A*	*PCYT1A*	0.86 (0.82,0.92)	9.27E-07	no	5.10E-01	yes	1.45E-03
cg04077085	chr4:9937674	*SLC2A9*	*SLC2A9*	0.86 (0.81,0.91)	5.34E-07	yes	9.54E-01	yes	1.65E-04
cg18912470	chr4:57848125	*POLR2B*	*POLR2B*	0.91 (0.87,0.94)	1.23E-06	no	8.94E-01	no	6.94E-01
cg26396815	chr4:102878132	*BANK1*	*BANK1*	0.89 (0.84,0.94)	1.24E-05	yes	7.85E-01	yes	6.99E-04
cg20866785	chr4:148733880	*ARHGAP10*	*Metazoa_SRP*	0.91 (0.87,0.95)	1.70E-05	no	4.11E-01	yes	4.87E-03
cg16362140	chr5:10708717	*DAP*	*DAP*	0.90 (0.87,0.94)	1.17E-06	yes	5.48E-01	yes	6.81E-04
cg22588983	chr5:38783142		*AK126213*	0.86 (0.80,0.92)	1.35E-05	yes	2.06E-01	yes	6.09E-03
cg00944309	chr5:60142446		*ELOVL7*	0.90 (0.86,0.94)	4.03E-07	yes	1.25E-02	yes	9.53E-04
cg14978242	chr5:79501131	*SERINC5*	*SERINC5*	0.93 (0.89,0.96)	1.74E-05	no	5.80E-01	yes	2.02E-02
cg09565310	chr5:112541553	*MCC*	*MCC*	0.89 (0.85,0.93)	3.10E-06	yes	2.27E-01	yes	1.39E-01
cg08969102	chr5:133563532		*PPP2CA*	0.91 (0.88,0.95)	1.54E-05	yes	1.93E-01	yes	3.90E-03
cg21627181	chr6:25754190	*SLC17A4*	*SLC17A4*	0.90 (0.86,0.95)	1.90E-05	yes	2.43E-01	yes	3.77E-02
cg09597192	chr6:32141591	*AGPAT1*	*PPT2*	0.88 (0.84,0.93)	4.29E-06	yes	1.44E-02	yes	6.25E-03
cg06426027	chr6:33232644	*VPS52*	*VPS52*	0.83 (0.77,0.90)	2.32E-06	yes	4.81E-01	yes	6.43E-02
cg18460809	chr6:57048049	*BAG2*	*BAG2*	0.89 (0.85,0.93)	6.05E-07	no	9.91E-01	yes	3.55E-03
cg15961693	chr6:139689053		*CITED2*	0.89 (0.84,0.94)	1.22E-05	yes	7.14E-01	yes	1.71E-02
cg26774971	chr6:158994407	*TMEM181*	*TMEM181*	0.90 (0.86,0.95)	1.88E-05	no	8.94E-01	yes	1.50E-03
cg05477517	chr6:164531576		*AK093114*	0.88 (0.83,0.92)	5.42E-07	no	8.79E-01	yes	1.28E-06
cg15304012	chr6:166876490	*RPS6KA2*	*RPS6KA2*	1.08 (1.04,1.13)	1.86E-05	yes	4.78E-01	no	5.98E-01
cg19851574	chr6:167178233	*RPS6KA2*	*RPS6KA2*	0.95 (0.94,0.97)	3.42E-06	yes	2.34E-01	yes	9.92E-03
cg03329755	chr6:167189272	*RPS6KA2*	*RPS6KA2*	0.91 (0.88,0.95)	6.14E-06	yes	1.94E-01	yes	2.81E-02
cg25270424	chr7:24965657	*OSBPL3*	*OSBPL3*	0.86 (0.82,0.92)	4.75E-07	yes	1.83E-01	yes	5.42E-02
cg04321303	chr7:44107504		*PGAM2*	0.91 (0.88,0.95)	2.72E-06	yes	3.49E-01	yes	2.11E-02
cg02435538	chr7:75507337	*RHBDD2*	*RHBDD2*	0.90 (0.86,0.94)	7.37E-07	no	6.48E-01	yes	3.60E-03
cg13007207	chr7:105279391	*ATXN7L1*	*ATXN7L1*	1.26 (1.13,1.40)	1.87E-05	no	1.04E-01	yes	9.82E-01
cg17947765	chr7:117857964		*ANKRD7*	0.86 (0.81,0.92)	1.17E-05	yes	4.12E-01	yes	1.23E-01
cg14678084	chr7:127627251	*SND1*	*SND1-IT1*	0.84 (0.78,0.90)	1.17E-06	no	7.92E-01	yes	1.92E-03
cg05184016	chr7:149543136	*ZNF862*	*BC045757*	0.85 (0.80,0.90)	2.74E-08	yes	1.84E-01	yes	1.38E-06

cg07970948	chr7:149543165	*ZNF862*	*BC045757*	0.91 (0.88,0.94)	6.39E-08	yes	2.04E-02	yes	1.51E-06
cg06558622	chr7:149543177	*ZNF862*	*BC045757*	0.88 (0.85,0.92)	3.39E-09	yes	4.12E-02	yes	1.01E-07
cg24576940	chr7:150648283	*KCNH2*	*KCNH2*	0.87 (0.81,0.93)	1.83E-05	yes	2.26E-02	yes	1.91E-03
cg23147443	chr7:150649655	*KCNH2*	*KCNH2*	0.89 (0.85,0.93)	1.83E-06	NA	NA	yes	1.96E-03
cg18666454	chr7:150651937	*KCNH2*	*KCNH2*	0.89 (0.86,0.93)	1.46E-07	yes	4.46E-01	yes	5.80E-04
cg02596233	chr7:150970209	*SMARCD3*	*SMARCD3*	0.86 (0.81,0.91)	2.11E-07	no	8.17E-01	yes	1.07E-01
cg23706836	chr8:6407997	*ANGPT2;MCPH1*	*ANGPT2*	0.92 (0.88,0.95)	5.63E-07	yes	2.98E-02	yes	3.03E-02
cg21919729	chr8:11719367	*CTSB*	*CTSB*	0.92 (0.89,0.95)	3.03E-06	yes	1.76E-01	yes	1.05E-01
cg03437605	chr8:22847209	*RHOBTB2*	*RHOBTB2*	0.87 (0.83,0.92)	1.05E-07	yes	4.00E-01	yes	5.92E-02
cg22816343	chr8:26243601	*BNIP3L*	*BNIP3L*	0.89 (0.85,0.93)	2.12E-06	no	8.60E-01	yes	1.59E-05
cg23205629	chr8:33421410	*RNF122*	*RNF122*	0.91 (0.88,0.95)	9.28E-06	yes	1.29E-01	yes	5.57E-01
cg10815420	chr8:105599835	*LRP12*	*LRP12*	0.86 (0.81,0.91)	2.66E-07	yes	2.98E-01	yes	2.51E-01
cg02133716	chr8:128981622	*PVT1*	*MIR1205*	0.85 (0.79,0.91)	8.64E-07	yes	3.91E-01	yes	3.47E-04
cg00736681	chr8:134546052	*ST3GAL1*	*ST3GAL1*	0.90 (0.87,0.94)	1.93E-06	yes	6.89E-01	yes	8.95E-01
cg09377531	chr8:141046469	*TRAPPC9*	*AX748239*	0.90 (0.87,0.93)	1.23E-08	yes	1.87E-01	yes	3.13E-05
cg14025883	chr9:5436224	*C9orf46*	*C9orf46*	0.89 (0.85,0.93)	8.42E-07	yes	5.90E-02	yes	5.17E-05
cg01499988	chr9:35755346	*MSMP*	*MSMP*	0.88 (0.84,0.93)	2.01E-06	yes	1.05E-01	yes	4.30E-03
cg13482814	chr9:82183332		*TLE4*	0.88 (0.84,0.93)	4.74E-06	yes	4.99E-01	yes	2.25E-04
cg13576859	chr9:97403129	*FBP1*	*FBP1*	0.92 (0.88,0.95)	1.37E-05	no	8.87E-01	yes	2.39E-03
cg20503329	chr9:101705792	*COL15A1*	*COL15A1*	0.82 (0.76,0.89)	3.10E-06	yes	3.35E-01	yes	1.70E-01
cg00045753	chr9:123630545	*PHF19*	*PHF19*	0.88 (0.83,0.93)	1.32E-05	yes	4.29E-01	yes	1.52E-01
cg13458609	chr9:130608923	*ENG*	*ENG*	0.89 (0.85,0.93)	5.74E-08	yes	3.81E-01	yes	5.87E-05
cg13835688	chr9:130859454	*SLC25A25*	*SLC25A25*	0.89 (0.86,0.93)	3.33E-09	yes	1.90E-02	yes	9.77E-04
cg13628444	chr9:134883788	*MED27*	*MED27*	0.89 (0.85,0.93)	7.76E-07	yes	3.70E-03	yes	3.48E-02
cg13850063	chr9:138362321		*AK096249*	0.78 (0.71,0.85)	5.49E-08	yes	8.89E-01	yes	7.10E-01
cg14011077	chr9:138362327		*AK096249*	0.86 (0.82,0.90)	7.02E-09	yes	9.10E-01	yes	4.25E-01
cg06958964	chr10:45494806	*C10orf25;ZNF22*	*ZNF22*	0.85 (0.80,0.91)	2.97E-06	no	3.07E-01	yes	2.79E-02
cg25854298	chr10:73936754	*ASCC1*	*ASCC1*	0.89 (0.84,0.94)	8.74E-06	yes	1.18E-01	yes	1.91E-03
cg04973995	chr10:74057977		*DDIT4*	0.92 (0.89,0.96)	1.10E-05	yes	5.68E-01	yes	8.10E-01
cg00366037	chr10:76781121	*MYST4*	*KAT6B*	0.88 (0.83,0.93)	1.45E-05	yes	2.11E-01	yes	7.89E-03
cg22235258	chr11:34675402	*EHF*	*EHF*	0.88 (0.83,0.93)	1.61E-05	yes	2.27E-01	yes	1.08E-03
cg24459209	chr11:57148215	*PRG3*	*PRG3*	0.86 (0.81,0.91)	8.52E-08	yes	5.07E-02	yes	9.52E-03
cg15700636	chr11:57156050	*PRG2*	*PRG2*	0.89 (0.85,0.93)	2.35E-07	no	8.75E-01	yes	1.59E-02
cg08773180	chr11:57157607	*PRG2*	*PRG2*	0.89 (0.85,0.93)	1.77E-07	no	5.88E-01	yes	1.99E-04
cg12819873	chr11:57157632	*PRG2*	*PRG2*	0.90 (0.86,0.94)	9.55E-06	yes	1.69E-01	yes	8.70E-03
cg27533472	chr11:59856225	*MS4A2*	*MS4A2*	0.82 (0.76,0.90)	4.09E-06	yes	3.44E-01	yes	4.65E-01
cg25087851	chr11:60623918	*GPR44*	*PTGDR2*	0.89 (0.85,0.93)	1.69E-08	yes	1.80E-01	yes	4.03E-02
cg13233042	chr11:63432489	*ATL3*	*ATL3*	0.88 (0.83,0.93)	3.59E-06	no	4.50E-01	yes	1.82E-03
cg05300717	chr11:65546210	*DKFZp761E198*	*DKFZp761E198*	0.86 (0.82,0.90)	6.51E-10	yes	4.86E-01	yes	1.41E-03
cg15219163	chr11:70842128	*SHANK2*	*SHANK2*	1.17 (1.09,1.26)	1.80E-05	yes	4.61E-01	no	3.35E-01

cg24368962	chr11:111570978	*SIK2*	*DQ599327*	0.85 (0.80,0.91)	1.28E-06	no	7.04E-01	yes	3.32E-04
cg19434937	chr12:7104184	*LPCAT3*	*EMG1*	0.91 (0.88,0.95)	1.55E-06	yes	3.37E-01	yes	1.82E-02
cg03014680	chr12:10122522	*CLEC12A*	*CLEC12A*	0.92 (0.88,0.95)	2.14E-06	yes	3.27E-01	yes	2.36E-01
cg09447105	chr12:15126020	*PDE6H*	*PDE6H*	0.88 (0.83,0.92)	7.60E-07	yes	1.90E-04	yes	6.53E-02
cg24028828	chr12:56694932	*CS*	*CS*	0.87 (0.82,0.92)	1.99E-06	yes	6.15E-01	yes	2.71E-04
cg21498475	chr12:113737469	*SLC24A6*	*SLC24A6*	0.90 (0.86,0.94)	5.44E-06	yes	2.79E-01	yes	2.43E-03
cg10065736	chr12:117440120	*FBXW8*	*AK055849*	0.90 (0.87,0.94)	1.41E-07	yes	8.32E-01	yes	4.36E-01
cg03131767	chr12:123446272	*ABCB9*	*ABCB9*	0.89 (0.85,0.93)	7.21E-07	yes	6.36E-01	no	8.41E-02
cg19928703	chr13:30143971	*SLC7A1*	*SLC7A1*	0.89 (0.84,0.94)	1.21E-05	yes	2.32E-01	yes	3.45E-03
cg07908654	chr13:41631052		*TRNA_Glu*	0.89 (0.85,0.93)	2.60E-07	yes	1.68E-01	yes	1.89E-04
cg24818699	chr13:43355514	*C13orf30*	*C13orf30*	0.87 (0.82,0.93)	8.53E-06	no	1.94E-01	yes	2.73E-02
cg08770358	chr13:48876684	*RB1*	*BC039553*	0.84 (0.78,0.91)	1.42E-05	yes	3.50E-01	yes	8.73E-04
cg00222125	chr13:53226144	*SUGT1*	*SUGT1*	0.90 (0.86,0.95)	1.43E-05	yes	9.45E-01	yes	2.95E-01
cg11770323	chr13:80066032	*NDFIP2*	*NDFIP2*	0.91 (0.87,0.95)	5.86E-06	yes	1.80E-01	yes	1.85E-04
cg25479097	chr13:113305704	*C13orf35*	*C13orf35*	0.89 (0.84,0.93)	9.11E-07	no	4.89E-01	yes	1.07E-02
cg18368116	chr14:21436271		*RNASE2*	0.89 (0.84,0.93)	4.93E-06	yes	2.16E-01	yes	6.19E-03
cg08077807	chr14:62001072	*PRKCH*	*PRKCH*	0.85 (0.80,0.90)	1.29E-07	no	9.48E-01	yes	5.21E-04
cg04933530	chr14:77419754		*IRF2BPL*	0.89 (0.85,0.93)	1.02E-07	yes	3.88E-01	yes	8.35E-04
cg01901579	chr14:95615731	*DICER1*	*DICER1*	0.91 (0.88,0.95)	5.86E-06	yes	7.73E-04	yes	2.91E-01
cg16409452	chr14:100610186	*EVL*	*AX747103*	0.91 (0.87,0.94)	4.89E-07	yes	3.79E-01	yes	5.53E-03
cg14084609	chr14:100610407	*EVL*	*AX747103*	0.89 (0.85,0.92)	2.96E-09	yes	1.97E-01	yes	6.81E-01
cg18550847	chr14:100610570	*EVL*	*AX747103*	0.91 (0.88,0.94)	7.10E-07	no	1.00E+00	yes	2.36E-02
cg01000631	chr14:100610667		*EVL*	0.91 (0.87,0.94)	4.88E-08	yes	7.95E-01	yes	2.70E-02
cg05875066	chr14:104625249	*KIF26A*	*KIF26A*	0.87 (0.83,0.92)	1.77E-07	yes	8.03E-01	yes	1.48E-02
cg18817654	chr15:39485138		*C15orf54*	0.87 (0.82,0.92)	3.41E-06	yes	5.33E-01	no	9.20E-01
cg25939647	chr15:40173065	*GPR176*	*GPR176*	0.91 (0.88,0.95)	1.91E-06	yes	2.61E-01	yes	2.18E-03
cg07177867	chr15:52030746	*LYSMD2*	*LYSMD2*	0.90 (0.86,0.94)	1.29E-05	yes	3.19E-03	yes	3.93E-02
cg11266582	chr15:64275853	*DAPK2*	*DAPK2*	0.89 (0.85,0.94)	1.52E-05	no	5.22E-01	yes	1.57E-03
cg10387956	chr15:72646210	*HEXA*	*BC034424*	0.91 (0.87,0.95)	2.72E-06	no	6.56E-01	yes	1.64E-03
cg23387863	chr15:77472416	*SGK269*	*AX747193*	0.91 (0.87,0.94)	1.51E-06	yes	6.99E-01	yes	4.93E-03
cg04497992	chr16:616212	*NHLRC4*	*C16orf11*	0.90 (0.87,0.94)	1.92E-06	yes	7.99E-01	yes	1.20E-01
cg08067346	chr16:25011481	*ARHGAP17*	*DQ583809*	0.90 (0.86,0.95)	1.60E-05	yes	8.15E-02	yes	1.26E-02
cg26134665	chr16:31021544	*STX1B*	*STX1B*	0.92 (0.88,0.95)	9.50E-06	yes	9.09E-01	yes	8.09E-01
cg09147843	chr16:53467612	*RBL2*	*RBL2*	0.89 (0.85,0.94)	8.89E-06	yes	1.52E-01	yes	1.26E-03
cg01998785	chr16:55542709	*LPCAT2*	*LPCAT2*	0.91 (0.87,0.94)	6.17E-07	yes	6.47E-01	yes	3.60E-03
cg27383865	chr16:84075870	*SLC38A8*	*SLC38A8*	1.11 (1.06,1.16)	1.73E-05	yes	7.77E-01	yes	5.82E-01
cg08640475	chr16:85551478		*KIAA0182*	0.92 (0.89,0.95)	2.36E-06	yes	9.26E-02	yes	1.20E-04
cg10099827	chr16:85551514		*KIAA0182*	0.92 (0.89,0.95)	1.32E-06	yes	4.54E-02	yes	3.95E-04
cg08940169	chr16:88540241	*ZFPM1*	*ZFPM1*	0.91 (0.87,0.94)	2.93E-07	yes	6.88E-02	yes	2.18E-05
cg04983687	chr16:88558223	*ZFPM1*	*ZFPM1*	0.93 (0.90,0.95)	1.33E-10	yes	1.82E-02	yes	5.27E-10

cg20315954	chr17:15137304	*PMP22*	*PMP22*	0.88 (0.84,0.93)	3.58E-06	no	9.09E-01	yes	1.95E-02
cg20885063	chr17:17939419	*ATPAF2*	*ATPAF2*	0.90 (0.86,0.94)	1.06E-06	yes	1.68E-01	yes	9.97E-03
cg14611258	chr17:17946468	*C17orf39*	*C17orf39*	0.89 (0.85,0.94)	6.41E-06	yes	2.75E-01	yes	1.74E-03
cg19468946	chr17:37922297	*IKZF3*	*IKZF3*	1.09 (1.05,1.13)	1.50E-05	yes	4.50E-01	no	5.77E-01
cg21723861	chr17:39686628		*KRT19*	0.87 (0.82,0.92)	1.59E-07	yes	4.81E-01	yes	1.26E-03
cg00170714	chr17:40724562	*MLX;PSMC3IP*	*PSMC3IP*	0.89 (0.85,0.93)	6.15E-08	no	5.98E-01	yes	5.88E-02
cg25173129	chr17:56269410	*EPX*	*EPX*	0.88 (0.84,0.93)	8.09E-07	yes	1.92E-01	yes	1.50E-01
cg02970679	chr17:56269818	*EPX*	*EPX*	0.88 (0.83,0.92)	9.99E-07	no	5.25E-01	yes	1.74E-03
cg17374802	chr17:56270828	*EPX*	*EPX*	0.90 (0.86,0.94)	2.06E-06	no	5.64E-01	yes	3.47E-02
cg17041511	chr17:61509620		*CYB561*	0.91 (0.87,0.95)	1.15E-05	yes	3.47E-02	yes	3.39E-02
cg22312249	chr17:72779428	*TMEM104*	*TMEM104*	0.91 (0.87,0.95)	8.73E-06	yes	6.60E-01	yes	1.90E-03
cg09705784	chr17:76565232	*DNAH17*	*DNAH17*	0.91 (0.88,0.94)	1.50E-07	yes	6.05E-02	yes	3.80E-03
cg06725287	chr17:80533762	*FOXK2*	*FOXK2*	0.87 (0.83,0.92)	9.07E-08	no	3.20E-01	yes	1.26E-05
cg13054523	chr17:81055722		*METRNL*	0.87 (0.83,0.91)	1.20E-08	yes	3.92E-01	yes	4.40E-01
cg18337287	chr19:930871	*ARID3A*	*ARID3A*	0.86 (0.81,0.91)	7.21E-08	yes	6.02E-01	yes	8.52E-05
cg12104982	chr19:5592815	*SAFB2*	*SAFB2*	0.86 (0.81,0.91)	1.13E-07	yes	1.59E-02	yes	1.49E-04
cg10644885	chr19:11687621	*ACP5*	*ACP5*	0.86 (0.82,0.90)	5.77E-11	yes	2.35E-01	yes	2.03E-03
cg02359181	chr19:34860339	*GPI*	*GPI*	0.88 (0.83,0.93)	2.68E-06	yes	8.27E-01	yes	5.69E-04
cg20673965	chr19:44220148	*IRGC*	*IRGC*	0.90 (0.85,0.94)	5.54E-06	yes	9.59E-01	yes	3.27E-02
cg26979537	chr19:48016860	*NAPA*	*NAPA*	0.83 (0.77,0.90)	1.31E-06	yes	3.68E-01	yes	2.13E-01
cg21073212	chr20:30866501	*KIF3B*	*KIF3B*	0.92 (0.89,0.96)	1.79E-05	no	7.85E-02	yes	4.58E-01
cg20226253	chr20:34022914	*GDF5*	*GDF5OS*	0.87 (0.81,0.92)	1.15E-05	yes	8.43E-01	yes	2.12E-01
cg21045547	chr20:35422703	*C20orf117*	*KIAA0889*	0.89 (0.85,0.94)	5.32E-06	no	9.41E-02	yes	4.39E-02
cg13792581	chr20:43590115	*TOMM34*	*TOMM34*	0.87 (0.82,0.93)	1.34E-05	yes	3.61E-01	yes	3.10E-04
cg13197551	chr20:60709957	*LSM14B*	*LSM14B*	0.86 (0.81,0.91)	9.23E-07	yes	5.26E-01	yes	1.21E-01
cg18042632	chr21:42520902	*C21orf130*	*LINC00323*	0.92 (0.88,0.95)	1.87E-06	no	9.54E-01	yes	5.57E-03
cg18879389	chr21:43771120	*TFF2*	*TFF2*	0.87 (0.82,0.92)	1.21E-06	yes	2.08E-01	yes	1.03E-01

* Annotation based on UCSC Known Gene also fills in nearest gene within 10 MB.

Table E7 *Lookup of 179 CpGs differentially methylated in blood in childhood relation to asthma, in an independent study of methylation in purified eosinophils (Eos) in relation to asthma.*

CpG	chr:position	UCSC RefGene Name	UCSC Known Gene*	PACE Discovery (N=647 cases)		Look-Up in Eos (N= 16 cases)	
				OR (CI)	P-value	Direction of Effect Concordant with PACE	P-value
cg06315149	chr1:2036398	*PRKCZ*	*PRKCZ*	0.89 (0.84,0.93)	6.08E-06	yes	2.43E-02
cg13066938	chr1:6341140	*ACOT7*	*ACOT7*	0.91 (0.88,0.95)	1.67E-05	yes	2.36E-02
cg21220721	chr1:6341230	*ACOT7*	*ACOT7*	0.94 (0.92,0.96)	1.02E-08	yes	1.80E-02
cg09249800	chr1:6341287	*ACOT7*	*ACOT7*	0.88 (0.84,0.92)	1.19E-08	yes	3.52E-02
cg11699125	chr1:6341327	*ACOT7*	*ACOT7*	0.90 (0.87,0.93)	7.54E-10	yes	4.74E-02
cg18783781	chr1:9599067	*SLC25A33*	*SLC25A33*	0.90 (0.86,0.94)	7.45E-06	yes	4.16E-02
cg02171825	chr1:26517586	*CATSPER4*	*CATSPER4*	0.88 (0.83,0.93)	9.01E-06	yes	2.31E-02
cg01942646	chr1:27240694	*NR0B2*	*NR0B2*	0.88 (0.83,0.93)	1.45E-06	yes	3.78E-02
cg16263722	chr1:29523841	*MECR*	*MECR*	0.89 (0.86,0.93)	2.14E-07	yes	3.24E-02
cg11987455	chr1:43290834	*ERMAP*	*ERMAP*	0.89 (0.85,0.93)	7.55E-07	yes	3.90E-02
cg11683482	chr1:44678623	*DMAP1*	*DMAP1*	0.90 (0.86,0.93)	5.39E-08	yes	3.32E-02
cg12643917	chr1:44715958	*ERI3*	*ERI3*	0.89 (0.85,0.94)	8.98E-06	yes	1.67E-02
cg26252077	chr1:61607055	*NFIA*	*NFIA*	0.88 (0.84,0.92)	2.18E-08	yes	3.82E-02
cg10704177	chr1:62209607	*INADL*	*INADL*	0.90 (0.87,0.94)	2.25E-07	yes	3.63E-02
cg01445399	chr1:87596934	*LOC339524*	*LOC339524*	0.91 (0.87,0.95)	1.72E-05	yes	3.23E-02
cg19805160	chr1:159870731	*CCDC19*	*CCDC19*	0.89 (0.85,0.94)	2.85E-06	yes	2.76E-02
cg09332506	chr1:160309220	*COPA*	*NCSTN*	0.86 (0.81,0.91)	1.00E-06	yes	2.66E-02
cg17971251	chr1:177907297	*SEC16B*	*SEC16B*	0.86 (0.82,0.91)	9.52E-09	yes	3.41E-02
cg26033504	chr1:201458737	*CSRP1*	*CSRP1*	0.91 (0.87,0.95)	6.35E-06	yes	5.95E-02
cg04895895	chr1:231005895	*C1orf198*	*C1orf198*	0.89 (0.84,0.93)	5.26E-06	yes	4.08E-02
cg02473287	chr2:9752386	*YWHAQ*	*YWHAQ*	0.90 (0.85,0.94)	8.00E-06	yes	3.18E-02
cg10142874	chr2:11917623	*LPIN1*	*LPIN1*	0.89 (0.85,0.93)	1.04E-06	yes	3.75E-02
cg26752663	chr2:25142016	*ADCY3*	*ADCY3*	1.12 (1.07,1.17)	1.79E-06	yes	3.75E-01
cg00043800	chr2:74612144	*LOC100189589*	*LOC100189589*	0.91 (0.87,0.95)	1.32E-05	yes	5.14E-02
cg17988187	chr2:74612222	*LOC100189589*	*LOC100189589*	0.90 (0.86,0.94)	1.21E-06	yes	2.62E-02
cg12077754	chr2:75089669	*HK2*	*HK2*	0.92 (0.89,0.96)	4.56E-06	yes	3.41E-02
cg22674082	chr2:98585733	*TMEM131*	*TMEM131*	0.89 (0.84,0.94)	1.44E-05	yes	2.99E-02
cg00327263	chr2:120019111	*STEAP3*	*STEAP3*	0.90 (0.86,0.94)	8.00E-06	yes	9.15E-02
cg25950520	chr2:121036760	*RALB*	*RALB*	0.85 (0.79,0.91)	1.31E-05	yes	5.60E-02
cg00213281	chr2:149639822	*KIF5C;MIR1978*	*JA429504*	0.88 (0.83,0.93)	1.24E-06	yes	2.29E-02
cg02494549	chr2:161798364		*TANK*	0.86 (0.82,0.91)	1.56E-07	yes	5.16E-02
cg01310029	chr3:3152374	*IL5RA*	*IL5RA*	0.89 (0.85,0.94)	4.18E-06	yes	3.68E-02
cg10159529	chr3:3152530	*IL5RA*	*IL5RA*	0.90 (0.86,0.94)	4.48E-06	yes	3.12E-02
cg25224369	chr3:12918528		*DQ581328*	0.90 (0.86,0.94)	7.75E-06	yes	4.65E-02
cg07386061	chr3:52492874	*NISCH*	*NISCH*	0.91 (0.88,0.95)	1.00E-06	yes	3.81E-02
cg17890764	chr3:52864816	*ITIH4*	*ITIH4*	0.91 (0.87,0.94)	8.95E-07	yes	9.14E-02
cg07410597	chr3:66404129	*SLC25A26*	*LRIG1*	0.88 (0.84,0.93)	2.70E-07	yes	3.02E-02
cg04217850	chr3:66428294	*SLC25A26*	*LRIG1*	0.88 (0.83,0.93)	2.35E-06	yes	4.53E-02
cg06070625	chr3:69812798	*MITF*	*MITF*	0.90 (0.86,0.94)	5.36E-06	yes	2.97E-02
cg06391412	chr3:71295684	*FOXP1*	*FOXP1*	0.87 (0.84,0.91)	3.00E-09	yes	2.70E-02
cg20263733	chr3:130616293	*ATP2C1*	*ATP2C1*	0.87 (0.82,0.92)	4.26E-07	yes	5.11E-02
cg09423651	chr3:136618442	*NCK1*	*NCK1*	0.88 (0.83,0.93)	9.72E-06	yes	3.98E-02
cg08698681	chr3:171091657	*TNIK*	*TNIK*	0.89 (0.84,0.93)	5.52E-06	yes	2.04E-02
cg25636075	chr3:185217761	*TMEM41A*	*TMEM41A*	0.87 (0.81,0.92)	5.59E-06	yes	2.23E-02
cg02803925	chr3:195974300	*PCYT1A*	*PCYT1A*	0.86 (0.82,0.92)	9.27E-07	yes	3.86E-02
cg04077085	chr4:9937674	*SLC2A9*	*SLC2A9*	0.86 (0.81,0.91)	5.34E-07	yes	3.42E-02
cg18912470	chr4:57848125	*POLR2B*	*POLR2B*	0.91 (0.87,0.94)	1.23E-06	yes	3.57E-02
cg26396815	chr4:102878132	*BANK1*	*BANK1*	0.89 (0.84,0.94)	1.24E-05	yes	3.87E-02
cg20866785	chr4:148733880	*ARHGAP10*	*Metazoa_SRP*	0.91 (0.87,0.95)	1.70E-05	yes	6.39E-02
cg16362140	chr5:10708717	*DAP*	*DAP*	0.90 (0.87,0.94)	1.17E-06	yes	3.66E-02
cg22588983	chr5:38783142		*AK126213*	0.86 (0.80,0.92)	1.35E-05	yes	4.05E-02
cg00944309	chr5:60142446		*ELOVL7*	0.90 (0.86,0.94)	4.03E-07	yes	4.96E-02
cg14978242	chr5:79501131	*SERINC5*	*SERINC5*	0.93 (0.89,0.96)	1.74E-05	yes	2.47E-02
cg09565310	chr5:112541553	*MCC*	*MCC*	0.89 (0.85,0.93)	3.10E-06	yes	3.03E-02
cg08969102	chr5:133563532		*PPP2CA*	0.91 (0.88,0.95)	1.54E-05	yes	3.31E-02
cg21627181	chr6:25754190	*SLC17A4*	*SLC17A4*	0.90 (0.86,0.95)	1.90E-05	yes	3.21E-02
cg09597192	chr6:32141591	*AGPAT1*	*PPT2*	0.88 (0.84,0.93)	4.29E-06	yes	1.99E-02
cg06426027	chr6:33232644	*VPS52*	*VPS52*	0.83 (0.77,0.90)	2.32E-06	yes	1.87E-02
cg18460809	chr6:57048049	*BAG2*	*BAG2*	0.89 (0.85,0.93)	6.05E-07	yes	3.41E-02
cg15961693	chr6:139689053		*CITED2*	0.89 (0.84,0.94)	1.22E-05	yes	3.02E-02
cg26774971	chr6:158994407	*TMEM181*	*TMEM181*	0.90 (0.86,0.95)	1.88E-05	yes	3.08E-02
cg05477517	chr6:164531576		*AK093114*	0.88 (0.83,0.92)	5.42E-07	yes	4.58E-02
cg15304012	chr6:166876490	*RPS6KA2*	*RPS6KA2*	1.08 (1.04,1.13)	1.86E-05	yes	2.13E-01
cg19851574	chr6:167178233	*RPS6KA2*	*RPS6KA2*	0.95 (0.94,0.97)	3.42E-06	yes	3.76E-02
cg03329755	chr6:167189272	*RPS6KA2*	*RPS6KA2*	0.91 (0.88,0.95)	6.14E-06	yes	3.04E-02
cg25270424	chr7:24965657	*OSBPL3*	*OSBPL3*	0.86 (0.82,0.92)	4.75E-07	yes	4.69E-02
cg04321303	chr7:44107504		*PGAM2*	0.91 (0.88,0.95)	2.72E-06	yes	3.02E-02
cg02435538	chr7:75507337	*RHBDD2*	*RHBDD2*	0.90 (0.86,0.94)	7.37E-07	yes	6.15E-02

cg13007207	chr7:105279391	*ATXN7L1*	*ATXN7L1*	1.26 (1.13,1.40)	1.87E-05	yes	6.20E-01
cg17947765	chr7:117857964		*ANKRD7*	0.86 (0.81,0.92)	1.17E-05	yes	1.41E-01
cg14678084	chr7:127627251	*SND1*	*SND1-IT1*	0.84 (0.78,0.90)	1.17E-06	yes	1.57E-02
cg05184016	chr7:149543136	*ZNF862*	*BC045757*	0.85 (0.80,0.90)	2.74E-08	yes	4.56E-02
cg07970948	chr7:149543165	*ZNF862*	*BC045757*	0.91 (0.88,0.94)	6.39E-08	yes	3.05E-02
cg06558622	chr7:149543177	*ZNF862*	*BC045757*	0.88 (0.85,0.92)	3.39E-09	yes	4.61E-02
cg24576940	chr7:150648283	*KCNH2*	*KCNH2*	0.87 (0.81,0.93)	1.83E-05	yes	3.44E-02
cg23147443	chr7:150649655	*KCNH2*	*KCNH2*	0.89 (0.85,0.93)	1.83E-06	yes	2.39E-02
cg18666454	chr7:150651937	*KCNH2*	*KCNH2*	0.89 (0.86,0.93)	1.46E-07	yes	2.53E-02
cg02596233	chr7:150970209	*SMARCD3*	*SMARCD3*	0.86 (0.81,0.91)	2.11E-07	yes	2.55E-02
cg23706836	chr8:6407997	*ANGPT2;MCPH1*	*ANGPT2*	0.92 (0.88,0.95)	5.63E-07	yes	3.33E-02
cg21919729	chr8:11719367	*CTSB*	*CTSB*	0.92 (0.89,0.95)	3.03E-06	yes	4.45E-02
cg03437605	chr8:22847209	*RHOBTB2*	*RHOBTB2*	0.87 (0.83,0.92)	1.05E-07	yes	6.06E-02
cg22816343	chr8:26243601	*BNIP3L*	*BNIP3L*	0.89 (0.85,0.93)	2.12E-06	yes	5.31E-02
cg23205629	chr8:33421410	*RNF122*	*RNF122*	0.91 (0.88,0.95)	9.28E-06	yes	4.96E-02
cg10815420	chr8:105599835	*LRP12*	*LRP12*	0.86 (0.81,0.91)	2.66E-07	yes	9.38E-02
cg02133716	chr8:128981622	*PVT1*	*MIR1205*	0.85 (0.79,0.91)	8.64E-07	yes	2.62E-02
cg00736681	chr8:134546052	*ST3GAL1*	*ST3GAL1*	0.90 (0.87,0.94)	1.93E-06	yes	2.41E-02
cg09377531	chr8:141046469	*TRAPPC9*	*AX748239*	0.90 (0.87,0.93)	1.23E-08	yes	4.19E-02
cg14025883	chr9:5436224	*C9orf46*	*C9orf46*	0.89 (0.85,0.93)	8.42E-07	yes	2.96E-02
cg01499988	chr9:35755346	*MSMP*	*MSMP*	0.88 (0.84,0.93)	2.01E-06	yes	3.59E-02
cg13482814	chr9:82183332		*TLE4*	0.88 (0.84,0.93)	4.74E-06	yes	2.99E-02
cg13576859	chr9:97403129	*FBP1*	*FBP1*	0.92 (0.88,0.95)	1.37E-05	yes	2.46E-02
cg20503329	chr9:101705792	*COL15A1*	*COL15A1*	0.82 (0.76,0.89)	3.10E-06	yes	2.35E-02
cg00045753	chr9:123630545	*PHF19*	*PHF19*	0.88 (0.83,0.93)	1.32E-05	yes	3.10E-02
cg13458609	chr9:130608923	*ENG*	*ENG*	0.89 (0.85,0.93)	5.74E-08	yes	4.21E-02
cg13835688	chr9:130859454	*SLC25A25*	*SLC25A25*	0.89 (0.86,0.93)	3.33E-09	yes	2.66E-02
cg13628444	chr9:134883788	*MED27*	*MED27*	0.89 (0.85,0.93)	7.76E-07	yes	3.53E-02
cg13850063	chr9:138362321		*AK096249*	0.78 (0.71,0.85)	5.49E-08	yes	3.02E-02
cg14011077	chr9:138362327		*AK096249*	0.86 (0.82,0.90)	7.02E-09	yes	3.48E-02
cg06958964	chr10:45494806	*C10orf25;ZNF22*	*ZNF22*	0.85 (0.80,0.91)	2.97E-06	yes	4.05E-02
cg25854298	chr10:73936754	*ASCC1*	*ASCC1*	0.89 (0.84,0.94)	8.74E-06	yes	2.58E-02
cg04973995	chr10:74057977		*DDIT4*	0.92 (0.89,0.96)	1.10E-05	yes	4.83E-01
cg00366037	chr10:76781121	*MYST4*	*KAT6B*	0.88 (0.83,0.93)	1.45E-05	yes	4.11E-02
cg22235258	chr11:34675402	*EHF*	*EHF*	0.88 (0.83,0.93)	1.61E-05	yes	4.94E-02
cg24459209	chr11:57148215	*PRG3*	*PRG3*	0.86 (0.81,0.91)	8.52E-08	yes	2.74E-02
cg15700636	chr11:57156050	*PRG2*	*PRG2*	0.89 (0.85,0.93)	2.35E-07	yes	3.13E-02
cg08773180	chr11:57157607	*PRG2*	*PRG2*	0.89 (0.85,0.93)	1.77E-07	yes	2.40E-02
cg12819873	chr11:57157632	*PRG2*	*PRG2*	0.90 (0.86,0.94)	9.55E-06	yes	4.33E-02
cg27533472	chr11:59856225	*MS4A2*	*MS4A2*	0.82 (0.76,0.90)	4.09E-06	yes	2.21E-02
cg25087851	chr11:60623918	*GPR44*	*PTGDR2*	0.89 (0.85,0.93)	1.69E-08	yes	3.14E-02
cg13233042	chr11:63432489	*ATL3*	*ATL3*	0.88 (0.83,0.93)	3.59E-06	yes	4.19E-02
cg05300717	chr11:65546210	*DKFZp761E198*	*DKFZp761E198*	0.86 (0.82,0.90)	6.51E-10	yes	1.25E-02
cg15219163	chr11:70842128	*SHANK2*	*SHANK2*	1.17 (1.09,1.26)	1.80E-05	no	1.09E-01
cg24368962	chr11:111570978	*SIK2*	*DQ599327*	0.85 (0.80,0.91)	1.28E-06	yes	3.42E-02
cg19434937	chr12:7104184	*LPCAT3*	*EMG1*	0.91 (0.88,0.95)	1.55E-06	yes	3.88E-02
cg03014680	chr12:10122522	*CLEC12A*	*CLEC12A*	0.92 (0.88,0.95)	2.14E-06	yes	4.57E-02
cg09447105	chr12:15126020	*PDE6H*	*PDE6H*	0.88 (0.83,0.92)	7.60E-07	yes	2.92E-02
cg24028828	chr12:56694932	*CS*	*CS*	0.87 (0.82,0.92)	1.99E-06	yes	2.24E-02
cg21498475	chr12:113737469	*SLC24A6*	*SLC24A6*	0.90 (0.86,0.94)	5.44E-06	yes	2.10E-02
cg10065736	chr12:117440120	*FBXW8*	*AK055849*	0.90 (0.87,0.94)	1.41E-07	yes	1.71E-02
cg03131767	chr12:123446272	*ABCB9*	*ABCB9*	0.89 (0.85,0.93)	7.21E-07	yes	3.09E-02
cg19928703	chr13:30143971	*SLC7A1*	*SLC7A1*	0.89 (0.84,0.94)	1.21E-05	yes	2.82E-02
cg07908654	chr13:41631052		*TRNA_Glu*	0.89 (0.85,0.93)	2.60E-07	yes	4.01E-02
cg24818699	chr13:43355514	*C13orf30*	*C13orf30*	0.87 (0.82,0.93)	8.53E-06	yes	8.31E-02
cg08770358	chr13:48876684	*RB1*	*BC039553*	0.84 (0.78,0.91)	1.42E-05	yes	4.03E-02
cg00222125	chr13:53226144	*SUGT1*	*SUGT1*	0.90 (0.86,0.95)	1.43E-05	yes	9.65E-01
cg11770323	chr13:80066032	*NDFIP2*	*NDFIP2*	0.91 (0.87,0.95)	5.86E-06	yes	3.73E-02
cg25479097	chr13:113305704	*C13orf35*	*C13orf35*	0.89 (0.84,0.93)	9.11E-07	yes	2.49E-02
cg18368116	chr14:21436271		*RNASE2*	0.89 (0.84,0.93)	4.93E-06	yes	2.25E-02
cg08077807	chr14:62001072	*PRKCH*	*PRKCH*	0.85 (0.80,0.90)	1.29E-07	yes	4.37E-02
cg04933530	chr14:77419754		*IRF2BPL*	0.89 (0.85,0.93)	1.02E-07	yes	2.64E-02
cg01901579	chr14:95615731	*DICER1*	*DICER1*	0.91 (0.88,0.95)	5.86E-06	yes	3.61E-02
cg16409452	chr14:100610186	*EVL*	*AX747103*	0.91 (0.87,0.94)	4.89E-07	yes	2.12E-02
cg14084609	chr14:100610407	*EVL*	*AX747103*	0.89 (0.85,0.92)	2.96E-09	yes	3.24E-02
cg18550847	chr14:100610570	*EVL*	*AX747103*	0.91 (0.88,0.94)	7.10E-07	yes	2.85E-02
cg01000631	chr14:100610667		*EVL*	0.91 (0.87,0.94)	4.88E-08	yes	2.75E-02
cg05875066	chr14:104625249	*KIF26A*	*KIF26A*	0.87 (0.83,0.92)	1.77E-07	yes	5.64E-02
cg18817654	chr15:39485138		*C15orf54*	0.87 (0.82,0.92)	3.41E-06	yes	7.10E-02
cg25939647	chr15:40173065	*GPR176*	*GPR176*	0.91 (0.88,0.95)	1.91E-06	yes	2.83E-02
cg07177867	chr15:52030746	*LYSMD2*	*LYSMD2*	0.90 (0.86,0.94)	1.29E-05	yes	3.26E-02
cg11266582	chr15:64275853	*DAPK2*	*DAPK2*	0.89 (0.85,0.94)	1.52E-05	yes	2.56E-02
cg10387956	chr15:72646210	*HEXA*	*BC034424*	0.91 (0.87,0.95)	2.72E-06	yes	4.78E-02
cg23387863	chr15:77472416	*SGK269*	*AX747193*	0.91 (0.87,0.94)	1.51E-06	yes	5.29E-02
cg04497992	chr16:616212	*NHLRC4*	*C16orf11*	0.90 (0.87,0.94)	1.92E-06	yes	4.10E-02
cg08067346	chr16:25011481	*ARHGAP17*	*DQ583809*	0.90 (0.86,0.95)	1.60E-05	yes	2.70E-02

cg26134665	chr16:31021544	*STX1B*	*STX1B*	0.92 (0.88,0.95)	9.50E-06	yes	7.87E-01
cg09147843	chr16:53467612	*RBL2*	*RBL2*	0.89 (0.85,0.94)	8.89E-06	yes	5.72E-02
cg01998785	chr16:55542709	*LPCAT2*	*LPCAT2*	0.91 (0.87,0.94)	6.17E-07	yes	3.52E-02
cg27383865	chr16:84075870	*SLC38A8*	*SLC38A8*	1.11 (1.06,1.16)	1.73E-05	no	2.63E-01
cg08640475	chr16:85551478		*KIAA0182*	0.92 (0.89,0.95)	2.36E-06	yes	1.99E-01
cg10099827	chr16:85551514		*KIAA0182*	0.92 (0.89,0.95)	1.32E-06	yes	1.48E-01
cg08940169	chr16:88540241	*ZFPM1*	*ZFPM1*	0.91 (0.87,0.94)	2.93E-07	yes	3.33E-02
cg04983687	chr16:88558223	*ZFPM1*	*ZFPM1*	0.93 (0.90,0.95)	1.33E-10	yes	3.29E-02
cg20315954	chr17:15137304	*PMP22*	*PMP22*	0.88 (0.84,0.93)	3.58E-06	yes	1.89E-02
cg20885063	chr17:17939419	*ATPAF2*	*ATPAF2*	0.90 (0.86,0.94)	1.06E-06	yes	3.13E-02
cg14611258	chr17:17946468	*C17orf39*	*C17orf39*	0.89 (0.85,0.94)	6.41E-06	yes	3.89E-02
cg19468946	chr17:37922297	*IKZF3*	*IKZF3*	1.09 (1.05,1.13)	1.50E-05	yes	4.02E-01
cg21723861	chr17:39686628		*KRT19*	0.87 (0.82,0.92)	1.59E-07	yes	2.68E-02
cg00170714	chr17:40724562	*MLX;PSMC3IP*	*PSMC3IP*	0.89 (0.85,0.93)	6.15E-08	yes	3.55E-02
cg25173129	chr17:56269410	*EPX*	*EPX*	0.88 (0.84,0.93)	8.09E-07	yes	2.54E-02
cg02970679	chr17:56269818	*EPX*	*EPX*	0.88 (0.83,0.92)	9.99E-07	yes	2.37E-02
cg17374802	chr17:56270828	*EPX*	*EPX*	0.90 (0.86,0.94)	2.06E-06	yes	2.64E-02
cg17041511	chr17:61509620		*CYB561*	0.91 (0.87,0.95)	1.15E-05	yes	3.37E-02
cg22312249	chr17:72779428	*TMEM104*	*TMEM104*	0.91 (0.87,0.95)	8.73E-06	yes	3.19E-02
cg09705784	chr17:76565232	*DNAH17*	*DNAH17*	0.91 (0.88,0.94)	1.50E-07	yes	2.96E-02
cg06725287	chr17:80533762	*FOXK2*	*FOXK2*	0.87 (0.83,0.92)	9.07E-08	yes	5.71E-02
cg13054523	chr17:81055722		*METRNL*	0.87 (0.83,0.91)	1.20E-08	yes	2.07E-02
cg18337287	chr19:930871	*ARID3A*	*ARID3A*	0.86 (0.81,0.91)	7.21E-08	yes	3.51E-02
cg12104982	chr19:5592815	*SAFB2*	*SAFB2*	0.86 (0.81,0.91)	1.13E-07	yes	1.55E-02
cg10644885	chr19:11687621	*ACP5*	*ACP5*	0.86 (0.82,0.90)	5.77E-11	yes	1.85E-02
cg02359181	chr19:34860339	*GPI*	*GPI*	0.88 (0.83,0.93)	2.68E-06	yes	3.91E-02
cg20673965	chr19:44220148	*IRGC*	*IRGC*	0.90 (0.85,0.94)	5.54E-06	yes	3.81E-02
cg26979537	chr19:48016860	*NAPA*	*NAPA*	0.83 (0.77,0.90)	1.31E-06	yes	3.93E-02
cg21073212	chr20:30866501	*KIF3B*	*KIF3B*	0.92 (0.89,0.96)	1.79E-05	yes	2.48E-02
cg20226253	chr20:34022914	*GDF5*	*GDF5OS*	0.87 (0.81,0.92)	1.15E-05	yes	4.10E-02
cg21045547	chr20:35422703	*C20orf117*	*KIAA0889*	0.89 (0.85,0.94)	5.32E-06	yes	2.86E-02
cg13792581	chr20:43590115	*TOMM34*	*TOMM34*	0.87 (0.82,0.93)	1.34E-05	yes	2.74E-02
cg13197551	chr20:60709957	*LSM14B*	*LSM14B*	0.86 (0.81,0.91)	9.23E-07	yes	2.25E-02
cg18042632	chr21:42520902	*C21orf130*	*LINC00323*	0.92 (0.88,0.95)	1.87E-06	yes	1.91E-02
cg18879389	chr21:43771120	*TFF2*	*TFF2*	0.87 (0.82,0.92)	1.21E-06	yes	1.57E-01

Table E8 *Association of methylation with gene expression in different datasets: (A) CpGs differentially methylated in newborns in relation to asthma; (B) Regions differentially methylated (DMRs) in newborns in relation to asthma development; (C) CpGs differentially methylated in childhood in relation to asthma; (D) Regions differentially methylated (DMRs) in older children in relation to school aged asthma.*

(A)

List of CpGs*	chr:pos	UCSC RefGene Name	UCSC Known Gene**	Significant*** (Y) association with gene expression in						N datasets showing association (max 6)
				GEO (N=38) cord blood	IoW (N=157) cord blood	INMA (N=113) cord blood	INMA (N=112) 4-year-olds	BAMSE (N=248) 16-year-olds	BIOS (N=3,096) adults	
cg13427149	chr1:217804379	*GPATCH2;SPATA17*	*GPATCH2*	N	N	N	N	Y	Y	2
cg17333211	chr4:141294016	*SCOC*	*LOC100129858*	N	Y	N	N	N	Y	2
cg13289553	chr5:32585524	*SUB1*	*SUB1*	N	N	Y	Y	N	N	2
cg02331902	chr5:90610303		*AK091866*	Y	N	Y	N	N	Y	3
ch.6.1218502R	chr6:51250028			N	NA	NA	NA	NA	N	0
cg21486411	chr11:77348243	*CLNS1A*	*CLNS1A*	N	NA	Y	Y	N	N	2
cg16792002	chr11:95788886	*MAML2*	*Mir_548*	N	N	N	N	N	N	0
ch.11.109687686R	chr11:110182476			N	NA	NA	NA	NA	N	0
cg07156990	chr14:102685678	*WDR20*	*WDR20*	Y	Y	N	Y	N	N	3
CpGs associated with gene expression in at least one of the datasets.										6

* ch probes (ch.11.109687686R and ch.6.1218502R) have been reported to be cross hybridizing and thus UCSC Known Gene is intentionally left blank.

** UCSC Known Gene fills in nearest genes for those missing gene annotation in the UCSC RefGene Name column.

*** P-value < 0.05 in the smaller GEO, IoW, INMA and BAMSE datasets and FDR < 0.05 in the larger BIOS dataset.

(B)

DMR chr:pos	Gene Name	Significant* (Y) correlation with gene expression in						N datasets showing association (max 5)
		GEO (N=38) cord blood	IoW (N=157) cord blood	INMA (N=113) cord blood	INMA (N=112) 4-year-olds	BAMSE (N=248) 16-year-olds	BIOS (3,096) adults	
chr1:1296093-1296489	*MXRA8*	Y	NA	Y	Y	N	Y	4
chr1:59280290-59280842	*LINC01135*	N	NA	Y	Y	Y	Y	4
chr1:220263017-220263699	*BPNT1;RNU5F-1*	Y	NA	Y	Y	N	Y	4
chr2:202097062-202097608	*CASP8*	N	NA	N	Y	Y	Y	3
chr2:235004843-235005012	*SPP2*	Y	NA	NA	NA	N	N	1
chr3:194188646-194189444	*ATP13A3*	N	NA	N	N	Y	Y	2
chr4:113218385-113218525	*ALPK1*	N	NA	N	N	Y	Y	2
chr5:64777678-64778186	*ADAMTS6*	Y	NA	N	Y	N	Y	3
chr5:81573780-81574461	*RPS23*	N	NA	N	Y	N	Y	2
chr5:158526108-158526694	*EBF1*	Y	NA	Y	Y	Y	Y	5
chr6:291687-292824	*DUSP22*	N	NA	Y	Y	Y	Y	4
chr6:26234819-26235610	*HIST1H1D*	N	NA	Y	Y	Y	Y	4
chr6:29648161-29649085	*ZFP57*	Y	NA	Y	Y	Y	Y	5
chr6:31055396-31055503	*C6orf15*	Y	NA	Y	N	N	Y	3
chr6:32799997-32801050	*TAP2*	Y	NA	N	N	N	Y	2
chr7:87974722-87975316	*STEAP4*	Y	NA	N	N	N	Y	2
chr7:106694832-106695007	*PRKAR2B*	N	NA	N	N	N	Y	1

chr7:158045980-158046359	*PTPRN2*	N	NA	N	N	NA	Y	1
chr8:33370172-33371226	*TTI2*	N	NA	Y	Y	N	Y	3
chr8:127889010-127889296	*PCAT1*	N	NA	N	Y	NA	N	1
chr10:65028929-65029169	*JMJD1C*	N	NA	Y	N	N	N	1
chr10:71871364-71871634	*H2AFY2*	N	NA	Y	Y	N	N	2
chr11:268923-269469	*NLRP6*	N	NA	Y	Y	N	Y	3
chr11:107328442-107328915	*CWF19L2*	N	NA	N	N	N	Y	1
chr12:58329764-58330116	*LOC100506844*	Y	NA	Y	Y	N	Y	4
chr12:74931289-74932008	*ATXN7L3B*	N	NA	N	N	NA	Y	1
chr13:31618695-31618744	*TEX26*	N	NA	Y	N	N	N	1
chr13:108953659-108954055	*TNFSF13B*	Y	NA	N	N	Y	Y	3
chr14:69341139-69341739	*ACTN1*	N	NA	Y	Y	Y	Y	4
chr16:20774873-20775353	*ACSM3*	Y	NA	N	N	Y	Y	3
chr17:21029189-21029296	*DHRS7B*	N	NA	Y	Y	N	Y	3
chr17:74667833-74668253	*LOC105274304*	Y	NA	N	N	N	Y	2
chr18:47813745-47815431	*CXXC1*	Y	NA	N	N	N	Y	2
chr21:36421467-36421956	*RUNX1*	N	NA	N	N	NA	Y	1
chr22:24372913-24374013	*LOC391322*	Y	NA	N	N	Y	Y	3
DMRs associated with gene expression in at least one of the datasets.								35

* P-value < 0.05 in the smaller GEO, IoW, INMA and BAMSE datasets and FDR < 0.05 in the larger BIOS dataset.

(C)

CpG	chr:pos	UCSC RefGene Name	UCSC Known Gene*	Significant** (Y) correlation with gene expression in						N datasets showing association (max 6)
				GEO (N=38) cord blood	IoW (N=157) cord blood	INMA (N=113) cord blood	INMA (N=112) 4-year-olds	BAMSE (N=248) 16-year-olds	BIOS (3,096) adults	
cg06315149	chr1:2036398	*PRKCZ*	*PRKCZ*	N	Y	Y	N	Y	Y	4
cg13066938	chr1:6341140	*ACOT7*	*ACOT7*	Y	Y	N	N	Y	Y	4
cg21220721	chr1:6341230	*ACOT7*	*ACOT7*	Y	N	Y	Y	Y	Y	5
cg09249800	chr1:6341287	*ACOT7*	*ACOT7*	Y	N	Y	Y	NA	Y	4
cg11699125	chr1:6341327	*ACOT7*	*ACOT7*	Y	Y	Y	Y	Y	Y	6
cg18783781	chr1:9599067	*SLC25A33*	*SLC25A33*	Y	Y	N	Y	Y	Y	5
cg02171825	chr1:26517586	*CATSPER4*	*CATSPER4*	Y	N	Y	Y	Y	Y	5
cg01942646	chr1:27240694	*NR0B2*	*NR0B2*	Y	N	Y	N	Y	Y	4
cg16263722	chr1:29523841	*MECR*	*MECR*	Y	N	Y	N	N	Y	3
cg11987455	chr1:43290834	*ERMAP*	*ERMAP*	Y	Y	Y	Y	N	Y	5
cg11683482	chr1:44678623	*DMAP1*	*DMAP1*	Y	N	N	Y	Y	Y	4
cg12643917	chr1:44715958	*ERI3*	*ERI3*	Y	NA	N	N	N	Y	2
cg26252077	chr1:61607055	*NFIA*	*NFIA*	N	NA	N	N	N	Y	1
cg10704177	chr1:62209607	*INADL*	*INADL*	N	N	N	N	Y	Y	2
cg01445399	chr1:87596934	*LOC339524*	*LOC339524*	N	N	Y	N	N	Y	2
cg19805160	chr1:159870731	*CCDC19*	*CCDC19*	Y	NA	N	Y	Y	Y	4
cg09332506	chr1:160309220	*COPA*	*NCSTN*	Y	Y	Y	N	Y	Y	5
cg17971251	chr1:177907297	*SEC16B*	*SEC16B*	N	N	N	N	N	Y	1

cg26033504	chr1:201458737	*CSRP1*	*CSRP1*	Y	Y	Y	Y	Y	Y	6
cg04895895	chr1:231005895	*C1orf198*	*C1orf198*	Y	Y	Y	N	N	Y	4
cg02473287	chr2:9752386	*YWHAQ*	*YWHAQ*	N	Y	N	Y	Y	Y	4
cg10142874	chr2:11917623	*LPIN1*	*LPIN1*	N	Y	N	Y	N	N	2
cg26752663	chr2:25142016	*ADCY3*	*ADCY3*	Y	N	N	N	Y	Y	3
cg00043800	chr2:74612144	*LOC100189589*	*LOC100189589*	Y	Y	Y	Y	Y	Y	6
cg17988187	chr2:74612222	*LOC100189589*	*LOC100189589*	Y	Y	Y	Y	Y	Y	6
cg12077754	chr2:75089669	*HK2*	*HK2*	N	Y	N	Y	N	Y	3
cg22674082	chr2:98585733	*TMEM131*	*TMEM131*	N	N	N	N	Y	Y	2
cg00327263	chr2:120019111	*STEAP3*	*STEAP3*	Y	NA	Y	N	N	Y	3
cg25950520	chr2:121036760	*RALB*	*RALB*	N	N	N	N	N	N	0
cg00213281	chr2:149639822	*KIF5C;MIR1978*	*JA429504*	Y	N	N	N	Y	Y	3
cg02494549	chr2:161798364		*TANK*	N	NA	N	N	N	Y	1
cg01310029	chr3:3152374	*IL5RA*	*IL5RA*	Y	Y	N	Y	Y	Y	5
cg10159529	chr3:3152530	*IL5RA*	*IL5RA*	Y	Y	N	Y	Y	Y	5
cg25224369	chr3:12918528		*DQ581328*	N	N	Y	Y	Y	Y	4
cg07386061	chr3:52492874	*NISCH*	*NISCH*	Y	Y	Y	Y	N	Y	5
cg17890764	chr3:52864816	*ITIH4*	*ITIH4*	Y	N	N	Y	N	Y	3
cg07410597	chr3:66404129	*SLC25A26*	*LRIG1*	Y	N	N	N	N	Y	2
cg04217850	chr3:66428294	*SLC25A26*	*LRIG1*	N	N	Y	N	N	Y	2
cg06070625	chr3:69812798	*MITF*	*MITF*	N	N	N	N	N	Y	1
cg06391412	chr3:71295684	*FOXP1*	*FOXP1*	N	N	N	N	N	Y	1
cg20263733	chr3:130616293	*ATP2C1*	*ATP2C1*	Y	N	N	N	Y	Y	3
cg09423651	chr3:136618442	*NCK1*	*NCK1*	Y	N	Y	N	N	Y	3
cg08698681	chr3:171091657	*TNIK*	*TNIK*	N	N	N	N	Y	Y	2
cg25636075	chr3:185217761	*TMEM41A*	*TMEM41A*	Y	N	Y	Y	N	N	3
cg02803925	chr3:195974300	*PCYT1A*	*PCYT1A*	Y	Y	N	N	Y	Y	4
cg04077085	chr4:9937674	*SLC2A9*	*SLC2A9*	Y	Y	Y	Y	N	Y	5
cg18912470	chr4:57848125	*POLR2B*	*POLR2B*	Y	N	N	N	N	Y	2
cg26396815	chr4:102878132	*BANK1*	*BANK1*	Y	N	N	N	N	Y	2
cg20866785	chr4:148733880	*ARHGAP10*	*Metazoa_SRP*	N	N	N	Y	Y	Y	3
cg16362140	chr5:10708717	*DAP*	*DAP*	Y	Y	Y	Y	N	Y	5
cg22588983	chr5:38783142		*AK126213*	Y	N	N	N	N	Y	2
cg00944309	chr5:60142446		*ELOVL7*	Y	N	N	N	N	Y	2
cg14978242	chr5:79501131	*SERINC5*	*SERINC5*	N	Y	Y	Y	N	Y	4
cg09565310	chr5:112541553	*MCC*	*MCC*	N	N	N	N	N	Y	1
cg08969102	chr5:133563532		*PPP2CA*	N	Y	N	N	N	Y	2
cg21627181	chr6:25754190	*SLC17A4*	*SLC17A4*	N	N	N	Y	N	Y	2
cg09597192	chr6:32141591	*AGPAT1*	*PPT2*	Y	Y	Y	N	Y	Y	5
cg06426027	chr6:33232644	*VPS52*	*VPS52*	Y	Y	Y	N	Y	Y	5
cg18460809	chr6:57048049	*BAG2*	*BAG2*	Y	N	Y	Y	N	Y	4
cg15961693	chr6:139689053		*CITED2*	Y	N	N	Y	N	Y	3
cg26774971	chr6:158994407	*TMEM181*	*TMEM181*	N	Y	Y	N	Y	N	3
cg05477517	chr6:164531576		*AK093114*	N	NA	N	N	NA	NA	0

cg15304012	chr6:166876490	*RPS6KA2*	*RPS6KA2*	Y	Y	N	N	N	N	2
cg19851574	chr6:167178233	*RPS6KA2*	*RPS6KA2*	N	NA	Y	Y	Y	Y	4
cg03329755	chr6:167189272	*RPS6KA2*	*RPS6KA2*	N	N	Y	N	Y	Y	3
cg25270424	chr7:24965657	*OSBPL3*	*OSBPL3*	N	N	N	N	N	Y	1
cg04321303	chr7:44107504		*PGAM2*	Y	N	N	N	Y	Y	3
cg02435538	chr7:75507337	*RHBDD2*	*RHBDD2*	Y	N	N	N	N	Y	2
cg13007207	chr7:105279391	*ATXN7L1*	*ATXN7L1*	N	N	N	N	Y	N	1
cg17947765	chr7:117857964		*ANKRD7*	Y	N	Y	Y	Y	N	4
cg14678084	chr7:127627251	*SND1*	*SND1-IT1*	N	NA	N	Y	Y	N	2
cg05184016	chr7:149543136	*ZNF862*	*BC045757*	Y	Y	Y	Y	Y	Y	6
cg07970948	chr7:149543165	*ZNF862*	*BC045757*	Y	Y	Y	Y	Y	Y	6
cg06558622	chr7:149543177	*ZNF862*	*BC045757*	Y	NA	N	Y	Y	Y	4
cg24576940	chr7:150648283	*KCNH2*	*KCNH2*	Y	Y	Y	N	N	Y	4
cg23147443	chr7:150649655	*KCNH2*	*KCNH2*	Y	Y	N	N	NA	Y	3
cg18666454	chr7:150651937	*KCNH2*	*KCNH2*	Y	N	Y	N	N	Y	3
cg02596233	chr7:150970209	*SMARCD3*	*SMARCD3*	Y	NA	N	N	Y	Y	3
cg23706836	chr8:6407997	*ANGPT2;MCPH1*	*ANGPT2*	N	NA	N	N	Y	Y	2
cg21919729	chr8:11719367	*CTSB*	*CTSB*	Y	Y	Y	Y	Y	Y	6
cg03437605	chr8:22847209	*RHOBTB2*	*RHOBTB2*	Y	N	Y	N	N	Y	3
cg22816343	chr8:26243601	*BNIP3L*	*BNIP3L*	Y	N	N	N	N	Y	2
cg23205629	chr8:33421410	*RNF122*	*RNF122*	Y	N	Y	Y	Y	Y	5
cg10815420	chr8:105599835	*LRP12*	*LRP12*	Y	Y	N	N	Y	Y	4
cg02133716	chr8:128981622	*PVT1*	*MIR1205*	Y	N	N	N	N	N	1
cg00736681	chr8:134546052	*ST3GAL1*	*ST3GAL1*	N	N	Y	N	N	N	1
cg09377531	chr8:141046469	*TRAPPC9*	*AX748239*	N	N	N	Y	N	Y	2
cg14025883	chr9:5436224	*C9orf46*	*C9orf46*	N	N	N	Y	Y	N	2
cg01499988	chr9:35755346	*MSMP*	*MSMP*	Y	Y	N	N	N	Y	3
cg13482814	chr9:82183332		*TLE4*	N	NA	Y	N	N	N	1
cg13576859	chr9:97403129	*FBP1*	*FBP1*	Y	N	Y	Y	Y	Y	5
cg20503329	chr9:101705792	*COL15A1*	*COL15A1*	Y	N	N	Y	Y	Y	4
cg00045753	chr9:123630545	*PHF19*	*PHF19*	Y	Y	N	Y	N	Y	4
cg13458609	chr9:130608923	*ENG*	*ENG*	Y	N	N	Y	Y	Y	4
cg13835688	chr9:130859454	*SLC25A25*	*SLC25A25*	Y	Y	Y	N	Y	Y	5
cg13628444	chr9:134883788	*MED27*	*MED27*	N	Y	Y	N	N	Y	3
cg13850063	chr9:138362321		*AK096249*	N	N	Y	N	N	Y	2
cg14011077	chr9:138362327		*AK096249*	Y	N	N	Y	Y	Y	4
cg06958964	chr10:45494806	*C10orf25;ZNF22*	*ZNF22*	Y	N	Y	Y	Y	Y	5
cg25854298	chr10:73936754	*ASCC1*	*ASCC1*	Y	Y	Y	N	Y	Y	5
cg04973995	chr10:74057977		*DDIT4*	N	N	Y	N	N	Y	2
cg00366037	chr10:76781121	*MYST4*	*KAT6B*	Y	N	N	N	N	Y	2
cg22235258	chr11:34675402	*EHF*	*EHF*	N	N	Y	Y	Y	Y	4
cg24459209	chr11:57148215	*PRG3*	*PRG3*	Y	N	Y	Y	Y	Y	5
cg15700636	chr11:57156050	*PRG2*	*PRG2*	Y	Y	Y	N	Y	Y	5
cg08773180	chr11:57157607	*PRG2*	*PRG2*	Y	NA	Y	Y	Y	Y	5

cg12819873	chr11:57157632	*PRG2*	*PRG2*	Y	Y	Y	Y	Y	Y	6
cg27533472	chr11:59856225	*MS4A2*	*MS4A2*	Y	N	N	N	Y	Y	3
cg25087851	chr11:60623918	*GPR44*	*PTGDR2*	Y	Y	Y	Y	Y	Y	6
cg13233042	chr11:63432489	*ATL3*	*ATL3*	Y	NA	N	Y	Y	Y	4
cg05300717	chr11:65546210	*DKFZp761E198*	*DKFZp761E198*	N	N	Y	N	Y	Y	3
cg15219163	chr11:70842128	*SHANK2*	*SHANK2*	N	NA	N	N	N	NA	0
cg24368962	chr11:111570978	*SIK2*	*DQ599327*	Y	N	N	Y	Y	Y	4
cg19434937	chr12:7104184	*LPCAT3*	*EMG1*	Y	Y	Y	Y	Y	Y	6
cg03014680	chr12:10122522	*CLEC12A*	*CLEC12A*	Y	Y	Y	Y	Y	Y	6
cg09447105	chr12:15126020	*PDE6H*	*PDE6H*	Y	Y	Y	N	N	Y	4
cg24028828	chr12:56694932	*CS*	*CS*	Y	N	N	Y	Y	Y	4
cg21498475	chr12:113737469	*SLC24A6*	*SLC24A6*	N	Y	Y	N	Y	N	3
cg10065736	chr12:117440120	*FBXW8*	*AK055849*	N	Y	N	N	Y	Y	3
cg03131767	chr12:123446272	*ABCB9*	*ABCB9*	Y	Y	Y	N	Y	Y	5
cg19928703	chr13:30143971	*SLC7A1*	*SLC7A1*	N	N	N	Y	Y	Y	3
cg07908654	chr13:41631052		*TRNA_Glu*	Y	N	N	Y	N	Y	3
cg24818699	chr13:43355514	*C13orf30*	*C13orf30*	N	N	Y	Y	Y	N	3
cg08770358	chr13:48876684	*RB1*	*BC039553*	Y	NA	N	N	Y	N	2
cg00222125	chr13:53226144	*SUGT1*	*SUGT1*	Y	N	N	Y	N	N	2
cg11770323	chr13:80066032	*NDFIP2*	*NDFIP2*	Y	N	N	Y	Y	Y	4
cg25479097	chr13:113305704	*C13orf35*	*C13orf35*	Y	N	N	N	N	Y	2
cg18368116	chr14:21436271		*RNASE2*	Y	Y	N	Y	Y	Y	5
cg08077807	chr14:62001072	*PRKCH*	*PRKCH*	N	N	N	Y	N	Y	2
cg04933530	chr14:77419754		*IRF2BPL*	Y	N	N	Y	Y	N	3
cg01901579	chr14:95615731	*DICER1*	*DICER1*	Y	N	N	N	N	Y	2
cg16409452	chr14:100610186	*EVL*	*AX747103*	N	N	Y	N	Y	Y	3
cg14084609	chr14:100610407	*EVL*	*AX747103*	Y	N	Y	N	N	Y	3
cg18550847	chr14:100610570	*EVL*	*AX747103*	Y	N	Y	Y	N	Y	4
cg01000631	chr14:100610667		*EVL*	N	N	Y	Y	N	Y	3
cg05875066	chr14:104625249	*KIF26A*	*KIF26A*	N	N	Y	Y	Y	Y	4
cg18817654	chr15:39485138		*C15orf54*	Y	NA	N	N	NA	N	1
cg25939647	chr15:40173065	*GPR176*	*GPR176*	Y	Y	Y	N	Y	Y	5
cg07177867	chr15:52030746	*LYSMD2*	*LYSMD2*	Y	Y	Y	Y	N	Y	5
cg11266582	chr15:64275853	*DAPK2*	*DAPK2*	Y	N	N	N	N	Y	2
cg10387956	chr15:72646210	*HEXA*	*BC034424*	N	Y	Y	Y	Y	N	4
cg23387863	chr15:77472416	*SGK269*	*AX747193*	Y	N	N	N	N	Y	2
cg04497992	chr16:616212	*NHLRC4*	*C16orf11*	Y	N	N	Y	Y	Y	4
cg08067346	chr16:25011481	*ARHGAP17*	*DQ583809*	Y	NA	N	Y	Y	Y	4
cg26134665	chr16:31021544	*STX1B*	*STX1B*	Y	Y	Y	Y	Y	Y	6
cg09147843	chr16:53467612	*RBL2*	*RBL2*	N	N	Y	N	N	Y	2
cg01998785	chr16:55542709	*LPCAT2*	*LPCAT2*	Y	Y	N	Y	N	Y	4
cg27383865	chr16:84075870	*SLC38A8*	*SLC38A8*	N	NA	Y	Y	N	Y	3
cg08640475	chr16:85551478		*KIAA0182*	N	N	N	N	N	Y	1
cg10099827	chr16:85551514		*KIAA0182*	Y	Y	N	Y	N	Y	4

cg08940169	chr16:88540241	*ZFPM1*	*ZFPM1*	N	Y	Y	N	Y	Y	4
cg04983687	chr16:88558223	*ZFPM1*	*ZFPM1*	Y	Y	Y	Y	Y	Y	6
cg20315954	chr17:15137304	*PMP22*	*PMP22*	N	Y	Y	Y	Y	Y	5
cg20885063	chr17:17939419	*ATPAF2*	*ATPAF2*	Y	N	N	Y	N	Y	3
cg14611258	chr17:17946468	*C17orf39*	*C17orf39*	Y	N	N	N	Y	Y	3
cg19468946	chr17:37922297	*IKZF3*	*IKZF3*	Y	Y	Y	Y	Y	Y	6
cg21723861	chr17:39686628		*KRT19*	Y	Y	Y	Y	Y	Y	6
cg00170714	chr17:40724562	*MLX;PSMC3IP*	*PSMC3IP*	Y	Y	Y	Y	Y	Y	6
cg25173129	chr17:56269410	*EPX*	*EPX*	Y	NA	Y	Y	N	Y	4
cg02970679	chr17:56269818	*EPX*	*EPX*	Y	N	Y	N	N	Y	3
cg17374802	chr17:56270828	*EPX*	*EPX*	Y	N	Y	N	N	Y	3
cg17041511	chr17:61509620		*CYB561*	N	N	N	N	N	Y	1
cg22312249	chr17:72779428	*TMEM104*	*TMEM104*	Y	Y	Y	Y	Y	Y	6
cg09705784	chr17:76565232	*DNAH17*	*DNAH17*	N	N	N	N	N	Y	1
cg06725287	chr17:80533762	*FOXK2*	*FOXK2*	Y	N	Y	Y	N	Y	4
cg13054523	chr17:81055722		*METRNL*	N	N	Y	N	Y	Y	3
cg18337287	chr19:930871	*ARID3A*	*ARID3A*	N	Y	Y	Y	Y	Y	5
cg12104982	chr19:5592815	*SAFB2*	*SAFB2*	N	Y	N	Y	N	Y	3
cg10644885	chr19:11687621	*ACP5*	*ACP5*	N	Y	N	Y	Y	Y	4
cg02359181	chr19:34860339	*GPI*	*GPI*	Y	N	N	Y	Y	Y	4
cg20673965	chr19:44220148	*IRGC*	*IRGC*	Y	N	Y	Y	Y	Y	5
cg26979537	chr19:48016860	*NAPA*	*NAPA*	Y	Y	N	N	N	Y	3
cg21073212	chr20:30866501	*KIF3B*	*KIF3B*	N	N	Y	Y	N	Y	3
cg20226253	chr20:34022914	*GDF5*	*GDF5OS*	Y	Y	N	Y	Y	Y	5
cg21045547	chr20:35422703	*C20orf117*	*KIAA0889*	Y	Y	N	Y	Y	Y	5
cg13792581	chr20:43590115	*TOMM34*	*TOMM34*	Y	Y	Y	Y	Y	Y	6
cg13197551	chr20:60709957	*LSM14B*	*LSM14B*	N	N	Y	Y	Y	Y	4
cg18042632	chr21:42520902	*C21orf130*	*LINC00323*	Y	N	Y	Y	Y	Y	5
cg18879389	chr21:43771120	*TFF2*	*TFF2*	Y	Y	N	Y	N	Y	4
CpGs associated with gene expression in at least one of the datasets.										176

* UCSC Known Gene fills in nearest genes for those missing gene annotation in the UCSC RefGene Name column.

** P-value < 0.05 in the smaller GEO, IoW, INMA and BAMSE datasets and FDR < 0.05 in the larger BIOS dataset.

(D)

DMR	Gene Name	Significant* (Y) correlation with gene expression in						N datasets showing association (max 5)
		GEO (N=38) cord blood	IoW (N=157) cord blood	INMA (N=113) cord blood	INMA (N=112) 4-year-olds	BAMSE (N=248) 16-year-olds	BIOS (3,096) adults	
chr1:2036283-2036644	*PRKCZ*	Y	NA	Y	N	Y	Y	4
chr1:87596820-87596935	*LINC01140*	N	NA	N	N	N	Y	1
chr1:161575716-161576323	*HSPA7*	Y	NA	Y	N	Y	Y	5
chr1:209979111-209979780	*IRF6*	Y	NA	Y	N	Y	Y	4
chr2:11917490-11917788	*LPIN1*	N	NA	N	N	N	Y	1
chr2:149639612-149640260	*KIF5C*	Y	NA	NA	NA	Y	Y	3

chr3:3151795-3152917	*IL5RA*	N	NA	Y	N	Y	Y	3
chr3:195974258-195974330	*PCYT1A*	Y	NA	Y	N	Y	Y	4
chr5:38445220-38446193	*EGFLAM*	N	NA	N	N	N	NA	1
chr5:132008525-132009631	*IL4*	N	NA	Y	N	Y	Y	3
chr6:112688010-112688931	*RFPL4B*	N	NA	Y	Y	Y	NA	3
chr6:166876490-166877039	*RPS6KA2;RPS6KA2-IT1*	N	NA	N	N	N	Y	1
chr7:65419185-65419289	*VKORC1L1*	Y	NA	Y	Y	Y	Y	5
chr7:149543136-149543178	*ZNF862*	Y	NA	Y	Y	Y	Y	5
chr7:156735383-156735657	*NOM1*	N	NA	Y	N	N	N	1
chr8:832917-833049	*ERICH1-AS1;DLGAP2*	N	NA	N	N	NA	Y	1
chr8:141046436-141046853	*TRAPPC9*	N	NA	N	N	N	Y	1
chr9:130859454-130859607	*SLC25A25*	Y	NA	Y	N	Y	Y	5
chr9:138362321-138362505	*PPP1R26-AS1*	N	NA	Y	N	N	Y	2
chr11:59856225-59856359	*MS4A2*	Y	NA	Y	Y	Y	Y	5
chr11:65545808-65547173	*AP5B1*	Y	NA	Y	Y	Y	Y	5
chr11:69291998-69292065	*LINC01488*	N	NA	Y	N	Y	Y	3
chr12:15125458-15126021	*PDE6H*	Y	NA	Y	Y	N	Y	4
chr14:100610071-100610668	*EVL*	Y	NA	Y	Y	Y	Y	5
chr15:64275810-64275854	*DAPK2*	N	NA	N	N	N	Y	1
chr15:99443213-99443667	*IGF1R*	Y	NA	Y	N	N	Y	2
chr16:615709-616221	*PRR35*	Y	NA	Y	Y	Y	Y	5
chr16:875257-875627	*PRR25*	Y	NA	Y	Y	Y	Y	5
chr16:85551478-85551749	*GSE1*	N	NA	N	N	N	Y	1
chr16:88539861-88540397	*ZFPM1*	N	NA	Y	Y	Y	Y	3
chr17:56269410-56270829	*EPX*	Y	NA	Y	Y	N	Y	4
chr17:78682785-78683458	*RPTOR*	N	NA	Y	Y	Y	Y	3
chr19:50553682-50554511	*LOC400710*	Y	NA	Y	N	Y	Y	4
chr19:51961666-51961938	*SIGLEC8*	Y	NA	Y	Y	Y	Y	5
chr20:35503832-35504554	*TLDC2*	Y	NA	Y	Y	Y	Y	5
chr21:42520365-42520903	*LINC00323*	Y	NA	N	Y	Y	Y	5
DMRs associated with gene expression in at least one of the datasets.								36

* P-value < 0.05 in the smaller GEO, IoW, INMA and BAMSE datasets and FDR < 0.05 in the larger BIOS dataset.

Table E9: Significantly enriched canonical pathways, diseases and biological functions from Ingenuity Pathway Analysis based on CpGs and regions differentially methylated in newborns in relation to asthma

CANONICAL PATHWAYS

Category	Genes	P-value
Granzyme B Signaling	CASP8,	0.029512092
Granzyme A Signaling	HIST1H1D,	0.031622777
D-myo-inositol (1,4,5)-trisphosphate Degradation	BPNT1,	0.033113112
Protein Kinase A Signaling	HIST1H1D,PRKAR2B,DUSP22	0.034673685
Inflammasome pathway	CASP8,	0.037153523
eNOS Signaling	PRKAR2B,CASP8	0.038904514
Superpathway of D-myo-inositol (1,4,5)-trisphosphate Metabolism	BPNT1,	0.044668359
Tumoricidal Function of Hepatic Natural Killer Cells	CASP8,	0.044668359
Sertoli Cell-Sertoli Cell Junction Signaling	PRKAR2B,ACTN1	0.044668359
NF-kB Signaling	TNFSF13B,CASP8	0.045708819

DISEASES AND BIOLOGICAL FUNCTIONS

Category	Disease and Biological Function*	P-value	Genes
Cellular Development	Arrest in differentiation of leukocytes	9.96E-06	TNFSF13B,EBF1,RUNX1,CASP8
	Arrest in differentiation of myeloid cells	2.07E-05	RUNX1,CASP8
	Arrest in differentiation of leukemia cells	3.44E-05	RUNX1,CASP8
	Differentiation of pre-B lymphocytes	0.000128	TNFSF13B,EBF1,RUNX1
	Expansion of leukocytes	0.000965	TNFSF13B,EBF1,RUNX1,CASP8
	Differentiation of B lymphocytes	0.00163	TNFSF13B,EBF1,RUNX1,CASP8
	Differentiation of pro-B lymphocytes	0.00176	EBF1,RUNX1
	Differentiation of neutrophils	0.00271	DHRS7B,RUNX1
	Arrest in differentiation of B lymphocytes	0.00297	TNFSF13B,EBF1
	Expansion of B lymphocytes	0.00297	TNFSF13B,EBF1
	Differentiation of phagocytes	0.00322	DHRS7B,EBF1,RUNX1,CASP8
	Thrombopoiesis	0.00325	ACTN1,CASP8
	Hematopoiesis in embryo	0.00517	RUNX1,CASP8
	Expansion of lymphocytes	0.00735	TNFSF13B,EBF1,CASP8
	Differentiation of hematopoietic progenitor cells	0.00811	TNFSF13B,EBF1,RUNX1,CASP8
	Differentiation of antigen presenting cells	0.0107	EBF1,RUNX1,CASP8
	Expansion of hematopoietic progenitor cells	0.0109	EBF1,RUNX1
	Proliferation of leukemia cell lines	0.0141	PRKAR2B,RUNX1,CASP8
	Development of hematopoietic progenitor cells	0.0194	TNFSF13B,EBF1,RUNX1
	Proliferation of hematopoietic progenitor cells	0.0223	EBF1,RUNX1,JMJD1C
	Differentiation of embryonic stem cells	0.0225	RUNX1,H2AFY2
	Differentiation of myeloid leukocytes	0.023	DHRS7B,RUNX1,CASP8
	Maturation of lymphocytes	0.026	TNFSF13B,RUNX1
	Formation of osteoclasts	0.0297	EBF1,RUNX1

	Proliferation of B lymphocytes	0.0302	TNFSF13B,EBF1,CASP8
	Differentiation of macrophages	0.0341	RUNX1,CASP8
	Commitment of cells	0.0373	EBF1,RUNX1
	Development of B lymphocytes	0.0373	TNFSF13B,EBF1
	Expansion of T lymphocytes	0.0443	TNFSF13B,CASP8
	Differentiation of leukemia cell lines	0.0456	PRKAR2B,RUNX1
	Proliferation of keratinocytes	0.0498	RUNX1,STEAP4
Cellular Growth and Proliferation	Arrest in differentiation of leukocytes	9.96E-06	TNFSF13B,EBF1,RUNX1,CASP8
	Arrest in differentiation of myeloid cells	2.07E-05	RUNX1,CASP8
	Differentiation of pre-B lymphocytes	0.000128	TNFSF13B,EBF1,RUNX1
	Expansion of leukocytes	0.000965	TNFSF13B,EBF1,RUNX1,CASP8
	Expansion of lymphatic system cells	0.00098	TNFSF13B,EBF1,RUNX1,CASP8
	Differentiation of B lymphocytes	0.00163	TNFSF13B,EBF1,RUNX1,CASP8
	Differentiation of pro-B lymphocytes	0.00176	EBF1,RUNX1
	Differentiation of neutrophils	0.00271	DHRS7B,RUNX1
	Arrest in differentiation of B lymphocytes	0.00297	TNFSF13B,EBF1
	Expansion of B lymphocytes	0.00297	TNFSF13B,EBF1
	Differentiation of phagocytes	0.00322	DHRS7B,EBF1,RUNX1,CASP8
	Thrombopoiesis	0.00325	ACTN1,CASP8
	Hematopoiesis in embryo	0.00517	RUNX1,CASP8
	Expansion of lymphocytes	0.00735	TNFSF13B,EBF1,CASP8
	Differentiation of hematopoietic progenitor cells	0.00811	TNFSF13B,EBF1,RUNX1,CASP8
	Differentiation of antigen presenting cells	0.0107	EBF1,RUNX1,CASP8
	Expansion of hematopoietic progenitor cells	0.0109	EBF1,RUNX1
	Proliferation of leukemia cell lines	0.0141	PRKAR2B,RUNX1,CASP8
	Development of hematopoietic progenitor cells	0.0194	TNFSF13B,EBF1,RUNX1
	Proliferation of hematopoietic progenitor cells	0.0223	EBF1,RUNX1,JMJD1C
	Differentiation of myeloid leukocytes	0.023	DHRS7B,RUNX1,CASP8
	Formation of osteoclasts	0.0297	EBF1,RUNX1
	Proliferation of B lymphocytes	0.0302	TNFSF13B,EBF1,CASP8
	Differentiation of macrophages	0.0341	RUNX1,CASP8
	Development of B lymphocytes	0.0373	TNFSF13B,EBF1
	Expansion of T lymphocytes	0.0443	TNFSF13B,CASP8
	Proliferation of keratinocytes	0.0498	RUNX1,STEAP4
Hematological System Development and Function	Arrest in differentiation of leukocytes	9.96E-06	TNFSF13B,EBF1,RUNX1,CASP8
	Arrest in differentiation of myeloid cells	2.07E-05	RUNX1,CASP8
	Differentiation of pre-B lymphocytes	0.000128	TNFSF13B,EBF1,RUNX1
	Survival of pre-B lymphocytes	0.00093	TNFSF13B,EBF1
	Expansion of leukocytes	0.000965	TNFSF13B,EBF1,RUNX1,CASP8
	Survival of hematopoietic cells	0.00131	TNFSF13B,EBF1,RUNX1

	Differentiation of B lymphocytes	0.00163	TNFSF13B,EBF1,RUNX1,CASP8
	Differentiation of pro-B lymphocytes	0.00176	EBF1,RUNX1
	Activation of B lymphocytes	0.0026	TNFSF13B,EBF1,CASP8
	Differentiation of neutrophils	0.00271	DHRS7B,RUNX1
	Arrest in differentiation of B lymphocytes	0.00297	TNFSF13B,EBF1
	Expansion of B lymphocytes	0.00297	TNFSF13B,EBF1
	Differentiation of phagocytes	0.00322	DHRS7B,EBF1,RUNX1,CASP8
	Thrombopoiesis	0.00325	ACTN1,CASP8
	Abnormal morphology of thymus gland	0.00331	HIST1H1D,RUNX1,CASP8
	Quantity of myeloid progenitor cells	0.00369	RUNX1,CASP8
	Activation of lymphocytes	0.00432	TNFSF13B,EBF1,RUNX1,DUSP22,CASP8
	Hematopoiesis in embryo	0.00517	RUNX1,CASP8
	Expansion of lymphocytes	0.00735	TNFSF13B,EBF1,CASP8
	Differentiation of hematopoietic progenitor cells	0.00811	TNFSF13B,EBF1,RUNX1,CASP8
	Cell viability of lymphocytes	0.0093	TNFSF13B,EBF1,CASP8
	Differentiation of antigen presenting cells	0.0107	EBF1,RUNX1,CASP8
	Expansion of hematopoietic progenitor cells	0.0109	EBF1,RUNX1
	Abnormal morphology of lymphoid organ	0.0113	HIST1H1D,TNFSF13B,RUNX1,CASP8
	Quantity of marginal-zone B lymphocytes	0.0133	TNFSF13B,CASP8
	Abnormal morphology of enlarged lymph node	0.0147	TNFSF13B,CASP8
	Development of hematopoietic progenitor cells	0.0194	TNFSF13B,EBF1,RUNX1
	Proliferation of hematopoietic progenitor cells	0.0223	EBF1,RUNX1,JMJD1C
	Differentiation of myeloid leukocytes	0.023	DHRS7B,RUNX1,CASP8
	Quantity of hematopoietic progenitor cells	0.0239	TNFSF13B,EBF1,RUNX1,CASP8
	Maturation of lymphocytes	0.026	TNFSF13B,RUNX1
	Quantity of pre-B lymphocytes	0.0271	TNFSF13B,EBF1
	Proliferation of B lymphocytes	0.0302	TNFSF13B,EBF1,CASP8
	Differentiation of macrophages	0.0341	RUNX1,CASP8
	Development of B lymphocytes	0.0373	TNFSF13B,EBF1
	Expansion of T lymphocytes	0.0443	TNFSF13B,CASP8
	T cell homeostasis	0.0472	TNFSF13B,EBF1,RUNX1,CASP8
	Activation of T lymphocytes	0.0474	RUNX1,DUSP22,CASP8
	Abnormal morphology of enlarged spleen	0.0488	TNFSF13B,CASP8
Hematopoiesis	Arrest in differentiation of leukocytes	9.96E-06	TNFSF13B,EBF1,RUNX1,CASP8
	Arrest in differentiation of myeloid cells	2.07E-05	RUNX1,CASP8
	Differentiation of pre-B lymphocytes	0.000128	TNFSF13B,EBF1,RUNX1
	Differentiation of B lymphocytes	0.00163	TNFSF13B,EBF1,RUNX1,CASP8
	Differentiation of pro-B lymphocytes	0.00176	EBF1,RUNX1
	Differentiation of neutrophils	0.00271	DHRS7B,RUNX1
	Arrest in differentiation of B lymphocytes	0.00297	TNFSF13B,EBF1

	Differentiation of phagocytes	0.00322	DHRS7B,EBF1,RUNX1,CASP8
	Thrombopoiesis	0.00325	ACTN1,CASP8
	Quantity of myeloid progenitor cells	0.00369	RUNX1,CASP8
	Hematopoiesis in embryo	0.00517	RUNX1,CASP8
	Differentiation of hematopoietic progenitor cells	0.00811	TNFSF13B,EBF1,RUNX1,CASP8
	Differentiation of antigen presenting cells	0.0107	EBF1,RUNX1,CASP8
	Expansion of hematopoietic progenitor cells	0.0109	EBF1,RUNX1
	Development of hematopoietic progenitor cells	0.0194	TNFSF13B,EBF1,RUNX1
	Proliferation of hematopoietic progenitor cells	0.0223	EBF1,RUNX1,JMJD1C
	Differentiation of myeloid leukocytes	0.023	DHRS7B,RUNX1,CASP8
	Quantity of hematopoietic progenitor cells	0.0239	TNFSF13B,EBF1,RUNX1,CASP8
	Quantity of pre-B lymphocytes	0.0271	TNFSF13B,EBF1
	Differentiation of macrophages	0.0341	RUNX1,CASP8
	Development of B lymphocytes	0.0373	TNFSF13B,EBF1
Lymphoid Tissue Structure and Development	Arrest in differentiation of leukocytes	9.96E-06	TNFSF13B,EBF1,RUNX1,CASP8
	Differentiation of pre-B lymphocytes	0.000128	TNFSF13B,EBF1,RUNX1
	Expansion of leukocytes	0.000965	TNFSF13B,EBF1,RUNX1,CASP8
	Expansion of lymphatic system cells	0.00098	TNFSF13B,EBF1,RUNX1,CASP8
	Differentiation of B lymphocytes	0.00163	TNFSF13B,EBF1,RUNX1,CASP8
	Differentiation of pro-B lymphocytes	0.00176	EBF1,RUNX1
	Frequency of B lymphocytes	0.00176	TNFSF13B,RUNX1
	Differentiation of neutrophils	0.00271	DHRS7B,RUNX1
	Arrest in differentiation of B lymphocytes	0.00297	TNFSF13B,EBF1
	Expansion of B lymphocytes	0.00297	TNFSF13B,EBF1
	Differentiation of phagocytes	0.00322	DHRS7B,EBF1,RUNX1,CASP8
	Abnormal morphology of thymus gland	0.00331	HIST1H1D,RUNX1,CASP8
	Quantity of myeloid progenitor cells	0.00369	RUNX1,CASP8
	Quantity of bone marrow cells	0.00627	EBF1,RUNX1,CASP8
	Expansion of lymphocytes	0.00735	TNFSF13B,EBF1,CASP8
	Differentiation of antigen presenting cells	0.0107	EBF1,RUNX1,CASP8
	Abnormal morphology of lymphoid organ	0.0113	HIST1H1D,TNFSF13B,RUNX1,CASP8
	Quantity of marginal-zone B lymphocytes	0.0133	TNFSF13B,CASP8
	Abnormal morphology of enlarged lymph node	0.0147	TNFSF13B,CASP8
	Differentiation of myeloid leukocytes	0.023	DHRS7B,RUNX1,CASP8
	Maturation of lymphocytes	0.026	TNFSF13B,RUNX1
	Quantity of pre-B lymphocytes	0.0271	TNFSF13B,EBF1
	Proliferation of B lymphocytes	0.0302	TNFSF13B,EBF1,CASP8
	Differentiation of macrophages	0.0341	RUNX1,CASP8
	Development of B lymphocytes	0.0373	TNFSF13B,EBF1
	Expansion of T lymphocytes	0.0443	TNFSF13B,CASP8

	Abnormal morphology of enlarged spleen	0.0488	TNFSF13B,CASP8
Tissue Development	Arrest in differentiation of leukocytes	9.96E-06	TNFSF13B,EBF1,RUNX1,CASP8
	Arrest in differentiation of myeloid cells	2.07E-05	RUNX1,CASP8
	Differentiation of pre-B lymphocytes	0.000128	TNFSF13B,EBF1,RUNX1
	Differentiation of B lymphocytes	0.00163	TNFSF13B,EBF1,RUNX1,CASP8
	Differentiation of pro-B lymphocytes	0.00176	EBF1,RUNX1
	Differentiation of neutrophils	0.00271	DHRS7B,RUNX1
	Arrest in differentiation of B lymphocytes	0.00297	TNFSF13B,EBF1
	Differentiation of phagocytes	0.00322	DHRS7B,EBF1,RUNX1,CASP8
	Thrombopoiesis	0.00325	ACTN1,CASP8
	Hematopoiesis in embryo	0.00517	RUNX1,CASP8
	Activation of osteoclasts	0.00667	EBF1,RUNX1
	Differentiation of hematopoietic progenitor cells	0.00811	TNFSF13B,EBF1,RUNX1,CASP8
	Differentiation of antigen presenting cells	0.0107	EBF1,RUNX1,CASP8
	Formation of coronary vessel	0.0122	ADAMTS6,RUNX1
	Development of hematopoietic progenitor cells	0.0194	TNFSF13B,EBF1,RUNX1
	Differentiation of myeloid leukocytes	0.023	DHRS7B,RUNX1,CASP8
	Formation of osteoclasts	0.0297	EBF1,RUNX1
	Differentiation of macrophages	0.0341	RUNX1,CASP8
	Development of B lymphocytes	0.0373	TNFSF13B,EBF1
	Proliferation of keratinocytes	0.0498	RUNX1,STEAP4
Cancer	Arrest in differentiation of leukemia cells	3.44E-05	RUNX1,CASP8
	Apoptosis of leukemia cells	0.000605	TNFSF13B,RUNX1,CASP8
	Type M4 acute myeloid leukemia	0.00648	RUNX1,STEAP4
	Precursor B-cell acute lymphoblastic leukemia	0.0264	EBF1,RUNX1
	Cecum adenocarcinoma	0.028	ATP13A3,TAP2,MXRA8,STEAP4
	Oral tumor	0.0329	ATP13A3,ADAMTS6,EBF1,WDR20,DUSP22,STEAP4,CASP8
Organismal Injury and Abnormalities	Arrest in differentiation of leukemia cells	3.44E-05	RUNX1,CASP8
	Apoptosis of leukemia cells	0.000605	TNFSF13B,RUNX1,CASP8
	Hemopericardium	0.00127	RUNX1,CASP8
	Primary Sjögren syndrome	0.00258	TNFSF13B,TAP2
	Abnormal morphology of thymus gland	0.00331	HIST1H1D,RUNX1,CASP8
	Insulin-dependent diabetes mellitus	0.00339	TNFSF13B,C6orf15,ADAMTS6,TAP2,ZFP57
	Advanced stage peripheral arterial disease	0.00367	SUB1,RUNX1,CASP8
	Intermediate disease stage peripheral arterial disease	0.00426	SUB1,RUNX1,CASP8
	Inflammation of joint	0.00508	TNFSF13B,C6orf15,ADAMTS6,TAP2,PTPRN2,STEAP4,CASP8,JMJD1C
	Type M4 acute myeloid leukemia	0.00648	RUNX1,STEAP4
	Non-traumatic arthropathy	0.00682	TNFSF13B,C6orf15,ADAMTS6,TAP2,PTPRN2,STEAP4,JMJD1C
	Hereditary bleeding disorder	0.00813	RUNX1,ACTN1
	Abnormal morphology of lymphoid organ	0.0113	HIST1H1D,TNFSF13B,RUNX1,CASP8

	Rheumatoid arthritis	0.0135	TNFSF13B,C6orf15,TAP2,PTPRN2,STEAP4,JMJD1C
	Abnormal morphology of enlarged lymph node	0.0147	TNFSF13B,CASP8
	Autosomal recessive immunodeficiency	0.0228	TAP2,CASP8
	Precursor B-cell acute lymphoblastic leukemia	0.0264	EBF1,RUNX1
	Cecum adenocarcinoma	0.028	ATP13A3,TAP2,MXRA8,STEAP4
	Oral tumor	0.0329	ATP13A3,ADAMTS6,EBF1,WDR20,DUSP22,STEAP4,CASP8
	Hepatic steatosis	0.0351	PRKAR2B,EBF1,STEAP4
	Abnormal morphology of enlarged spleen	0.0488	TNFSF13B,CASP8
Tumor Morphology	Arrest in differentiation of leukemia cells	3.44E-05	RUNX1,CASP8
	Apoptosis of leukemia cells	0.000605	TNFSF13B,RUNX1,CASP8
Embryonic Development	Differentiation of pre-B lymphocytes	0.000128	TNFSF13B,EBF1,RUNX1
	Differentiation of B lymphocytes	0.00163	TNFSF13B,EBF1,RUNX1,CASP8
	Differentiation of pro-B lymphocytes	0.00176	EBF1,RUNX1
	Arrest in differentiation of B lymphocytes	0.00297	TNFSF13B,EBF1
	Remodeling of vitelline vessel	0.0034	RUNX1,CASP8
	Hematopoiesis in embryo	0.00517	RUNX1,CASP8
	Formation of coronary vessel	0.0122	ADAMTS6,RUNX1
	Abnormal morphology of yolk sac	0.0192	HIST1H1D,CASP8
	Differentiation of embryonic stem cells	0.0225	RUNX1,H2AFY2
	Abnormal morphology of vitelline vessel	0.0228	HIST1H1D,CASP8
	Development of B lymphocytes	0.0373	TNFSF13B,EBF1
Humoral Immune Response	Differentiation of pre-B lymphocytes	0.000128	TNFSF13B,EBF1,RUNX1
	Differentiation of B lymphocytes	0.00163	TNFSF13B,EBF1,RUNX1,CASP8
	Differentiation of pro-B lymphocytes	0.00176	EBF1,RUNX1
	Activation of B lymphocytes	0.0026	TNFSF13B,EBF1,CASP8
	Arrest in differentiation of B lymphocytes	0.00297	TNFSF13B,EBF1
	Expansion of B lymphocytes	0.00297	TNFSF13B,EBF1
	Quantity of marginal-zone B lymphocytes	0.0133	TNFSF13B,CASP8
	Quantity of pre-B lymphocytes	0.0271	TNFSF13B,EBF1
	Proliferation of B lymphocytes	0.0302	TNFSF13B,EBF1,CASP8
	Development of B lymphocytes	0.0373	TNFSF13B,EBF1
Organ Development	Differentiation of pre-B lymphocytes	0.000128	TNFSF13B,EBF1,RUNX1
	Differentiation of B lymphocytes	0.00163	TNFSF13B,EBF1,RUNX1,CASP8
	Differentiation of pro-B lymphocytes	0.00176	EBF1,RUNX1
	Arrest in differentiation of B lymphocytes	0.00297	TNFSF13B,EBF1
	Formation of coronary vessel	0.0122	ADAMTS6,RUNX1
	Development of B lymphocytes	0.0373	TNFSF13B,EBF1
	Proliferation of keratinocytes	0.0498	RUNX1,STEAP4
Organismal Development	Differentiation of pre-B lymphocytes	0.000128	TNFSF13B,EBF1,RUNX1
	Differentiation of B lymphocytes	0.00163	TNFSF13B,EBF1,RUNX1,CASP8

	Differentiation of pro-B lymphocytes	0.00176	EBF1,RUNX1
	Arrest in differentiation of B lymphocytes	0.00297	TNFSF13B,EBF1
	Paleness of liver	0.00297	RUNX1,BPNT1
	Thrombopoiesis	0.00325	ACTN1,CASP8
	Abnormal morphology of thymus gland	0.00331	HIST1H1D,RUNX1,CASP8
	Hematopoiesis in embryo	0.00517	RUNX1,CASP8
	Formation of coronary vessel	0.0122	ADAMTS6,RUNX1
	Differentiation of embryonic stem cells	0.0225	RUNX1,H2AFY2
	Abnormal morphology of vitelline vessel	0.0228	HIST1H1D,CASP8
	Development of artery	0.0357	ADAMTS6,RUNX1
	Development of B lymphocytes	0.0373	TNFSF13B,EBF1
	Morphology of liver	0.0479	RUNX1,BPNT1,STEAP4
	Abnormal morphology of enlarged spleen	0.0488	TNFSF13B,CASP8
Connective Tissue Development and Function	Quantity of adipose tissue	0.000387	C6orf15,PRKAR2B,EBF1,STEAP4,CASP8
	Thrombopoiesis	0.00325	ACTN1,CASP8
	Quantity of connective tissue	0.00366	C6orf15,PRKAR2B,EBF1,RUNX1,STEAP4,CASP8
	Activation of osteoclasts	0.00667	EBF1,RUNX1
	Quantity of subcutaneous fat	0.00667	EBF1,STEAP4
	Formation of osteoclasts	0.0297	EBF1,RUNX1
	Proliferation of keratinocytes	0.0498	RUNX1,STEAP4
Tissue Morphology	Quantity of adipose tissue	0.000387	C6orf15,PRKAR2B,EBF1,STEAP4,CASP8
	Abnormal morphology of thymus gland	0.00331	HIST1H1D,RUNX1,CASP8
	Remodeling of vitelline vessel	0.0034	RUNX1,CASP8
	Quantity of connective tissue	0.00366	C6orf15,PRKAR2B,EBF1,RUNX1,STEAP4,CASP8
	Quantity of myeloid progenitor cells	0.00369	RUNX1,CASP8
	Quantity of bone marrow cells	0.00627	EBF1,RUNX1,CASP8
	Quantity of subcutaneous fat	0.00667	EBF1,STEAP4
	Abnormal morphology of lymphoid organ	0.0113	HIST1H1D,TNFSF13B,RUNX1,CASP8
	Quantity of marginal-zone B lymphocytes	0.0133	TNFSF13B,CASP8
	Abnormal morphology of enlarged lymph node	0.0147	TNFSF13B,CASP8
	Abnormal morphology of yolk sac	0.0192	HIST1H1D,CASP8
	Abnormal morphology of vitelline vessel	0.0228	HIST1H1D,CASP8
	Quantity of hematopoietic progenitor cells	0.0239	TNFSF13B,EBF1,RUNX1,CASP8
	Quantity of pre-B lymphocytes	0.0271	TNFSF13B,EBF1
	Abnormal morphology of membrane tissue	0.0479	HIST1H1D,NLRP6
	Abnormal morphology of enlarged spleen	0.0488	TNFSF13B,CASP8
Cell Death and Survival	Apoptosis of leukemia cells	0.000605	TNFSF13B,RUNX1,CASP8
	Apoptosis of lymphoma cell lines	0.000705	TNFSF13B,EBF1,RUNX1,CASP8
	Survival of pre-B lymphocytes	0.00093	TNFSF13B,EBF1
	Survival of hematopoietic cells	0.00131	TNFSF13B,EBF1,RUNX1

	Cell death of macrophage cancer cell lines	0.00465	RUNX1,CASP8
	Cell viability of blood cells	0.00486	TNFSF13B,EBF1,RUNX1,CASP8
	Cell death of motor neurons	0.0077	RUNX1,CASP8
	Cell viability of lymphocytes	0.0093	TNFSF13B,EBF1,CASP8
	Cell viability of leukemia cell lines	0.0109	TNFSF13B,JMJD1C
	Apoptosis of myeloma cell lines	0.0127	TNFSF13B,CASP8
	Killing of cells	0.0135	TNFSF13B,RUNX1,CASP8
	Killing of tumor cell lines	0.0173	RUNX1,CASP8
	Apoptosis of T lymphocytes	0.0257	TNFSF13B,RUNX1,CASP8
	Apoptosis of leukemia cell lines	0.0289	TNFSF13B,RUNX1,CASP8
	Apoptosis of thymocytes	0.0309	RUNX1,CASP8
	Apoptosis of B lymphocytes	0.0313	TNFSF13B,CASP8
	Cell viability	0.0323	TNFSF13B,EBF1,RUNX1,CLNS1A,PTPRN2,DUSP22,CASP8,JMJD1C
Organismal Survival	Viability	0.000756	RUNX1,CXXC1,CASP8
	Organismal death	0.0244	HIST1H1D,TNFSF13B,EBF1,RUNX1,CLNS1A,SUB1,CXXC1,NLRP6,ZFP57,PTPRN2,BPNT1,CASP8
Cardiovascular Disease	Hemopericardium	0.00127	RUNX1,CASP8
	Advanced stage peripheral arterial disease	0.00367	SUB1,RUNX1,CASP8
	Intermediate disease stage peripheral arterial disease	0.00426	SUB1,RUNX1,CASP8
Connective Tissue Disorders	Inflammation of joint	0.00508	TNFSF13B,C6orf15,ADAMTS6,TAP2,PTPRN2,STEAP4,CASP8,JMJD1C
	Non-traumatic arthropathy	0.00682	TNFSF13B,C6orf15,ADAMTS6,TAP2,PTPRN2,STEAP4,JMJD1C
	Rheumatoid arthritis	0.0135	TNFSF13B,C6orf15,TAP2,PTPRN2,STEAP4,JMJD1C
Immunological Disease	Primary Sjögren syndrome	0.00258	TNFSF13B,TAP2
	Abnormal morphology of thymus gland	0.00331	HIST1H1D,RUNX1,CASP8
	Insulin-dependent diabetes mellitus	0.00339	TNFSF13B,C6orf15,ADAMTS6,TAP2,ZFP57
	Systemic autoimmune syndrome	0.00418	TNFSF13B,C6orf15,ADAMTS6,TAP2,ZFP57,PTPRN2,STEAP4,CASP8,JMJD1C
	Type M4 acute myeloid leukemia	0.00648	RUNX1,STEAP4
	Abnormal morphology of lymphoid organ	0.0113	HIST1H1D,TNFSF13B,RUNX1,CASP8
	Rheumatoid arthritis	0.0135	TNFSF13B,C6orf15,TAP2,PTPRN2,STEAP4,JMJD1C
	Abnormal morphology of enlarged lymph node	0.0147	TNFSF13B,CASP8
	Immunodeficiency	0.0165	TNFSF13B,TAP2,CASP8
	Autosomal recessive immunodeficiency	0.0228	TAP2,CASP8
	Precursor B-cell acute lymphoblastic leukemia	0.0264	EBF1,RUNX1
	Primary immunodeficiency disorder	0.0447	TAP2,CASP8
	Abnormal morphology of enlarged spleen	0.0488	TNFSF13B,CASP8
Inflammatory Disease	Inflammation of joint	0.00508	TNFSF13B,C6orf15,ADAMTS6,TAP2,PTPRN2,STEAP4,CASP8,JMJD1C
	Rheumatoid arthritis	0.0135	TNFSF13B,C6orf15,TAP2,PTPRN2,STEAP4,JMJD1C
Skeletal and Muscular Disorders	Inflammation of joint	0.00508	TNFSF13B,C6orf15,ADAMTS6,TAP2,PTPRN2,STEAP4,CASP8,JMJD1C
	Non-traumatic arthropathy	0.00682	TNFSF13B,C6orf15,ADAMTS6,TAP2,PTPRN2,STEAP4,JMJD1C
	Rheumatoid arthritis	0.0135	TNFSF13B,C6orf15,TAP2,PTPRN2,STEAP4,JMJD1C
Hematological Disease	Type M4 acute myeloid leukemia	0.00648	RUNX1,STEAP4

	Hereditary bleeding disorder	0.00813	RUNX1,ACTN1
	Precursor B-cell acute lymphoblastic leukemia	0.0264	EBF1,RUNX1
Cardiovascular System Development	Formation of coronary vessel	0.0122	ADAMTS6,RUNX1
and Function	Development of artery	0.0357	ADAMTS6,RUNX1
Cell Cycle	Binding of protein binding site	0.0283	EBF1,RUNX1,SUB1
	Binding of DNA	0.0404	TNFSF13B,EBF1,RUNX1,SUB1
Cellular Function and Maintenance	T cell homeostasis	0.0472	TNFSF13B,EBF1,RUNX1,CASP8
Developmental Disorder	Dysmorphogenesis	0.0173	HIST1H1D,CXXC1
	Abnormal morphology of yolk sac	0.0192	HIST1H1D,CASP8
	Abnormal morphology of vitelline vessel	0.0228	HIST1H1D,CASP8
Hereditary Disorder	Hereditary bleeding disorder	0.00813	RUNX1,ACTN1
	Autosomal recessive immunodeficiency	0.0228	TAP2,CASP8
Cellular Movement	Cell movement of leukemia cell lines	0.0438	RUNX1,ACTN1
Gastrointestinal Disease	Primary Sjögren syndrome	0.00258	TNFSF13B,TAP2
	Insulin-dependent diabetes mellitus	0.00339	TNFSF13B,C6orf15,ADAMTS6,TAP2,ZFP57
	Cecum adenocarcinoma	0.028	ATP13A3,TAP2,MXRA8,STEAP4
	Oral tumor	0.0329	ATP13A3,ADAMTS6,EBF1,WDR20,DUSP22,STEAP4,CASP8
	Hepatic steatosis	0.0351	PRKAR2B,EBF1,STEAP4
Organ Morphology	Paleness of liver	0.00297	RUNX1,BPNT1
	Abnormal morphology of thymus gland	0.00331	HIST1H1D,RUNX1,CASP8
	Abnormal morphology of lymphoid organ	0.0113	HIST1H1D,TNFSF13B,RUNX1,CASP8
	Abnormal morphology of enlarged lymph node	0.0147	TNFSF13B,CASP8
	Morphology of liver	0.0479	RUNX1,BPNT1,STEAP4
	Abnormal morphology of enlarged spleen	0.0488	TNFSF13B,CASP8
Inflammatory Response	Activation of B lymphocytes	0.0026	TNFSF13B,EBF1,CASP8
	Activation of lymphocytes	0.00432	TNFSF13B,EBF1,RUNX1,DUSP22,CASP8
	Inflammation of joint	0.00508	TNFSF13B,C6orf15,ADAMTS6,TAP2,PTPRN2,STEAP4,CASP8,JMJD1C
	Rheumatoid arthritis	0.0135	TNFSF13B,C6orf15,TAP2,PTPRN2,STEAP4,JMJD1C
	Activation of T lymphocytes	0.0474	RUNX1,DUSP22,CASP8
Cell-mediated Immune Response	T cell homeostasis	0.0472	TNFSF13B,EBF1,RUNX1,CASP8
Metabolic Disease	Insulin-dependent diabetes mellitus	0.00339	TNFSF13B,C6orf15,ADAMTS6,TAP2,ZFP57
	Glucose metabolism disorder	0.0166	TNFSF13B,C6orf15,ADAMTS6,TAP2,EBF1,ZFP57,STEAP4,CASP8
	DNA repair-deficiency disorder	0.0264	TAP2,RUNX1
	Hepatic steatosis	0.0351	PRKAR2B,EBF1,STEAP4
Endocrine System Disorders	Insulin-dependent diabetes mellitus	0.00339	TNFSF13B,C6orf15,ADAMTS6,TAP2,ZFP57
Ophthalmic Disease	Primary Sjögren syndrome	0.00258	TNFSF13B,TAP2
Cell-To-Cell Signaling and Interaction	Activation of B lymphocytes	0.0026	TNFSF13B,EBF1,CASP8
	Activation of lymphocytes	0.00432	TNFSF13B,EBF1,RUNX1,DUSP22,CASP8
	Activation of osteoclasts	0.00667	EBF1,RUNX1
	Activation of T lymphocytes	0.0474	RUNX1,DUSP22,CASP8

Immune Cell Trafficking	Activation of B lymphocytes	0.0026	TNFSF13B,EBF1,CASP8
	Activation of lymphocytes	0.00432	TNFSF13B,EBF1,RUNX1,DUSP22,CASP8
	Activation of T lymphocytes	0.0474	RUNX1,DUSP22,CASP8
Digestive System Development and Function	Paleness of liver	0.00297	RUNX1,BPNT1
	Morphology of liver	0.0479	RUNX1,BPNT1,STEAP4
Hepatic System Development and Function	Paleness of liver	0.00297	RUNX1,BPNT1
	Morphology of liver	0.0479	RUNX1,BPNT1,STEAP4
Endocrine System Development and Function	Glucose tolerance	0.00374	PRKAR2B,PTPRN2,STEAP4,CASP8
Gene Expression	Transcription of RNA	0.00648	HIST1H1D,PRKAR2B,EBF1,RUNX1,SUB1,CXXC1,H2AFY2,ZFP57,DUSP22,CASP8,JMJD1C
	Transcription	0.00708	HIST1H1D,TNFSF13B,PRKAR2B,EBF1,RUNX1,SUB1,CXXC1,H2AFY2,ZFP57,DUSP22,CASP8,JMJD1C
	Expression of RNA	0.0109	HIST1H1D,PRKAR2B,EBF1,RUNX1,SUB1,CXXC1,RPS23,H2AFY2,ZFP57,DUSP22,CASP8,JMJD1C
	Transcription of DNA	0.0163	HIST1H1D,EBF1,RUNX1,SUB1,CXXC1,H2AFY2,ZFP57,DUSP22,JMJD1C
	Binding of protein binding site	0.0283	EBF1,RUNX1,SUB1
	Activation of DNA endogenous promoter	0.0371	HIST1H1D,EBF1,RUNX1,SUB1,H2AFY2,ZFP57,DUSP22
	Binding of DNA	0.0404	TNFSF13B,EBF1,RUNX1,SUB1
Skeletal and Muscular System Development and Function	Activation of osteoclasts	0.00667	EBF1,RUNX1
	Formation of osteoclasts	0.0297	EBF1,RUNX1
Hair and Skin Development and Function	Proliferation of keratinocytes	0.0498	RUNX1,STEAP4
Carbohydrate Metabolism	Uptake of D-glucose	0.0133	TNFSF13B,EBF1,STEAP4
Lipid Metabolism	Concentration of lipid	0.0197	PRKAR2B,RUNX1,PTPRN2,BPNT1,STEAP4,CASP8
	Quantity of sphingolipid	0.0222	RUNX1,CASP8
	Concentration of cholesterol	0.0342	PRKAR2B,BPNT1,STEAP4
Small Molecule Biochemistry	Incorporation of thymidine	0.0125	TNFSF13B,PRKAR2B
	Uptake of D-glucose	0.0133	TNFSF13B,EBF1,STEAP4
	Concentration of lipid	0.0197	PRKAR2B,RUNX1,PTPRN2,BPNT1,STEAP4,CASP8
	Quantity of sphingolipid	0.0222	RUNX1,CASP8
	Concentration of cholesterol	0.0342	PRKAR2B,BPNT1,STEAP4
Molecular Transport	Uptake of D-glucose	0.0133	TNFSF13B,EBF1,STEAP4
	Concentration of lipid	0.0197	PRKAR2B,RUNX1,PTPRN2,BPNT1,STEAP4,CASP8
	Quantity of sphingolipid	0.0222	RUNX1,CASP8
	Concentration of cholesterol	0.0342	PRKAR2B,BPNT1,STEAP4
DNA Replication, Recombination, and Repair	Incorporation of thymidine	0.0125	TNFSF13B,PRKAR2B
	DNA damage	0.0131	EBF1,RUNX1,CASP8
Nucleic Acid Metabolism	Incorporation of thymidine	0.0125	TNFSF13B,PRKAR2B
Protein Synthesis	Quantity of leptin in blood	0.0253	PRKAR2B,STEAP4
Hepatic System Disease	Hepatic steatosis	0.0351	PRKAR2B,EBF1,STEAP4
Post-Translational Modification	Dephosphorylation of protein	0.0286	PTPRN2,DUSP22
Cell Signaling	I-kappaB kinase/NF-kappaB cascade	0.0369	NLRP6,CASP8

Table E10: Significantly enriched canonical pathways, diseases and biological functions from Ingenuity Pathway Analysis based on CpGs and regions differentially methylated in older children relation to asthma

CANONICAL PATHWAYS

Category	Genes	P-value
p70S6K Signaling	RALB,YWHAQ,IL4,PRKCH,PRKCZ,PPP2CA	0.000870964
Glycolysis I	FBP1,PGAM2,GPI	0.000954993
Gluconeogenesis I	FBP1,PGAM2,GPI	0.001096478
mTOR Signaling	RALB,RPTOR,RPS6KA2,DDIT4,PRKCH,PRKCZ,PPP2CA	0.00128825
ERK5 Signaling	RALB,YWHAQ,RPS6KA2,PRKCZ	0.002630268
Glioma Signaling	IGF1R,RALB,RBL2,PRKCH,PRKCZ	0.002951209
UDP-N-acetyl-D-galactosamine Biosynthesis II	HK2,GPI	0.003467369
ErbB4 Signaling	RALB,NCSTN,PRKCH,PRKCZ	0.003548134
Myc Mediated Apoptosis Signaling	IGF1R,RALB,YWHAQ,PRKCZ	0.003548134
Fc Epsilon RI Signaling	RALB,IL4,PRKCH,PRKCZ,MS4A2	0.003715352
Growth Hormone Signaling	IGF1R,RPS6KA2,PRKCH,PRKCZ	0.005011872
HIPPO signaling	PATJ,YWHAQ,PRKCZ,PPP2CA	0.005011872
α-Adrenergic Signaling	RALB,ADCY3,PRKCH,PRKCZ	0.006606934
UVC-Induced MAPK Signaling	RALB,PRKCH,PRKCZ	0.007079458
Hepatic Cholestasis	ADCY3,IL4,PRKCH,PRKCZ,NR0B2	0.009549926
ErbB Signaling	RALB,PRKCH,PRKCZ,NCK1	0.01023293
Melanocyte Development and Pigmentation Signaling	RALB,ADCY3,RPS6KA2,MITF	0.01023293
IGF-1 Signaling	IGF1R,RALB,YWHAQ,PRKCZ	0.013182567
Synaptic Long Term Depression	IGF1R,RALB,PRKCH,PRKCZ,PPP2CA	0.013803843
RAR Activation	ADCY3,SMARCD3,PRKCH,PRKCZ,CITED2	0.018197009
Natural Killer Cell Signaling	RALB,PRKCH,PRKCZ,NCK1	0.018197009
PI3K/AKT Signaling	RALB,YWHAQ,PRKCZ,PPP2CA	0.019952623
Renin-Angiotensin Signaling	RALB,ADCY3,PRKCH,PRKCZ	0.020417379
Thrombopoietin Signaling	RALB,PRKCH,PRKCZ	0.020417379
Estrogen Receptor Signaling	POLR2B,RALB,MED27,NR0B2	0.023442288
14-3-3-mediated Signaling	RALB,YWHAQ,PRKCH,PRKCZ	0.025703958
P2Y Purigenic Receptor Signaling Pathway	RALB,ADCY3,PRKCH,PRKCZ	0.027542287
Breast Cancer Regulation by Stathmin1	RALB,ADCY3,PRKCH,PRKCZ,PPP2CA	0.028183829
Insulin Receptor Signaling	RALB,RPTOR,PRKCZ,NCK1	0.029512092
Angiopoietin Signaling	RALB,ANGPT2,NCK1	0.030902954
CREB Signaling in Neurons	POLR2B,RALB,ADCY3,PRKCH,PRKCZ	0.032359366
Airway Inflammation in Asthma	IL4,	0.032359366
Role of NFAT in Cardiac Hypertrophy	IGF1R,RALB,ADCY3,PRKCH,PRKCZ	0.034673685
Erythropoietin Signaling	RALB,PRKCH,PRKCZ	0.034673685
IL-3 Signaling	RALB,PRKCH,PRKCZ	0.034673685
Macropinocytosis Signaling	RALB,PRKCH,PRKCZ	0.034673685
Prolactin Signaling	RALB,PRKCH,PRKCZ	0.036307805
Neuregulin Signaling	RALB,PRKCH,PRKCZ	0.038904514
Fcγ Receptor-mediated Phagocytosis in Macrophages and Monocytes	PRKCH,PRKCZ,NCK1	0.039810717
LPS-stimulated MAPK Signaling	RALB,PRKCH,PRKCZ	0.040738028

NF-kB Activation by Viruses	RALB,PRKCH,PRKCZ	0.040738028
Dopamine-DARPP32 Feedback in cAMP Signaling	ADCY3,PRKCH,PRKCZ,PPP2CA	0.040738028
Rapoport-Luebering Glycolytic Shunt	PGAM2,	0.040738028
Trehalose Degradation II (Trehalase)	HK2,	0.040738028
HER-2 Signaling in Breast Cancer	RALB,PRKCH,PRKCZ	0.041686938
VEGF Family Ligand-Receptor Interactions	RALB,PRKCH,PRKCZ	0.041686938
Mechanisms of Viral Exit from Host Cells	PRKCH,PRKCZ	0.044668359
Triacylglycerol Biosynthesis	LPIN1,LPCAT2	0.044668359
Ceramide Signaling	RALB,PRKCZ,PPP2CA	0.044668359
Tight Junction Signaling	PATJ,NAPA,PRKCZ,PPP2CA	0.045708819
eNOS Signaling	ADCY3,SLC7A1,PRKCH,PRKCZ	0.046773514
PPAR Signaling	RALB,CITED2,NR0B2	0.046773514
GDP-mannose Biosynthesis	GPI,	0.047863009
Opioid Signaling Pathway	RALB,ADCY3,RPS6KA2,PRKCH,PRKCZ	0.047863009
GNRH Signaling	RALB,ADCY3,PRKCH,PRKCZ	0.048977882

DISEASES AND BIOLOGICAL FUNCTIONS

Category	**Disease and Biological Function***	**P-value**	**Genes**
Cell-To-Cell Signaling and Interaction	Activation of basophils	1.97E-07	PRG2,PTGDR2,IL4,EPX,PRG3
	Activation of myeloid cells	0.000194	IRF6,PRG2,PTGDR2,SIGLEC8,ANGPT2,FOXP1,TFF2,IL4,METRNL,IL5RA,EPX,PRG3
	Activation of granulocytes	0.000552	PRG2,PTGDR2,IL4,IL5RA,EPX,PRG3
	Inflammatory response of tumor cell lines	0.00136	CTSB,ENG
	Activation of phagocytes	0.00156	IRF6,PRG2,SIGLEC8,ANGPT2,FOXP1,TFF2,IL4,METRNL,EPX,RNASE2,PRG3
	Activation of eosinophils	0.00168	PTGDR2,IL4,IL5RA
	Immune response of tumor cell lines	0.00263	RALB,DICER1,FOXP1,CTSB,IL4,ENG
	Activation of mast cells	0.00304	PRG2,SIGLEC8,IL4,EPX
	Activation of cells	0.00308	PRG2,TANK,SIGLEC8,PTGDR2,ANGPT2,FOXP1,DDIT4,IL4,METRNL,IL5RA,PRG3,CLEC12A,IRF6,RPTOR,TFF2,EPX,PRKCZ,NCK1,BANK1,RNASE2,PPP2CA
	Contact growth inhibition	0.00341	IGF1R,RBL2,IL4,IKZF3,PRKCZ,GPI
	Priming of synaptic vesicles	0.00653	NAPA,STX1B
	Recruitment of muscle cells	0.00653	IL4,ENG
	Activation of blood cells	0.00675	PRG2,SIGLEC8,PTGDR2,ANGPT2,FOXP1,IL4,METRNL,IL5RA,PRG3,IRF6,RPTOR,TFF2,EPX,NCK1,BANK1,RNASE2
	Detachment of cells	0.00719	IGF1R,ANGPT2,NAPA,ENG
	Activation of Th2 cells	0.00742	PTGDR2,IL4
	Activation of leukocytes	0.00789	PRG2,PTGDR2,SIGLEC8,ANGPT2,FOXP1,IL4,METRNL,IL5RA,PRG3,IRF6,TFF2,EPX,BANK1,NCK1,RNASE2
	Fusion of myotube	0.00836	IGF1R,IL4
	Fusion of plasma membrane	0.0138	RALB,NAPA
	Stimulation of epithelial cells	0.0151	IL4,EPX
Hematological System Development and Function	Activation of basophils	1.97E-07	PRG2,PTGDR2,IL4,EPX,PRG3
	Activation of myeloid cells	0.000194	IRF6,PRG2,PTGDR2,SIGLEC8,ANGPT2,FOXP1,TFF2,IL4,METRNL,IL5RA,EPX,PRG3
	Proliferation of B lymphocytes	0.000195	TANK,LPIN1,RPTOR,DICER1,PCYT1A,RBL2,IL4,IL5RA,IKZF3,PRKCZ,BANK1
	Abnormal morphology of eosinophils	0.000199	PRG2,EPX
	Activation of granulocytes	0.000552	PRG2,PTGDR2,IL4,IL5RA,EPX,PRG3
	Quantity of naive B cells	0.000656	IL4,IKZF3
	Abnormal morphology of reticulocytes	0.000979	SLC7A1,STEAP3

	Quantity of B-1 lymphocytes	0.00101	RPTOR,IL4,IL5RA,ARID3A,BANK1
	Morphology of lymph follicle	0.00112	IL4,IKZF3,PRKCZ,TLE4,BANK1,PPT2
	Proliferation of lymphocytes	0.00119	TANK,SLC7A1,RBL2,IL4,IL5RA,IKZF3,IRF6,IGF1R,NCSTN,LPIN1,RPTOR,DICER1,PCYT1A,PRKCH,PRKCZ,BANK1,NCK1,GPI
	Migration of basophils	0.00136	PTGDR2,ENG
	Activation of phagocytes	0.00156	IRF6,PRG2,SIGLEC8,ANGPT2,FOXP1,TFF2,IL4,METRNL,EPX,RNASE2,PRG3
	Granulopoiesis	0.00159	IGF1R,ZFPM1,RALB,SIGLEC8,IL4,CITED2
	Activation of eosinophils	0.00168	PTGDR2,IL4,IL5RA
	Morphology of granulocytes	0.00246	PRG2,IL4,EPX
	Homing of Th2 cells	0.00287	PTGDR2,IL4
	Activation of mast cells	0.00304	PRG2,SIGLEC8,IL4,EPX
	Quantity of blood cells	0.00333	TANK,SIGLEC8,PTGDR2,SLC7A1,RBL2,BNIP3L,IL4,IL5RA,IKZF3,IRF6,IGF1R,RPTOR,DICER1,CTSB,STEAP3,PRKCH,ARID3A,BANK1,TLE4,ST3GAL1,PPT2,PPP2CA
	Survival of follicular B lymphocytes	0.00349	DICER1,IL4
	Myelopoiesis of leukocytes	0.00393	IGF1R,ZFPM1,RALB,SIGLEC8,FOXP1,IL4,CITED2
	Quantity of B-1a lymphocytes	0.00397	RPTOR,ARID3A,BANK1
	Quantity of B lymphocytes	0.00447	TANK,RPTOR,CTSB,IL4,IL5RA,PRKCH,IKZF3,ARID3A,BANK1,TLE4
	Migration of B-lymphocyte derived cell lines	0.00653	PTGDR2,ENG
	Proliferation of germinal center B lymphocytes	0.00653	DICER1,IL4
	Activation of blood cells	0.00675	PRG2,SIGLEC8,PTGDR2,ANGPT2,FOXP1,IL4,METRNL,IL5RA,PRG3,IRF6,RPTOR,TFF2,EPX,NCK1,BANK1,RNASE2
	Quantity of myeloid cells	0.0073	IRF6,IGF1R,PTGDR2,SIGLEC8,RBL2,CTSB,IL4,IL5RA,ARID3A,TLE4,PPT2,PPP2CA
	Activation of Th2 cells	0.00742	PTGDR2,IL4
	Development of plasma cells	0.00742	DICER1,IL4
	Activation of leukocytes	0.00789	PRG2,PTGDR2,SIGLEC8,ANGPT2,FOXP1,IL4,METRNL,IL5RA,PRG3,IRF6,TFF2,EPX,BANK1,NCK1,RNASE2
	Quantity of leukocytes	0.00815	TANK,SIGLEC8,PTGDR2,RBL2,IL4,IL5RA,IKZF3,IRF6,IGF1R,RPTOR,DICER1,CTSB,PRKCH,ARID3A,BANK1,TLE4,ST3GAL1,PPT2,PPP2CA
	Development of PBMCs	0.00836	DICER1,IL4
	Differentiation of memory B cells	0.00836	FOXP1,IL4
	Cellular infiltration by granulocytes	0.00869	IRF6,PTGDR2,SIGLEC8,ANGPT2,DICER1,CTSB,IL4
	Differentiation of eosinophils	0.00936	SIGLEC8,IL4
	Leukopoiesis	0.00985	ZFPM1,SIGLEC8,FOXP1,RBL2,IL4,IL5RA,IKZF3,CITED2,NR0B2,IGF1R,RALB,RPTOR,DICER1,PRKCH,PRKCZ,ARID3A,TLE4
	Hematopoiesis in embryo	0.0114	ZFPM1,ENG,ARID3A
	Migration of Langerhans cells	0.0115	RPTOR,IL4
	Abnormal morphology of germinal center	0.015	IL4,IKZF3,BANK1
	Abnormal morphology of lymphoid organ	0.0151	BNIP3L,STEAP3,IL5RA,PRKCH,IKZF3,BANK1,TLE4,CITED2,PPT2
	Morphology of lymphoid tissue	0.0162	RBL2,BNIP3L,STEAP3,IL4,IL5RA,PRKCH,IKZF3,PRKCZ,BANK1,TLE4,CITED2,PPT2
Hypersensitivity Response	Activation of basophils	1.97E-07	PRG2,PTGDR2,IL4,EPX,PRG3
	Abnormal morphology of eosinophils	0.000199	PRG2,EPX
	Migration of basophils	0.00136	PTGDR2,ENG
	Activation of eosinophils	0.00168	PTGDR2,IL4,IL5RA
	Activation of mast cells	0.00304	PRG2,SIGLEC8,IL4,EPX
	Degranulation of BMMC cells	0.0126	IL4,EHF
Immune Cell Trafficking	Activation of basophils	1.97E-07	PRG2,PTGDR2,IL4,EPX,PRG3

	Activation of granulocytes	0.000552	PRG2,PTGDR2,IL4,IL5RA,EPX,PRG3
	Migration of basophils	0.00136	PTGDR2,ENG
	Activation of phagocytes	0.00156	IRF6,PRG2,SIGLEC8,ANGPT2,FOXP1,TFF2,IL4,METRNL,EPX,RNASE2,PRG3
	Activation of eosinophils	0.00168	PTGDR2,IL4,IL5RA
	Homing of Th2 cells	0.00287	PTGDR2,IL4
	Activation of mast cells	0.00304	PRG2,SIGLEC8,IL4,EPX
	Migration of B-lymphocyte derived cell lines	0.00653	PTGDR2,ENG
	Activation of Th2 cells	0.00742	PTGDR2,IL4
	Activation of leukocytes	0.00789	PRG2,PTGDR2,SIGLEC8,ANGPT2,FOXP1,IL4,METRNL,IL5RA,PRG3,IRF6,TFF2,EPX,BANK1,NCK1,RNASE2
	Cellular infiltration by granulocytes	0.00869	IRF6,PTGDR2,SIGLEC8,ANGPT2,DICER1,CTSB,IL4
	Migration of Langerhans cells	0.0115	RPTOR,IL4
Inflammatory Response	Activation of basophils	1.97E-07	PRG2,PTGDR2,IL4,EPX,PRG3
	Activation of granulocytes	0.000552	PRG2,PTGDR2,IL4,IL5RA,EPX,PRG3
	Inflammatory response of tumor cell lines	0.00136	CTSB,ENG
	Activation of phagocytes	0.00156	IRF6,PRG2,SIGLEC8,ANGPT2,FOXP1,TFF2,IL4,METRNL,EPX,RNASE2,PRG3
	Activation of eosinophils	0.00168	PTGDR2,IL4,IL5RA
	Degranulation of cells	0.00183	ZFPM1,PRG2,RALB,LPIN1,DICER1,IL4,EHF,MS4A2
	Immune response of tumor cell lines	0.00263	RALB,DICER1,FOXP1,CTSB,IL4,ENG
	Activation of mast cells	0.00304	PRG2,SIGLEC8,IL4,EPX
	Inflammatory response	0.00327	PRG2,DAPK2,PTGDR2,ANGPT2,FOXP1,IL4,METRNL,ENG,PRG3,CLEC12A,MS4A2,IRF6,RALB,DICER1,TFF2,CTSB,EPX,RNASE2
	Activation of Th2 cells	0.00742	PTGDR2,IL4
	Activation of leukocytes	0.00789	PRG2,PTGDR2,SIGLEC8,ANGPT2,FOXP1,IL4,METRNL,IL5RA,PRG3,IRF6,TFF2,EPX,BANK1,NCK1,RNASE2
	Size of phagocytes	0.0104	RPTOR,IL4
	Antiviral response	0.0109	SERINC5,DICER1,BNIP3L,IL4,DDIT4,RNASE2
	Migration of Langerhans cells	0.0115	RPTOR,IL4
	Degranulation of BMMC cells	0.0126	IL4,EHF
Carbohydrate Metabolism	Glycolysis of cells	3.26E-06	IGF1R,RPTOR,IL4,DDIT4,FBP1,PGAM2,HK2,CITED2,GPI
	Modification of glucose-6-phosphate	0.000396	HK2,GPI
	Flux of carbohydrate	0.000846	PCYT1A,PGAM2,GPI
	Flux of D-glucose	0.000979	PGAM2,GPI
	Metabolism of monosaccharide	0.00479	IGF1R,NISCH,FBP1,HK2,GPI
	Catabolism of proteoglycan	0.00836	CTSB,IL4
	Metabolism of D-hexose	0.00957	IGF1R,NISCH,FBP1,HK2
	Gluconeogenesis	0.0102	SOGA1,FBP1,PGAM2,NR0B2
Cell Death and Survival	Cell death of epithelial cells	3.54E-05	PRG2,ITIH4,YWHAQ,RBL2,BNIP3L,IL4,ENG,MITF,CITED2,NR0B2,IGF1R,DICER1,CTSB,EPX,HK2,PMP22,PPP2CA
	Necrosis of epithelial tissue	0.000119	PRG2,ITIH4,YWHAQ,ANGPT2,RBL2,BNIP3L,IL4,ENG,MITF,CITED2,NR0B2,IGF1R,DICER1,CTSB,EPX,HK2,PMP22,PPP2CA
	Necrosis	0.000612	DAPK2,RBL2,BNIP3L,EHF,MITF,RALB,LRIG1,DICER1,ATP2C1,EMG1,PRKCH,NCK1,TLE4,GPI,DDIT4,ENG,CITED2,IGF1R,RPTOR,RPS6KA2,CS,PPT2,YWHAQ,SIGLEC8,FOXP1,RHOBTB2,NAPA,IKZF3,MS4A2,STEAP3,STX1B,EPX,PRKCZ,HK2,TLDC2,ST3GAL1,PMP22,PPP2CA,PRG2,ITIH4,TANK,PTGDR2,ANGPT2,IL4,IL5RA,NR0B2,CTSB,FOXK2,RNASE2
	Cell death of connective tissue cells	0.00255	TANK,RBL2,BNIP3L,DDIT4,IL4,ENG,NR0B2,IGF1R,RALB,DICER1,RPS6KA2,CTSB,PRKCZ,NCK1,GPI
	Survival of follicular B lymphocytes	0.00349	DICER1,IL4
	Apoptosis of hepatoma cell lines	0.00391	IGF1R,CTSB,IL4,PRKCZ,PPP2CA,NR0B2

	Cell death of blood cells	0.004	DAPK2,SIGLEC8,FOXP1,BNIP3L,DDIT4,IL4,IL5RA,IKZF3,MS4A2,LRIG1,RPTOR,DICER1,CTSB,PRKCZ,TLE4,ST3GAL1
	Apoptosis of tumor	0.00417	IGF1R,ANGPT2
	Cell death of lymphatic system cells	0.00457	LRIG1,DICER1,FOXP1,CTSB,BNIP3L,STEAP3,DDIT4,IL4,IL5RA,TLE4,ST3GAL1
	Cell death of immune cells	0.0054	DAPK2,SIGLEC8,FOXP1,DDIT4,IL4,IL5RA,IKZF3,MS4A2,LRIG1,RPTOR,DICER1,CTSB,PRKCZ,TLE4,ST3GAL1
	Cell death of lung cells	0.00595	IGF1R,PRG2,EPX
	Cell death of embryonic cell lines	0.00617	IGF1R,TANK,YWHAQ,RBL2,CTSB,BNIP3L,DDIT4,HK2,CITED2,PMP22
	Apoptosis	0.00701	DAPK2,YWHAQ,SIGLEC8,FOXP1,RHOBTB2,RBL2,NAPA,BNIP3L,EHF,IKZF3,MITF,MS4A2,KCNH2,RALB,LRIG1,DICER1,ATP2C1,STEAP3,PRKCH,PRKCZ,HK2,NCK1,ST3GAL1,TLE4,GPI,PMP22,PPP2CA,ITIH4,ANGPT2,DAP,DDIT4,IL4,IL5RA,ENG,CITED2,NR0B2,IGF1R,NCSTN,RPTOR,RPS6KA2,CTSB,CS,FOXK2,PPT2
	Cell death	0.00769	DAPK2,RBL2,BNIP3L,EHF,MITF,RALB,LRIG1,DICER1,ATP2C1,EMG1,PRKCH,NCK1,TLE4,GPI,DAP,DDIT4,ENG,PRG3,CITED2,IGF1R,RPTOR,RPS6KA2,CS,PPT2,YWHAQ,SIGLEC8,FOXP1,RHOBTB2,NAPA,IKZF3,MS4A2,KCNH2,KRT19,STEAP3,STX1B,EPX,PRKCZ,HK2,TLDC2,ST3GAL1,PMP22,PPP2CA,PRG2,ITIH4,TANK,PTGDR2,ANGPT2,IL4,IL5RA,NR0B2,NCSTN,CTSB,FOXK2,RNASE2
	Cell death of mononuclear leukocytes	0.00868	LRIG1,DICER1,FOXP1,CTSB,DDIT4,IL4,IL5RA,TLE4,ST3GAL1,MS4A2
	Apoptosis of hepatocytes	0.00904	ITIH4,DICER1,CTSB,IL4,NR0B2
	Apoptosis of epithelial cells	0.00929	ITIH4,DICER1,RBL2,CTSB,IL4,ENG,MITF,NR0B2
	Cell death of B lymphocytes	0.01	LRIG1,DICER1,FOXP1,CTSB,IL4
	Cell viability of cancer cells	0.0113	IGF1R,RALB,IL4,MITF
	Cell death of pneumocytes	0.0138	PRG2,EPX
	Cell viability of muscle cell lines	0.0138	IGF1R,CTSB
	Cell viability of muscle cells	0.015	IGF1R,ANGPT2,HK2
	Apoptosis of lymphatic system cells	0.0163	LRIG1,DICER1,FOXP1,BNIP3L,STEAP3,IL4,IL5RA,ST3GAL1,TLE4
Organismal Injury and Abnormalities	Cell death of epithelial cells	3.54E-05	PRG2,ITIH4,YWHAQ,RBL2,BNIP3L,IL4,ENG,MITF,CITED2,NR0B2,IGF1R,DICER1,CTSB,EPX,HK2,PMP22,PPP2CA
	Necrosis of epithelial tissue	0.000119	PRG2,ITIH4,YWHAQ,ANGPT2,RBL2,BNIP3L,IL4,ENG,MITF,CITED2,NR0B2,IGF1R,DICER1,CTSB,EPX,HK2,PMP22,PPP2CA
	Inhibition of tumor cells	0.000402	DDIT4,IL4,HK2
	Goiter	0.000474	IGF1R,KRT19,DICER1
	Inhibition of mammary tumor cells	0.000656	IL4,HK2
	Colony formation of tumor cells	0.000996	DICER1,RHOBTB2,CTSB,SUGT1
	Immortalization of fibroblasts	0.00122	RBL2,PGAM2,ARID3A
	Abnormal ratio tissue	0.00145	KRT19,IL5RA,ENG,PRKCZ,MS4A2
	Failure of heart looping	0.00225	NCSTN,RBL2,ENG
	Chronic idiopathic urticaria	0.00231	IL5RA,MS4A2
	Growth of pancreatic endocrine tumor	0.00287	CTSB,ENG
	Metastasis of colorectal cancer cell lines	0.00291	IGF1R,DICER1,RPTOR
	Development of angioma	0.00352	ANGPT2,DICER1,IKZF3,KAT6B
	Precancerous condition	0.00368	IL4,ENG,PRKCH,ASCC1,PRKCZ
	Apoptosis of tumor	0.00417	IGF1R,ANGPT2
	Nodular goiter	0.00417	KRT19,DICER1
	Colony formation of cancer cells	0.00426	DICER1,CTSB,SUGT1
	Follicular thyroid tumor	0.00462	KRT19,ANGPT2,CTSB,ENG
	Skin papilloma	0.00523	ATP2C1,ENG,PRKCH
	Damage of hepatocytes	0.00569	IGF1R,DICER1
	Polyp	0.00593	IL5RA,ENG,PRKCZ,MS4A2

	Abnormal morphology of hair follicle	0.00595	IGF1R,DICER1,RBL2
	Cell death of lung cells	0.00595	IGF1R,PRG2,EPX
	Abnormal morphology of epidermis	0.00668	IGF1R,LRIG1,DICER1,RBL2,CTSB
	Hydronephrosis	0.00693	IGF1R,SLC2A9,IL4,NFIA
	Diabetes mellitus	0.0077	ITIH4,COL15A1,FOXP1,SLC17A4,IL4,NISCH,IKZF3,CLEC12A,NR0B2,KCNH2,IGF1R,SLC2A9,LRIG1,PCYT1A,CTSB,MED27,FBP1,HK2,BANK1,DLGAP2,PPT2
	Hereditary myopathy	0.00857	LPIN1,PTGDR2,AP5B1,BNIP3L,ENG,SLC25A33,KIF26A,ASCC1,ATPAF2,CYB561,PMP22,KCNH2
	Apoptosis of hepatocytes	0.00904	ITIH4,DICER1,CTSB,IL4,NR0B2
	Apoptosis of epithelial cells	0.00929	ITIH4,DICER1,RBL2,CTSB,IL4,ENG,MITF,NR0B2
	Hemangioblastoma	0.0104	DICER1,IKZF3,KAT6B
	Polyposis	0.0104	IL5RA,ENG,MS4A2
	Parakeratosis	0.0104	LRIG1,RBL2
	Hemangioma	0.0108	IGF1R,ANGPT2,DICER1,IKZF3,KAT6B
	Juvenile dermatomyositis	0.0109	BNIP3L,ENG,CYB561
	Neurodegeneration of cerebellum	0.0109	DICER1,CTSB,PPT2
	Cell viability of cancer cells	0.0113	IGF1R,RALB,IL4,MITF
	Congenital malformation of brain	0.0123	RALB,KIF5C,RPTOR,DICER1,ATP2C1,EMG1,NFIA,CITED2,KIF3B
	Autosomal dominant Emery-Dreifuss muscular dystrophy	0.0125	BNIP3L,ENG,CYB561
	Proliferation of ovarian cancer cells	0.0126	IGF1R,PPP2CA
	Lymphatic system tumor	0.013	FOXP1,RBL2,ATXN7L1,LPCAT2,IKZF3,BAG2,KCNH2,POLR2B,TRAPPC9,LPIN1,TNIK,LRIG1,ADCY3,DICER1,STEAP3,EGFLAM,PRKCZ,HK2,PPP2CA,ANGPT2,COL15A1,DAP,IL4,ENG,PSMC3IP,CITED2,IGF1R,RPTOR,ACP5,SHANK2,TMEM131,SMARCD3
	Cell death of pneumocytes	0.0138	PRG2,EPX
	Injury of renal glomerulus	0.0138	ANGPT2,DICER1
	Metastasis of tumor cell lines	0.0145	IGF1R,RALB,ANGPT2,RPTOR,DICER1,CTSB,GPI
	Abnormal morphology of germinal center	0.015	IL4,IKZF3,BANK1
	Familial pervasive developmental disorder	0.0151	FOXP1,SHANK2
	Abnormal morphology of lymphoid organ	0.0151	BNIP3L,STEAP3,IL5RA,PRKCH,IKZF3,BANK1,TLE4,CITED2,PPT2
	Neoplasia of leukocytes	0.0156	FOXP1,RBL2,ATXN7L1,LPCAT2,IKZF3,BAG2,MS4A2,KCNH2,TRAPPC9,LPIN1,TNIK,LRIG1,ADCY3,DICER1,STEAP3,EGFLAM,PRKCZ,HK2,PPP2CA,ANGPT2,COL15A1,DAP,IL4,ENG,PSMC3IP,CITED2,RPTOR,ACP5,SHANK2,TMEM131,SMARCD3
	Barrett syndrome	0.0156	IL4,ENG,ASCC1
Hematological Disease	Eosinophilia of tissue	0.000145	SIGLEC8,PTGDR2,IL4
	Anisopoikilocytosis	0.00231	SLC7A1,STEAP3
	Hypercholesterolemia	0.00593	ITIH4,LPIN1,RPTOR,NR0B2
	Neoplasia of leukocytes	0.0156	FOXP1,RBL2,ATXN7L1,LPCAT2,IKZF3,BAG2,MS4A2,KCNH2,TRAPPC9,LPIN1,TNIK,LRIG1,ADCY3,DICER1,STEAP3,EGFLAM,PRKCZ,HK2,PPP2CA,ANGPT2,COL15A1,DAP,IL4,ENG,PSMC3IP,CITED2,RPTOR,ACP5,SHANK2,TMEM131,SMARCD3
Immunological Disease	Eosinophilia of tissue	0.000145	SIGLEC8,PTGDR2,IL4
	Abnormal morphology of eosinophils	0.000199	PRG2,EPX
	Chronic idiopathic urticaria	0.00231	IL5RA,MS4A2
	Abnormal morphology of germinal center	0.015	IL4,IKZF3,BANK1
	Abnormal morphology of lymphoid organ	0.0151	BNIP3L,STEAP3,IL5RA,PRKCH,IKZF3,BANK1,TLE4,CITED2,PPT2

	Neoplasia of leukocytes	0.0156	FOXP1,RBL2,ATXN7L1,LPCAT2,IKZF3,BAG2,MS4A2,KCNH2,TRAPPC9,LPIN1,TNIK,LRIG1,ADCY3,DICER1,STEAP3,EGFLAM,PRKCZ,HK2,PPP2CA,ANGPT2,COL15A1,DAP,IL4,ENG,PSMC3IP,CITED2,RPTOR,ACP5,SHANK2,TMEM131,SMARCD3
Lipid Metabolism	Release of leukotriene	0.000186	PRG2,IL4,PRG3,MS4A2
	Release of eicosanoid	0.000315	IGF1R,PRG2,LPIN1,CTSB,IL4,PRG3,MS4A2
	Release of leukotriene C4	0.00074	PRG2,IL4,PRG3
	Catabolism of fatty acid	0.0151	LPIN1,ACOT7
Molecular Transport	Release of leukotriene	0.000186	PRG2,IL4,PRG3,MS4A2
	Release of eicosanoid	0.000315	IGF1R,PRG2,LPIN1,CTSB,IL4,PRG3,MS4A2
	Release of leukotriene C4	0.00074	PRG2,IL4,PRG3
	Flux of D-glucose	0.000979	PGAM2,GPI
	Priming of synaptic vesicles	0.00653	NAPA,STX1B
	Release of histamine	0.00712	PRG2,IL4,PRG3
	Exocytosis by eukaryotic cells	0.00842	IGF1R,NAPA,IL4
	Translocation of Ca2+	0.00936	SLC8B1,ATP2C1
Small Molecule Biochemistry	Release of leukotriene	0.000186	PRG2,IL4,PRG3,MS4A2
	Release of eicosanoid	0.000315	IGF1R,PRG2,LPIN1,CTSB,IL4,PRG3,MS4A2
	Modification of glucose-6-phosphate	0.000396	HK2,GPI
	Release of leukotriene C4	0.00074	PRG2,IL4,PRG3
	Flux of D-glucose	0.000979	PGAM2,GPI
	Release of histamine	0.00712	PRG2,IL4,PRG3
	Catabolism of proteoglycan	0.00836	CTSB,IL4
	Metabolism of D-hexose	0.00957	IGF1R,NISCH,FBP1,HK2
	Catabolism of fatty acid	0.0151	LPIN1,ACOT7
Cellular Development	Differentiation of tumor cell lines	0.000186	FOXP1,RBL2,IL4,IGF1R,TRAPPC9,DICER1,PCYT1A,ATP2C1,MCC,PRKCH,PRKCZ,NCK1,RNASE2
	Proliferation of B lymphocytes	0.000195	TANK,LPIN1,RPTOR,DICER1,PCYT1A,RBL2,IL4,IL5RA,IKZF3,PRKCZ,BANK1
	Colony formation of tumor cells	0.000996	DICER1,RHOBTB2,CTSB,SUGT1
	Proliferation of lymphocytes	0.00119	TANK,SLC7A1,RBL2,IL4,IL5RA,IKZF3,IRF6,IGF1R,NCSTN,LPIN1,RPTOR,DICER1,PCYT1A,PRKCH,PRKCZ,BANK1,NCK1,GPI
	Immortalization of fibroblasts	0.00122	RBL2,PGAM2,ARID3A
	Granulopoiesis	0.00159	IGF1R,ZFPM1,RALB,SIGLEC8,IL4,CITED2
	Myelination of cells	0.00257	SERINC5,DICER1,DDIT4,HEXA,PMP22
	Myelopoiesis of leukocytes	0.00393	IGF1R,ZFPM1,RALB,SIGLEC8,FOXP1,IL4,CITED2
	Colony formation of cancer cells	0.00426	DICER1,CTSB,SUGT1
	Morphogenesis of neurons	0.00452	CSRP1,NFIA,HEXA,KIF3B,IGF1R,RALB,TNIK,ADCY3,DICER1,FBXW8,SHANK2,LRP12,PRKCZ,PMP22,PPP2CA
	Delay in differentiation of cells	0.0049	IGF1R,ATP2C1,CTSB
	Proliferation of germinal center B lymphocytes	0.00653	DICER1,IL4
	Development of plasma cells	0.00742	DICER1,IL4
	Proliferation of skeletal muscle cells	0.00742	IGF1R,ANGPT2
	Development of PBMCs	0.00836	DICER1,IL4
	Differentiation of memory B cells	0.00836	FOXP1,IL4
	Proliferation of myofibroblasts	0.00836	CTSB,IL4
	Axonogenesis	0.00885	IGF1R,ADCY3,DICER1,NFIA,PRKCZ,PMP22,PPP2CA
	Differentiation of eosinophils	0.00936	SIGLEC8,IL4

	Differentiation of neuroblastoma cell lines	0.00936	IGF1R,PCYT1A,ATP2C1
	Epithelial-mesenchymal transition	0.00951	IGF1R,RPTOR,DICER1,SLC25A33,PRKCZ,GPI,PPP2CA
	Proliferation of liver cells	0.00961	IGF1R,ITIH4,DICER1,CTSB,IL4,CITED2
	Neuritogenesis	0.00966	CSRP1,NFIA,KIF3B,IGF1R,RALB,TNIK,ADCY3,DICER1,FBXW8,SHANK2,LRP12,PRKCZ,PMP22,PPP2CA
	Leukopoiesis	0.00985	ZFPM1,SIGLEC8,FOXP1,RBL2,IL4,IL5RA,IKZF3,CITED2,NR0B2,IGF1R,RALB,RPTOR,DICER1,PRKCH,PRKCZ,ARID3A,TLE4
	Hematopoiesis in embryo	0.0114	ZFPM1,ENG,ARID3A
	Cell proliferation of fibroblasts	0.0121	IGF1R,NCSTN,CTSB,IL4,ENG,PGAM2,ARID3A,CITED2,GPI
	Proliferation of ovarian cancer cells	0.0126	IGF1R,PPP2CA
	Cell proliferation of tumor cell lines	0.0128	DAPK2,YWHAQ,DMAP1,FOXP1,RHOBTB2,RBL2,EHF,MITF,IRF6,RALB,TNIK,LRIG1,KRT19,FBXW8,STEAP3,PRKCH,PRKCZ,HK2,ARID3A,TLE4,PPP2CA,ELOVL7,ANGPT2,IL4,ENG,IGF1R,NCSTN,RPTOR,TFF2,CTSB
	Differentiation of keratinocytes	0.0131	IRF6,LPIN1,LRIG1,RBL2,PRKCH
	Proliferation of hepatocytes	0.0137	IGF1R,ITIH4,DICER1,IL4,CITED2
	Myelination of axons	0.0138	DICER1,PMP22
	Proliferation of endocrine cells	0.0144	IGF1R,ANGPT2,DICER1,TFF2
Cellular Growth and Proliferation	Proliferation of B lymphocytes	0.000195	TANK,LPIN1,RPTOR,DICER1,PCYT1A,RBL2,IL4,IL5RA,IKZF3,PRKCZ,BANK1
	Inhibition of tumor cells	0.000402	DDIT4,IL4,HK2
	Inhibition of mammary tumor cells	0.000656	IL4,HK2
	Colony formation of tumor cells	0.000996	DICER1,RHOBTB2,CTSB,SUGT1
	Proliferation of lymphocytes	0.00119	TANK,SLC7A1,RBL2,IL4,IL5RA,IKZF3,IRF6,IGF1R,NCSTN,LPIN1,RPTOR,DICER1,PCYT1A,PRKCH,PRKCZ,BANK1,NCK1,GPI
	Proliferation of bone marrow cell lines	0.00145	IGF1R,RALB,RBL2,IL4,PPP2CA
	Granulopoiesis	0.00159	IGF1R,ZFPM1,RALB,SIGLEC8,IL4,CITED2
	Colony formation of cells	0.0021	DMAP1,RHOBTB2,RBL2,BNIP3L,IL4,EHF,MITF,IGF1R,KRT19,DICER1,CTSB,SUGT1,PRKCZ,PPP2CA
	Myelination of cells	0.00257	SERINC5,DICER1,DDIT4,HEXA,PMP22
	Contact growth inhibition	0.00341	IGF1R,RBL2,IL4,IKZF3,PRKCZ,GPI
	Myelopoiesis of leukocytes	0.00393	IGF1R,ZFPM1,RALB,SIGLEC8,FOXP1,IL4,CITED2
	Colony formation of cancer cells	0.00426	DICER1,CTSB,SUGT1
	Morphogenesis of neurons	0.00452	CSRP1,NFIA,HEXA,KIF3B,IGF1R,RALB,TNIK,ADCY3,DICER1,FBXW8,SHANK2,LRP12,PRKCZ,PMP22,PPP2CA
	Proliferation of germinal center B lymphocytes	0.00653	DICER1,IL4
	Colony formation of tumor cell lines	0.00654	IGF1R,KRT19,DMAP1,DICER1,RBL2,CTSB,IL4,EHF,MITF
	Proliferation of connective tissue cells	0.00708	RBL2,IL4,ENG,CITED2,IRF6,IGF1R,NCSTN,LRIG1,DICER1,CTSB,PRKCH,PGAM2,ARID3A,GPI
	Development of plasma cells	0.00742	DICER1,IL4
	Proliferation of skeletal muscle cells	0.00742	IGF1R,ANGPT2
	Development of PBMCs	0.00836	DICER1,IL4
	Differentiation of memory B cells	0.00836	FOXP1,IL4
	Proliferation of myofibroblasts	0.00836	CTSB,IL4
	Axonogenesis	0.00885	IGF1R,ADCY3,DICER1,NFIA,PRKCZ,PMP22,PPP2CA
	Differentiation of eosinophils	0.00936	SIGLEC8,IL4
	Proliferation of epithelial cells	0.00947	IRF6,IGF1R,NCSTN,ITIH4,LRIG1,DICER1,RBL2,IL4,MCC,ENG,PRKCH,CITED2
	Proliferation of liver cells	0.00961	IGF1R,ITIH4,DICER1,CTSB,IL4,CITED2
	Neuritogenesis	0.00966	CSRP1,NFIA,KIF3B,IGF1R,RALB,TNIK,ADCY3,DICER1,FBXW8,SHANK2,LRP12,PRKCZ,PMP22,PPP2CA
	Leukopoiesis	0.00985	ZFPM1,SIGLEC8,FOXP1,RBL2,IL4,IL5RA,IKZF3,CITED2,NR0B2,IGF1R,RALB,RPTOR,DICER1,PRKCH,PRKCZ,ARID3A,TLE4

	Hematopoiesis in embryo	0.0114	ZFPM1,ENG,ARID3A
	Cell proliferation of fibroblasts	0.0121	IGF1R,NCSTN,CTSB,IL4,ENG,PGAM2,ARID3A,CITED2,GPI
	Proliferation of heart cells	0.0124	DICER1,FOXP1,RBL2,CITED2
	Colony formation of stomach cancer cell lines	0.0126	IGF1R,DMAP1
	Proliferation of ovarian cancer cells	0.0126	IGF1R,PPP2CA
	Cell proliferation of tumor cell lines	0.0128	DAPK2,YWHAQ,DMAP1,FOXP1,RHOBTB2,RBL2,EHF,MITF,IRF6,RALB,TNIK,LRIG1,KRT19,FBXW8,STEAP3,PRKCH,PRKCZ,HK2,ARID3A,TLE4,PPP2CA,ELOVL7,ANGPT2,IL4,ENG,IGF1R,NCSTN,RPTOR,TFF2,CTSB
	Proliferation of hepatocytes	0.0137	IGF1R,ITIH4,DICER1,IL4,CITED2
	Myelination of axons	0.0138	DICER1,PMP22
	Proliferation of endocrine cells	0.0144	IGF1R,ANGPT2,DICER1,TFF2
	Stimulation of epithelial cells	0.0151	IL4,EPX
Humoral Immune Response	Proliferation of B lymphocytes	0.000195	TANK,LPIN1,RPTOR,DICER1,PCYT1A,RBL2,IL4,IL5RA,IKZF3,PRKCZ,BANK1
	Quantity of naive B cells	0.000656	IL4,IKZF3
	Quantity of B-1 lymphocytes	0.00101	RPTOR,IL4,IL5RA,ARID3A,BANK1
	Quantity of IgM	0.00108	TANK,IL4,IL5RA,IKZF3,ARID3A,BANK1
	Quantity of B-1a lymphocytes	0.00397	RPTOR,ARID3A,BANK1
	Quantity of IgA	0.00404	TANK,IL4,IL5RA,IKZF3
	Quantity of B lymphocytes	0.00447	TANK,RPTOR,CTSB,IL4,IL5RA,PRKCH,IKZF3,ARID3A,BANK1,TLE4
	Quantity of IgG1	0.0056	TANK,IL4,IL5RA,IKZF3,ARID3A
	Proliferation of germinal center B lymphocytes	0.00653	DICER1,IL4
	Development of plasma cells	0.00742	DICER1,IL4
	Differentiation of memory B cells	0.00836	FOXP1,IL4
	Quantity of IgG2a	0.0124	TANK,IL4,IKZF3,BANK1
	Abnormal morphology of germinal center	0.015	IL4,IKZF3,BANK1
Lymphoid Tissue Structure and Development	Proliferation of B lymphocytes	0.000195	TANK,LPIN1,RPTOR,DICER1,PCYT1A,RBL2,IL4,IL5RA,IKZF3,PRKCZ,BANK1
	Quantity of naive B cells	0.000656	IL4,IKZF3
	Quantity of B-1 lymphocytes	0.00101	RPTOR,IL4,IL5RA,ARID3A,BANK1
	Morphology of lymph follicle	0.00112	IL4,IKZF3,PRKCZ,TLE4,BANK1,PPT2
	Proliferation of lymphocytes	0.00119	TANK,SLC7A1,RBL2,IL4,IL5RA,IKZF3,IRF6,IGF1R,NCSTN,LPIN1,RPTOR,DICER1,PCYT1A,PRKCH,PRKCZ,BANK1,NCK1,GPI
	Granulopoiesis	0.00159	IGF1R,ZFPM1,RALB,SIGLEC8,IL4,CITED2
	Homing of Th2 cells	0.00287	PTGDR2,IL4
	Myelopoiesis of leukocytes	0.00393	IGF1R,ZFPM1,RALB,SIGLEC8,FOXP1,IL4,CITED2
	Quantity of B-1a lymphocytes	0.00397	RPTOR,ARID3A,BANK1
	Quantity of B lymphocytes	0.00447	TANK,RPTOR,CTSB,IL4,IL5RA,PRKCH,IKZF3,ARID3A,BANK1,TLE4
	Proliferation of germinal center B lymphocytes	0.00653	DICER1,IL4
	Development of plasma cells	0.00742	DICER1,IL4
	Development of PBMCs	0.00836	DICER1,IL4
	Differentiation of memory B cells	0.00836	FOXP1,IL4
	Differentiation of eosinophils	0.00936	SIGLEC8,IL4
	Leukopoiesis	0.00985	ZFPM1,SIGLEC8,FOXP1,RBL2,IL4,IL5RA,IKZF3,CITED2,NR0B2,IGF1R,RALB,RPTOR,DICER1,PRKCH,PRKCZ,ARID3A,TLE4
	Quantity of lymph follicle	0.0144	IKZF3,ARID3A,PRKCZ,BANK1,TLE4
	Abnormal morphology of germinal center	0.015	IL4,IKZF3,BANK1

	Abnormal morphology of lymphoid organ	0.0151	BNIP3L,STEAP3,IL5RA,PRKCH,IKZF3,BANK1,TLE4,CITED2,PPT2
	Morphology of lymphoid tissue	0.0162	RBL2,BNIP3L,STEAP3,IL4,IL5RA,PRKCH,IKZF3,PRKCZ,BANK1,TLE4,CITED2,PPT2
Cell Morphology	Abnormal morphology of eosinophils	0.000199	PRG2,EPX
	Autophagy of tumor cell lines	0.000208	KIF5C,YWHAQ,RPTOR,DICER1,BNIP3L,DDIT4,MITF,CATSPER4
	Morphology of blood cells	0.000254	ZFPM1,PRG2,SLC7A1,BNIP3L,IL4,IL5RA,MITF,CITED2,RPTOR,STEAP3,PRKCH,EPX,ARID3A,PRKCZ
	Autophagy	0.00033	DAPK2,KIF5C,YWHAQ,SOGA1,BNIP3L,DAP,DDIT4,ENG,MITF,CATSPER4,CLEC12A,IGF1R,RPTOR,DICER1
	Conversion of placental cells	0.000656	SMARCD3,MITF
	Orientation of axons	0.000656	NFIA,PRKCZ
	Abnormal morphology of reticulocytes	0.000979	SLC7A1,STEAP3
	Conversion of chondrocytes	0.000979	SMARCD3,MITF
	Autophagy of cells	0.00111	DAPK2,KIF5C,YWHAQ,RPTOR,DICER1,BNIP3L,DDIT4,ENG,MITF,CATSPER4
	Morphology of thyroid cells	0.00136	IGF1R,CTSB
	Transepithelial electrical resistance of cells	0.00168	IL4,PRKCZ,PPP2CA
	Morphology of granulocytes	0.00246	PRG2,IL4,EPX
	Morphology of hematopoietic progenitor cells	0.00341	ZFPM1,SLC7A1,RPTOR,STEAP3,ARID3A,CITED2
	Transepithelial electrical resistance of colorectal cancer cell lines	0.00349	IL4,PPP2CA
	Morphology of tumor cell lines	0.00441	IGF1R,IRF6,DICER1,RBL2,PRKCH,MITF,PRKCZ,GPI
	Morphogenesis of neurons	0.00452	CSRP1,NFIA,HEXA,KIF3B,IGF1R,RALB,TNIK,ADCY3,DICER1,FBXW8,SHANK2,LRP12,PRKCZ,PMP22,PPP2CA
	Cell flattening of tumor cell lines	0.00569	RBL2,PRKCH
	Size of antigen presenting cells	0.00653	RPTOR,IL4
	Reorganization of actin cytoskeleton	0.00707	LPIN1,TNIK,ATP2C1,ENG,PRKCZ
	Morphology of leukocytes	0.0075	PRG2,RPTOR,IL4,IL5RA,PRKCH,EPX,MITF,ARID3A,PRKCZ
	Axonogenesis	0.00885	IGF1R,ADCY3,DICER1,NFIA,PRKCZ,PMP22,PPP2CA
	Neuritogenesis	0.00966	CSRP1,NFIA,KIF3B,IGF1R,RALB,TNIK,ADCY3,DICER1,FBXW8,SHANK2,LRP12,PRKCZ,PMP22,PPP2CA
	Size of phagocytes	0.0104	RPTOR,IL4
	Abnormal morphology of hematopoietic progenitor cells	0.0108	ZFPM1,SLC7A1,STEAP3,ARID3A,CITED2
	Reorganization of cytoskeleton	0.0113	LPIN1,TNIK,ATP2C1,ENG,PRKCZ,MS4A2
	Permeability of colorectal cancer cell lines	0.0115	IL4,PPP2CA
	Enlargement of cells	0.0118	DAPK2,LPIN1,ANGPT2,DICER1,RPS6KA2,CTSB,IL4,PRKCH,PMP22
	Myelination of axons	0.0138	DICER1,PMP22
Cellular Function and Maintenance	Autophagy of tumor cell lines	0.000208	KIF5C,YWHAQ,RPTOR,DICER1,BNIP3L,DDIT4,MITF,CATSPER4
	Autophagy	0.00033	DAPK2,KIF5C,YWHAQ,SOGA1,BNIP3L,DAP,DDIT4,ENG,MITF,CATSPER4,CLEC12A,IGF1R,RPTOR,DICER1
	Autophagy of cells	0.00111	DAPK2,KIF5C,YWHAQ,RPTOR,DICER1,BNIP3L,DDIT4,ENG,MITF,CATSPER4
	Organization of actin cytoskeleton	0.00125	RALB,LPIN1,TNIK,CSRP1,ATP2C1,ENG,EVL,PRKCZ,NCK1,GPI
	Cellular homeostasis	0.00184	ZFPM1,DAPK2,YWHAQ,FOXP1,SOGA1,RBL2,BNIP3L,SLC25A33,MITF,MS4A2,KCNH2,DICER1,ATP2C1,PRKCH,PRKCZ,GPI,PPP2CA,KIF5C,ANGPT2,SLC25A25,SLC8B1,DAP,DDIT4,IL4,IL5RA,ENG,CATSPER4,CLEC12A,NR0B2,IGF1R,NCSTN,RPTOR
	Instability of microtubules	0.00417	KIF5C,KIF3B
	Priming of synaptic vesicles	0.00653	NAPA,STX1B
	Reorganization of actin cytoskeleton	0.00707	LPIN1,TNIK,ATP2C1,ENG,PRKCZ
	Exocytosis by eukaryotic cells	0.00842	IGF1R,NAPA,IL4
	Axonogenesis	0.00885	IGF1R,ADCY3,DICER1,NFIA,PRKCZ,PMP22,PPP2CA

	Neuritogenesis	0.00966	CSRP1,NFIA,KIF3B,IGF1R,RALB,TNIK,ADCY3,DICER1,FBXW8,SHANK2,LRP12,PRKCZ,PMP22,PPP2CA
	Reorganization of cytoskeleton	0.0113	LPIN1,TNIK,ATP2C1,ENG,PRKCZ,MS4A2
	Permeability of colorectal cancer cell lines	0.0115	IL4,PPP2CA
	Myelination of axons	0.0138	DICER1,PMP22
	Homeostasis of blood cells	0.0139	ZFPM1,FOXP1,RBL2,IL4,IL5RA,NR0B2,IGF1R,NCSTN,RPTOR,DICER1,PRKCH,PRKCZ,GPI
	Organization of cytoplasm	0.0142	SEC16B,CSRP1,SLC25A33,HEXA,MS4A2,LPIN1,RALB,TNIK,ADCY3,DICER1,FBXW8,ATP2C1,LRP12,PRKCH,PRKCZ,NCK1,GPI,PMP22,PPP2CA,KIF5C,ANGPT2,ENG,NFIA,ATL3,KIF3B,IGF1R,SHANK2,EVL
Cell Cycle	Arrest in G1 phase of keratinocytes	0.000396	LPIN1,PRKCH
	Homologous pairing of DNA	0.000979	EVL,PSMC3IP
	Arrest in cell cycle progression	0.00225	IGF1R,IRF6,KRT19,RPTOR,RBL2,DDIT4,EHF,PRKCH,PGAM2,MITF
	Arrest in cell cycle progression of tumor cell lines	0.00341	IGF1R,KRT19,RBL2,DDIT4,EHF,PRKCH
	Contact growth inhibition	0.00341	IGF1R,RBL2,IL4,IKZF3,PRKCZ,GPI
	Cell cycle progression of prostate cancer cell lines	0.00341	LRIG1,DDIT4,EHF
	Fission	0.00426	SEC16B,LPIN1,RPTOR
	Cell cycle progression of tumor cell lines	0.00656	IGF1R,KRT19,LRIG1,RHOBTB2,RBL2,DDIT4,EHF,PRKCH
	Cell cycle progression	0.00868	RHOBTB2,RBL2,DDIT4,IL4,EHF,MITF,IKZF3,CITED2,IRF6,IGF1R,LRIG1,KRT19,RPTOR,DICER1,RPS6KA2,SUGT1,PRKCH,PGAM2,PRKCZ,GPI,PPP2CA
	Arrest in cell cycle progression of prostate cancer cell lines	0.0115	DDIT4,EHF
Hair and Skin Development and Function	Arrest in G1 phase of keratinocytes	0.000396	LPIN1,PRKCH
	Transepithelial electrical resistance of cells	0.00168	IL4,PRKCZ,PPP2CA
	Transepithelial electrical resistance of colorectal cancer cell lines	0.00349	IL4,PPP2CA
	Differentiation of keratinocytes	0.0131	IRF6,LPIN1,LRIG1,RBL2,PRKCH
Cancer	Inhibition of tumor cells	0.000402	DDIT4,IL4,HK2
	Inhibition of mammary tumor cells	0.000656	IL4,HK2
	Transformation of prostate cancer cell lines	0.000656	IGF1R,DDIT4
	Colony formation of tumor cells	0.000996	DICER1,RHOBTB2,CTSB,SUGT1
	Immortalization of fibroblasts	0.00122	RBL2,PGAM2,ARID3A
	Growth of pancreatic endocrine tumor	0.00287	CTSB,ENG
	Metastasis of colorectal cancer cell lines	0.00291	IGF1R,DICER1,RPTOR
	Development of angioma	0.00352	ANGPT2,DICER1,IKZF3,KAT6B
	Precancerous condition	0.00368	IL4,ENG,PRKCH,ASCC1,PRKCZ
	Apoptosis of tumor	0.00417	IGF1R,ANGPT2
	Colony formation of cancer cells	0.00426	DICER1,CTSB,SUGT1
	Follicular thyroid tumor	0.00462	KRT19,ANGPT2,CTSB,ENG
	Skin papilloma	0.00523	ATP2C1,ENG,PRKCH
	Hyperplasia of cell lines	0.00836	IGF1R,IL4
	Hemangioblastoma	0.0104	DICER1,IKZF3,KAT6B
	Polyposis	0.0104	IL5RA,ENG,MS4A2
	Hemangioma	0.0108	IGF1R,ANGPT2,DICER1,IKZF3,KAT6B
	Cell viability of cancer cells	0.0113	IGF1R,RALB,IL4,MITF
	Proliferation of ovarian cancer cells	0.0126	IGF1R,PPP2CA
	Lymphatic system tumor	0.013	FOXP1,RBL2,ATXN7L1,LPCAT2,IKZF3,BAG2,KCNH2,POLR2B,TRAPPC9,LPIN1,TNIK,LRIG1,ADCY3,DICER1,STEAP3,EGF

			LAM,PRKCZ,HK2,PPP2CA,ANGPT2,COL15A1,DAP,IL4,ENG,PSMC3IP,CITED2,IGF1R,RPTOR,ACP5,SHANK2,TMEM131,SMARCD3
	Metastasis of tumor cell lines	0.0145	IGF1R,RALB,ANGPT2,RPTOR,DICER1,CTSB,GPI
	Neoplasia of leukocytes	0.0156	FOXP1,RBL2,ATXN7L1,LPCAT2,IKZF3,BAG2,MS4A2,KCNH2,TRAPPC9,LPIN1,TNIK,LRIG1,ADCY3,DICER1,STEAP3,EGFLAM,PRKCZ,HK2,PPP2CA,ANGPT2,COL15A1,DAP,IL4,ENG,PSMC3IP,CITED2,RPTOR,ACP5,SHANK2,TMEM131,SMARCD3
	Barrett syndrome	0.0156	IL4,ENG,ASCC1
Organismal Functions	Inhibition of tumor cells	0.000402	DDIT4,IL4,HK2
	Inhibition of mammary tumor cells	0.000656	IL4,HK2
Tumor Morphology	Inhibition of tumor cells	0.000402	DDIT4,IL4,HK2
	Inhibition of mammary tumor cells	0.000656	IL4,HK2
	Colony formation of tumor cells	0.000996	DICER1,RHOBTB2,CTSB,SUGT1
	Colony formation of cancer cells	0.00426	DICER1,CTSB,SUGT1
	Cell viability of cancer cells	0.0113	IGF1R,RALB,IL4,MITF
	Proliferation of ovarian cancer cells	0.0126	IGF1R,PPP2CA
Endocrine System Disorders	Goiter	0.000474	IGF1R,KRT19,DICER1
	Growth of pancreatic endocrine tumor	0.00287	CTSB,ENG
	Nodular goiter	0.00417	KRT19,DICER1
	Follicular thyroid tumor	0.00462	KRT19,ANGPT2,CTSB,ENG
	Diabetes mellitus	0.0077	ITIH4,COL15A1,FOXP1,SLC17A4,IL4,NISCH,IKZF3,CLEC12A,NR0B2,KCNH2,IGF1R,SLC2A9,LRIG1,PCYT1A,CTSB,MED27,FBP1,HK2,BANK1,DLGAP2,PPT2
	Proliferation of ovarian cancer cells	0.0126	IGF1R,PPP2CA
Cellular Assembly and Organization	Orientation of axons	0.000656	NFIA,PRKCZ
	Organization of actin cytoskeleton	0.00125	RALB,LPIN1,TNIK,CSRP1,ATP2C1,ENG,EVL,PRKCZ,NCK1,GPI
	Instability of microtubules	0.00417	KIF5C,KIF3B
	Priming of synaptic vesicles	0.00653	NAPA,STX1B
	Reorganization of actin cytoskeleton	0.00707	LPIN1,TNIK,ATP2C1,ENG,PRKCZ
	Fusion of myotube	0.00836	IGF1R,IL4
	Axonogenesis	0.00885	IGF1R,ADCY3,DICER1,NFIA,PRKCZ,PMP22,PPP2CA
	Neuritogenesis	0.00966	CSRP1,NFIA,KIF3B,IGF1R,RALB,TNIK,ADCY3,DICER1,FBXW8,SHANK2,LRP12,PRKCZ,PMP22,PPP2CA
	Accumulation of lysosome	0.0104	IGF1R,CTSB
	Reorganization of cytoskeleton	0.0113	LPIN1,TNIK,ATP2C1,ENG,PRKCZ,MS4A2
	Fusion of plasma membrane	0.0138	RALB,NAPA
	Myelination of axons	0.0138	DICER1,PMP22
	Organization of cytoplasm	0.0142	SEC16B,CSRP1,SLC25A33,HEXA,MS4A2,LPIN1,RALB,TNIK,ADCY3,DICER1,FBXW8,ATP2C1,LRP12,PRKCH,PRKCZ,NCK1,GPI,PMP22,PPP2CA,KIF5C,ANGPT2,ENG,NFIA,ATL3,KIF3B,IGF1R,SHANK2,EVL
Nervous System Development and Function	Orientation of axons	0.000656	NFIA,PRKCZ
	Myelination of cells	0.00257	SERINC5,DICER1,DDIT4,HEXA,PMP22
	Morphogenesis of neurons	0.00452	CSRP1,NFIA,HEXA,KIF3B,IGF1R,RALB,TNIK,ADCY3,DICER1,FBXW8,SHANK2,LRP12,PRKCZ,PMP22,PPP2CA
	Migration of cerebellar granule cell	0.00653	IGF1R,NFIA
	Axonogenesis	0.00885	IGF1R,ADCY3,DICER1,NFIA,PRKCZ,PMP22,PPP2CA
	Neuritogenesis	0.00966	CSRP1,NFIA,KIF3B,IGF1R,RALB,TNIK,ADCY3,DICER1,FBXW8,SHANK2,LRP12,PRKCZ,PMP22,PPP2CA
	Myelination of axons	0.0138	DICER1,PMP22
Tissue Morphology	Quantity of naive B cells	0.000656	IL4,IKZF3

	Abnormal morphology of reticulocytes	0.000979	SLC7A1,STEAP3
	Quantity of B-1 lymphocytes	0.00101	RPTOR,IL4,IL5RA,ARID3A,BANK1
	Morphology of lymph follicle	0.00112	IL4,IKZF3,PRKCZ,TLE4,BANK1,PPT2
	Quantity of blood cells	0.00333	TANK,SIGLEC8,PTGDR2,SLC7A1,RBL2,BNIP3L,IL4,IL5RA,IKZF3,IRF6,IGF1R,RPTOR,DICER1,CTSB,STEAP3,PRKCH,ARID3A,BANK1,TLE4,ST3GAL1,PPT2,PPP2CA
	Size of embryo	0.00348	ZFPM1,IGF1R,NCSTN,DICER1,RBL2,ATP2C1,ENG,CITED2,KIF3B,PPP2CA
	Quantity of B-1a lymphocytes	0.00397	RPTOR,ARID3A,BANK1
	Contraction of vein	0.00417	DICER1,IL4
	Quantity of B lymphocytes	0.00447	TANK,RPTOR,CTSB,IL4,IL5RA,PRKCH,IKZF3,ARID3A,BANK1,TLE4
	Quantity of cells	0.00532	SIGLEC8,RBL2,BNIP3L,MITF,IKZF3,IRF6,KRT19,DICER1,ATP2C1,STEAP3,STX1B,PRKCH,ARID3A,TLE4,ST3GAL1,PMP22,PPP2CA,TANK,PTGDR2,KIF5C,ANGPT2,SLC7A1,IL4,IL5RA,ENG,NFIA,CITED2,IGF1R,RPTOR,TFF2,CTSB,BANK1,PPT2
	Quantity of epithelial tissue	0.00586	IGF1R,ANGPT2,DICER1,TFF2,CTSB,MITF
	Quantity of myeloid cells	0.0073	IRF6,IGF1R,PTGDR2,SIGLEC8,RBL2,CTSB,IL4,IL5RA,ARID3A,TLE4,PPT2,PPP2CA
	Quantity of leukocytes	0.00815	TANK,SIGLEC8,PTGDR2,RBL2,IL4,IL5RA,IKZF3,IRF6,IGF1R,RPTOR,DICER1,CTSB,PRKCH,ARID3A,BANK1,TLE4,ST3GAL1,PPT2,PPP2CA
	Quantity of lymph follicle	0.0144	IKZF3,ARID3A,PRKCZ,BANK1,TLE4
	Abnormal morphology of germinal center	0.015	IL4,IKZF3,BANK1
	Quantity of glandular epithelial cells	0.0151	DICER1,TFF2
	Abnormal morphology of lymphoid organ	0.0151	BNIP3L,STEAP3,IL5RA,PRKCH,IKZF3,BANK1,TLE4,CITED2,PPT2
	Morphology of lymphoid tissue	0.0162	RBL2,BNIP3L,STEAP3,IL4,IL5RA,PRKCH,IKZF3,PRKCZ,BANK1,TLE4,CITED2,PPT2
Cardiovascular System Development and Function	Stroke volume index	0.000656	ANGPT2,ENG
	Muscularization of artery	0.00287	RPTOR,IL4
	Ejection fraction of heart	0.00316	IGF1R,ANGPT2,ENG
	Contraction of vein	0.00417	DICER1,IL4
	Proliferation of heart cells	0.0124	DICER1,FOXP1,RBL2,CITED2
Organ Development	Stroke volume index	0.000656	ANGPT2,ENG
	Ejection fraction of heart	0.00316	IGF1R,ANGPT2,ENG
	Development of plasma cells	0.00742	DICER1,IL4
	Proliferation of skeletal muscle cells	0.00742	IGF1R,ANGPT2
	Differentiation of memory B cells	0.00836	FOXP1,IL4
	Proliferation of myofibroblasts	0.00836	CTSB,IL4
	Proliferation of liver cells	0.00961	IGF1R,ITIH4,DICER1,CTSB,IL4,CITED2
	Proliferation of heart cells	0.0124	DICER1,FOXP1,RBL2,CITED2
	Differentiation of keratinocytes	0.0131	IRF6,LPIN1,LRIG1,RBL2,PRKCH
	Proliferation of hepatocytes	0.0137	IGF1R,ITIH4,DICER1,IL4,CITED2
	Abnormal morphology of germinal center	0.015	IL4,IKZF3,BANK1
Hematopoiesis	Abnormal morphology of reticulocytes	0.000979	SLC7A1,STEAP3
	Granulopoiesis	0.00159	IGF1R,ZFPM1,RALB,SIGLEC8,IL4,CITED2
	Morphology of hematopoietic progenitor cells	0.00341	ZFPM1,SLC7A1,RPTOR,STEAP3,ARID3A,CITED2
	Myelopoiesis of leukocytes	0.00393	IGF1R,ZFPM1,RALB,SIGLEC8,FOXP1,IL4,CITED2
	Development of plasma cells	0.00742	DICER1,IL4
	Development of PBMCs	0.00836	DICER1,IL4
	Differentiation of memory B cells	0.00836	FOXP1,IL4
	Differentiation of eosinophils	0.00936	SIGLEC8,IL4

	Leukopoiesis	0.00985	ZFPM1,SIGLEC8,FOXP1,RBL2,IL4,IL5RA,IKZF3,CITED2,NR0B2,IGF1R,RALB,RPTOR,DICER1,PRKCH,PRKCZ,ARID3A,TLE4
	Abnormal morphology of hematopoietic progenitor cells	0.0108	ZFPM1,SLC7A1,STEAP3,ARID3A,CITED2
	Hematopoiesis in embryo	0.0114	ZFPM1,ENG,ARID3A
DNA Replication, Recombination, and Repair	Homologous pairing of DNA	0.000979	EVL,PSMC3IP
	Synthesis of genomic DNA	0.0151	IL4,PRKCH
Protein Synthesis	Quantity of IgM	0.00108	TANK,IL4,IL5RA,IKZF3,ARID3A,BANK1
	Quantity of IgA	0.00404	TANK,IL4,IL5RA,IKZF3
	Quantity of IgG1	0.0056	TANK,IL4,IL5RA,IKZF3,ARID3A
	Quantity of IgG2a	0.0124	TANK,IL4,IKZF3,BANK1
Gene Expression	Transcription of DNA	0.00126	ZFPM1,YWHAQ,DMAP1,FOXP1,EHF,MITF,IKZF3,POLR2B,IRF6,LPIN1,DICER1,MED27,FBP1,IRF2BPL,ASCC1,ARID3A,PHF19,NCK1,TLE4,PPP2CA,DAP,IL4,ENG,NFIA,PSMC3IP,CITED2,NR0B2,IGF1R,SMARCD3,FOXK2,KAT6B
	Expression of RNA	0.00157	SEC16B,ZFPM1,YWHAQ,DMAP1,FOXP1,RBL2,EHF,MITF,IKZF3,POLR2B,IRF6,NDFIP2,LPIN1,DICER1,ATP2C1,MED27,STX1B,FBP1,IRF2BPL,PRKCZ,ASCC1,ARID3A,PHF19,NCK1,TLE4,PPP2CA,TANK,DAP,IL4,ENG,NFIA,PSMC3IP,PRG3,CITED2,NR0B2,IGF1R,RPS6KA2,SMARCD3,FOXK2,KAT6B,BANK1
	Transcription of RNA	0.00175	ZFPM1,YWHAQ,DMAP1,FOXP1,RBL2,EHF,MITF,IKZF3,POLR2B,IRF6,LPIN1,DICER1,ATP2C1,MED27,FBP1,IRF2BPL,PRKCZ,ASCC1,ARID3A,PHF19,NCK1,TLE4,PPP2CA,TANK,DAP,IL4,ENG,NFIA,PSMC3IP,CITED2,NR0B2,IGF1R,SMARCD3,FOXK2,KAT6B
	Transcription	0.00196	SEC16B,ZFPM1,YWHAQ,DMAP1,FOXP1,RBL2,EHF,MITF,IKZF3,POLR2B,IRF6,NDFIP2,LPIN1,DICER1,ATP2C1,MED27,STX1B,FBP1,IRF2BPL,PRKCZ,ASCC1,ARID3A,PHF19,NCK1,TLE4,PPP2CA,TANK,DAP,IL4,ENG,NFIA,PSMC3IP,CITED2,NR0B2,IGF1R,RPS6KA2,SMARCD3,FOXK2,KAT6B
	Activation of DNA endogenous promoter	0.00599	ZFPM1,DMAP1,IL4,EHF,ENG,MITF,NFIA,PSMC3IP,IKZF3,CITED2,NR0B2,POLR2B,IRF6,LPIN1,DICER1,MED27,FOXK2,FBP1,IRF2BPL,ARID3A,PHF19,NCK1,TLE4,PPP2CA
Cellular Movement	Migration of basophils	0.00136	PTGDR2,ENG
	Invasion of cells	0.00279	YWHAQ,ANGPT2,FOXP1,RHOBTB2,ENG,MITF,KCNH2,PLGRKT,IRF6,IGF1R,RALB,LRIG1,KRT19,ADCY3,RPTOR,DICER1,TFF2,CTSB,PRKCZ,ST3GAL1,GPI
	Homing of Th2 cells	0.00287	PTGDR2,IL4
	Invasion of lymphoma cell lines	0.00349	PLGRKT,CTSB
	Cell movement of prostate cell lines	0.0049	IGF1R,ENG
	Cell movement	0.00559	DAPK2,SIGLEC8,FOXP1,RHOBTB2,EHF,MITF,KCNH2,PLGRKT,IRF6,PATJ,RALB,TNIK,LRIG1,KRT19,ADCY3,DICER1,LRP12,PRKCZ,NCK1,GPI,PMP22,PTGDR2,ANGPT2,DDIT4,IL4,IL5RA,NISCH,ENG,NFIA,CATSPER4,CITED2,IGF1R,RPTOR,ACP5,TFF2,CTSB,EVL,RNASE2,PPT2
	Dissemination of tumor cells	0.00653	IGF1R,ANGPT2
	Migration of B-lymphocyte derived cell lines	0.00653	PTGDR2,ENG
	Migration of cerebellar granule cell	0.00653	IGF1R,NFIA
	Recruitment of muscle cells	0.00653	IL4,ENG
	Migration of cells	0.00752	DAPK2,SIGLEC8,FOXP1,RHOBTB2,EHF,MITF,KCNH2,PLGRKT,IRF6,PATJ,RALB,KRT19,ADCY3,DICER1,LRP12,PRKCZ,NCK1,GPI,PMP22,PTGDR2,ANGPT2,DDIT4,IL4,NISCH,ENG,NFIA,CITED2,IGF1R,RPTOR,ACP5,TFF2,CTSB,EVL,RNASE2,PPT2
	Cellular infiltration by granulocytes	0.00869	IRF6,PTGDR2,SIGLEC8,ANGPT2,DICER1,CTSB,IL4
	Migration of myeloma cell lines	0.00936	IGF1R,RALB
	Invasion of carcinoma cell lines	0.01	IRF6,RALB,FOXP1,CTSB,MITF,PRKCZ,ST3GAL1
	Invasion of tumor cell lines	0.0109	YWHAQ,FOXP1,MITF,IRF6,PLGRKT,IGF1R,RALB,KRT19,LRIG1,RPTOR,DICER1,CTSB,TFF2,PRKCZ,ST3GAL1,GPI

	Migration of Langerhans cells	0.0115	RPTOR,IL4
Endocrine System Development and Function	Morphology of thyroid cells	0.00136	IGF1R,CTSB
	Proliferation of endocrine cells	0.0144	IGF1R,ANGPT2,DICER1,TFF2
Organ Morphology	Morphology of thyroid cells	0.00136	IGF1R,CTSB
	Abnormal morphology of hair follicle	0.00595	IGF1R,DICER1,RBL2
	Abnormal morphology of epidermis	0.00668	IGF1R,LRIG1,DICER1,RBL2,CTSB
	Quantity of glandular epithelial cells	0.0151	DICER1,TFF2
	Abnormal morphology of lymphoid organ	0.0151	BNIP3L,STEAP3,IL5RA,PRKCH,IKZF3,BANK1,TLE4,CITED2,PPT2
Organismal Development	Morphology of thyroid cells	0.00136	IGF1R,CTSB
	Muscularization of artery	0.00287	RPTOR,IL4
	Size of embryo	0.00348	ZFPM1,IGF1R,NCSTN,DICER1,RBL2,ATP2C1,ENG,CITED2,KIF3B,PPP2CA
	Morphogenesis of neurons	0.00452	CSRP1,NFIA,HEXA,KIF3B,IGF1R,RALB,TNIK,ADCY3,DICER1,FBXW8,SHANK2,LRP12,PRKCZ,PMP22,PPP2CA
	Development of plasma cells	0.00742	DICER1,IL4
	Development of PBMCs	0.00836	DICER1,IL4
	Differentiation of memory B cells	0.00836	FOXP1,IL4
	Axonogenesis	0.00885	IGF1R,ADCY3,DICER1,NFIA,PRKCZ,PMP22,PPP2CA
	Neuritogenesis	0.00966	CSRP1,NFIA,KIF3B,IGF1R,RALB,TNIK,ADCY3,DICER1,FBXW8,SHANK2,LRP12,PRKCZ,PMP22,PPP2CA
	Hematopoiesis in embryo	0.0114	ZFPM1,ENG,ARID3A
	Differentiation of keratinocytes	0.0131	IRF6,LPIN1,LRIG1,RBL2,PRKCH
	Myelination of axons	0.0138	DICER1,PMP22
	Abnormal morphology of germinal center	0.015	IL4,IKZF3,BANK1
Tissue Development	Granulopoiesis	0.00159	IGF1R,ZFPM1,RALB,SIGLEC8,IL4,CITED2
	Myelopoiesis of leukocytes	0.00393	IGF1R,ZFPM1,RALB,SIGLEC8,FOXP1,IL4,CITED2
	Morphogenesis of neurons	0.00452	CSRP1,NFIA,HEXA,KIF3B,IGF1R,RALB,TNIK,ADCY3,DICER1,FBXW8,SHANK2,LRP12,PRKCZ,PMP22,PPP2CA
	Growth of epithelial tissue	0.00596	ITIH4,ANGPT2,RBL2,IL4,ENG,CITED2,IRF6,IGF1R,NCSTN,LRIG1,RPTOR,DICER1,CTSB,MCC,PRKCH,PRKCZ
	Proliferation of connective tissue cells	0.00708	RBL2,IL4,ENG,CITED2,IRF6,IGF1R,NCSTN,LRIG1,DICER1,CTSB,PRKCH,PGAM2,ARID3A,GPI
	Development of plasma cells	0.00742	DICER1,IL4
	Proliferation of skeletal muscle cells	0.00742	IGF1R,ANGPT2
	Development of PBMCs	0.00836	DICER1,IL4
	Differentiation of memory B cells	0.00836	FOXP1,IL4
	Proliferation of myofibroblasts	0.00836	CTSB,IL4
	Axonogenesis	0.00885	IGF1R,ADCY3,DICER1,NFIA,PRKCZ,PMP22,PPP2CA
	Accumulation of lymphatic system cells	0.00936	NCSTN,IL4
	Differentiation of eosinophils	0.00936	SIGLEC8,IL4
	Proliferation of epithelial cells	0.00947	IRF6,IGF1R,NCSTN,ITIH4,LRIG1,DICER1,RBL2,IL4,MCC,ENG,PRKCH,CITED2
	Neuritogenesis	0.00966	CSRP1,NFIA,KIF3B,IGF1R,RALB,TNIK,ADCY3,DICER1,FBXW8,SHANK2,LRP12,PRKCZ,PMP22,PPP2CA
	Leukopoiesis	0.00985	ZFPM1,SIGLEC8,FOXP1,RBL2,IL4,IL5RA,IKZF3,CITED2,NR0B2,IGF1R,RALB,RPTOR,DICER1,PRKCH,PRKCZ,ARID3A,TLE4
	Hematopoiesis in embryo	0.0114	ZFPM1,ENG,ARID3A
	Cell proliferation of fibroblasts	0.0121	IGF1R,NCSTN,CTSB,IL4,ENG,PGAM2,ARID3A,CITED2,GPI
	Differentiation of keratinocytes	0.0131	IRF6,LPIN1,LRIG1,RBL2,PRKCH
	Proliferation of hepatocytes	0.0137	IGF1R,ITIH4,DICER1,IL4,CITED2
	Myelination of axons	0.0138	DICER1,PMP22
	Abnormal morphology of germinal center	0.015	IL4,IKZF3,BANK1

Cellular Compromise	Degranulation of cells	0.00183	ZFPM1,PRG2,RALB,LPIN1,DICER1,IL4,EHF,MS4A2
	Instability of microtubules	0.00417	KIF5C,KIF3B
	Damage of hepatocytes	0.00569	IGF1R,DICER1
	Degranulation of BMMC cells	0.0126	IL4,EHF
Cardiovascular Disease	Failure of heart looping	0.00225	NCSTN,RBL2,ENG
	Development of angioma	0.00352	ANGPT2,DICER1,IKZF3,KAT6B
	Hypercholesterolemia	0.00593	ITIH4,LPIN1,RPTOR,NR0B2
	Hemangioblastoma	0.0104	DICER1,IKZF3,KAT6B
	Congenital anomaly of cardiovascular system	0.0104	NCSTN,ANGPT2,DICER1,RBL2,ENG,KAT6B,CITED2,KCNH2
	Hemangioma	0.0108	IGF1R,ANGPT2,DICER1,IKZF3,KAT6B
Developmental Disorder	Failure of heart looping	0.00225	NCSTN,RBL2,ENG
	Susceptibility to autism type 1	0.00569	FOXP1,SHANK2
	Congenital anomaly of cardiovascular system	0.0104	NCSTN,ANGPT2,DICER1,RBL2,ENG,KAT6B,CITED2,KCNH2
	Congenital malformation of brain	0.0123	RALB,KIF5C,RPTOR,DICER1,ATP2C1,EMG1,NFIA,CITED2,KIF3B
	Autosomal dominant Emery-Dreifuss muscular dystrophy	0.0125	BNIP3L,ENG,CYB561
Dermatological Diseases and Conditions	Chronic idiopathic urticaria	0.00231	IL5RA,MS4A2
	Skin papilloma	0.00523	ATP2C1,ENG,PRKCH
	Abnormal morphology of hair follicle	0.00595	IGF1R,DICER1,RBL2
	Abnormal morphology of epidermis	0.00668	IGF1R,LRIG1,DICER1,RBL2,CTSB
	Parakeratosis	0.0104	LRIG1,RBL2
	Juvenile dermatomyositis	0.0109	BNIP3L,ENG,CYB561
Organismal Survival	Morbidity or mortality	0.00265	ZFPM1,DMAP1,RBL2,CSRP1,BNIP3L,VPS52,MITF,IKZF3,HEXA,KCNH2,RALB,KRT19,ADCY3,DICER1,FBXW8,PCYT1A,ATP2C1,STX1B,EPX,PRKCH,HK2,ARID3A,NCK1,TLE4,PMP22,PPP2CA,TANK,ANGPT2,SLC25A25,SLC7A1,IL4,ENG,NFIA,KIF26A,CLEC12A,CITED2,KIF3B,IGF1R,NCSTN,SLC2A9,RPTOR,CTSB,SHANK2,PPT2
	Organismal death	0.00368	ZFPM1,DMAP1,RBL2,CSRP1,BNIP3L,VPS52,MITF,IKZF3,HEXA,KCNH2,RALB,KRT19,ADCY3,DICER1,FBXW8,PCYT1A,ATP2C1,STX1B,EPX,PRKCH,HK2,ARID3A,NCK1,TLE4,PMP22,PPP2CA,TANK,ANGPT2,SLC25A25,SLC7A1,IL4,ENG,NFIA,KIF26A,CITED2,KIF3B,IGF1R,NCSTN,SLC2A9,RPTOR,CTSB,SHANK2,PPT2
Gastrointestinal Disease	Growth of pancreatic endocrine tumor	0.00287	CTSB,ENG
	Damage of hepatocytes	0.00569	IGF1R,DICER1
	Polyp	0.00593	IL5RA,ENG,PRKCZ,MS4A2
	Diabetes mellitus	0.0077	ITIH4,COL15A1,FOXP1,SLC17A4,IL4,NISCH,IKZF3,CLEC12A,NR0B2,KCNH2,IGF1R,SLC2A9,LRIG1,PCYT1A,CTSB,MED27,FBP1,HK2,BANK1,DLGAP2,PPT2
	Apoptosis of hepatocytes	0.00904	ITIH4,DICER1,CTSB,IL4,NR0B2
	Polyposis	0.0104	IL5RA,ENG,MS4A2
	Barrett syndrome	0.0156	IL4,ENG,ASCC1
Cell-mediated Immune Response	Homing of Th2 cells	0.00287	PTGDR2,IL4
Skeletal and Muscular System Development and Function	Muscularization of artery	0.00287	RPTOR,IL4
	Proliferation of skeletal muscle cells	0.00742	IGF1R,ANGPT2
	Fusion of myotube	0.00836	IGF1R,IL4
	Proliferation of myofibroblasts	0.00836	CTSB,IL4
	Cell viability of muscle cell lines	0.0138	IGF1R,CTSB
	Cell viability of muscle cells	0.015	IGF1R,ANGPT2,HK2
Embryonic Development	Size of embryo	0.00348	ZFPM1,IGF1R,NCSTN,DICER1,RBL2,ATP2C1,ENG,CITED2,KIF3B,PPP2CA

	Cell death of embryonic cell lines	0.00617	IGF1R,TANK,YWHAQ,RBL2,CTSB,BNIP3L,DDIT4,HK2,CITED2,PMP22
	Development of plasma cells	0.00742	DICER1,IL4
	Differentiation of memory B cells	0.00836	FOXP1,IL4
	Hematopoiesis in embryo	0.0114	ZFPM1,ENG,ARID3A
	Differentiation of keratinocytes	0.0131	IRF6,LPIN1,LRIG1,RBL2,PRKCH
	Abnormal morphology of germinal center	0.015	IL4,IKZF3,BANK1
Inflammatory Disease	Severe asthma	0.00417	IL5RA,MS4A2
	Juvenile dermatomyositis	0.0109	BNIP3L,ENG,CYB561
	Barrett syndrome	0.0156	IL4,ENG,ASCC1
Respiratory Disease	Severe asthma	0.00417	IL5RA,MS4A2
	Cell death of lung cells	0.00595	IGF1R,PRG2,EPX
	Cell death of pneumocytes	0.0138	PRG2,EPX
Free Radical Scavenging	Production of superoxide	0.0051	PRG2,ANGPT2,IL4,PRKCZ,PRG3
	Synthesis of reactive oxygen species	0.00713	PRG2,IRF6,ITIH4,ANGPT2,BNIP3L,SHANK2,DDIT4,IL4,FBP1,PRKCZ,HK2,PRG3
Hepatic System Disease	Damage of hepatocytes	0.00569	IGF1R,DICER1
	Apoptosis of hepatocytes	0.00904	ITIH4,DICER1,CTSB,IL4,NR0B2
Neurological Disease	Susceptibility to autism type 1	0.00569	FOXP1,SHANK2
	Demyelination of neurons	0.0104	LPIN1,DICER1
	Neurodegeneration of cerebellum	0.0109	DICER1,CTSB,PPT2
	Congenital malformation of brain	0.0123	RALB,KIF5C,RPTOR,DICER1,ATP2C1,EMG1,NFIA,CITED2,KIF3B
	Familial pervasive developmental disorder	0.0151	FOXP1,SHANK2
Psychological Disorders	Susceptibility to autism type 1	0.00569	FOXP1,SHANK2
	Familial pervasive developmental disorder	0.0151	FOXP1,SHANK2
Metabolic Disease	Hypercholesterolemia	0.00593	ITIH4,LPIN1,RPTOR,NR0B2
	Diabetes mellitus	0.0077	ITIH4,COL15A1,FOXP1,SLC17A4,IL4,NISCH,IKZF3,CLEC12A,NR0B2,KCNH2,IGF1R,SLC2A9,LRIG1,PCYT1A,CTSB,MED27,FBP1,HK2,BANK1,DLGAP2,PPT2
	Glucose metabolism disorder	0.0112	ITIH4,COL15A1,FOXP1,SLC17A4,IL4,NISCH,IKZF3,CLEC12A,NR0B2,KCNH2,IGF1R,LPIN1,SLC2A9,LRIG1,DICER1,PCYT1A,CTSB,MED27,SMARCD3,FBP1,HK2,BANK1,DLGAP2,PPT2
Renal and Urological Disease	Hydronephrosis	0.00693	IGF1R,SLC2A9,IL4,NFIA
	Injury of renal glomerulus	0.0138	ANGPT2,DICER1
Connective Tissue Development and Function	Proliferation of connective tissue cells	0.00708	RBL2,IL4,ENG,CITED2,IRF6,IGF1R,NCSTN,LRIG1,DICER1,CTSB,PRKCH,PGAM2,ARID3A,GPI
	Development of PBMCs	0.00836	DICER1,IL4
	Proliferation of myofibroblasts	0.00836	CTSB,IL4
	Cell proliferation of fibroblasts	0.0121	IGF1R,NCSTN,CTSB,IL4,ENG,PGAM2,ARID3A,CITED2,GPI
Digestive System Development and Function	Proliferation of liver cells	0.00961	IGF1R,ITIH4,DICER1,CTSB,IL4,CITED2
	Proliferation of hepatocytes	0.0137	IGF1R,ITIH4,DICER1,IL4,CITED2
Hereditary Disorder	Hereditary myopathy	0.00857	LPIN1,PTGDR2,AP5B1,BNIP3L,ENG,SLC25A33,KIF26A,ASCC1,ATPAF2,CYB561,PMP22,KCNH2
	Autosomal dominant Emery-Dreifuss muscular dystrophy	0.0125	BNIP3L,ENG,CYB561
	Familial pervasive developmental disorder	0.0151	FOXP1,SHANK2
Skeletal and Muscular Disorders	Hereditary myopathy	0.00857	LPIN1,PTGDR2,AP5B1,BNIP3L,ENG,SLC25A33,KIF26A,ASCC1,ATPAF2,CYB561,PMP22,KCNH2
	Juvenile dermatomyositis	0.0109	BNIP3L,ENG,CYB561
	Autosomal dominant Emery-Dreifuss muscular dystrophy	0.0125	BNIP3L,ENG,CYB561

Reproductive System Disease	Proliferation of ovarian cancer cells	0.0126	IGF1R,PPP2CA
Cell Signaling	Translocation of Ca2+	0.00936	SLC8B1,ATP2C1
Vitamin and Mineral Metabolism	Translocation of Ca2+	0.00936	SLC8B1,ATP2C1
Hepatic System Development and Function	Proliferation of liver cells	0.00961	IGF1R,ITIH4,DICER1,CTSB,IL4,CITED2
	Proliferation of hepatocytes	0.0137	IGF1R,ITIH4,DICER1,IL4,CITED2
Antimicrobial Response	Antiviral response	0.0109	SERINC5,DICER1,BNIP3L,IL4,DDIT4,RNASE2

*Diseases and biological functions which had only one gene involved were removed.

Table E11 *Druggable targets of genes to which the 179 significant CpGs annotated in analysis of asthma in relation to DNA methylation in childhood.*

CpG	chr:pos	Gene*	ChEMBL Target ID	Approved drugs and clinical candidates [ChEMBL ID]	Approved drugs and Clinical candidates [Name]	Mechanism of Action
cg01942646	chr1:27240694	NR0B2	CHEMBL5603	No	No	
cg26752663	chr2:25142016	ADCY3	CHEMBL2097167	No	No	
cg01310029	chr3:3152374	IL5RA	CHEMBL3580483	CHEMBL1742991	BENRALIZUMAB	Interleukin-5 receptor subunit alpha inhibitor
cg10159529	chr3:3152530	IL5RA	CHEMBL3580483	CHEMBL1742991	BENRALIZUMAB	Interleukin-5 receptor subunit alpha inhibitor
cg07386061	chr3:52492874	NISCH	CHEMBL3923	No	No	
cg06070625	chr3:69812798	MITF	CHEMBL1741165	No	No	
cg09423651	chr3:136618442	NCK1	CHEMBL4846	No	No	
cg08698681	chr3:171091657	TNIK	CHEMBL4527	No	No	
cg09597192	chr6:32141591	PPT2	CHEMBL2189137	No	No	
cg24576940	chr7:150648283	KCNH2	CHEMBL240	CHEMBL473	DOFETILIDE	HERG blocker
				CHEMBL1700	SOTALOL HYDROCHLORIDE	HERG blocker
				CHEMBL1083993	AMIODARONE HYDROCHLORIDE	HERG blocker
				CHEMBL1200564	IBUTILIDE FUMARATE	HERG blocker
				CHEMBL3545040	AZD7009	HERG blocker
				CHEMBL3545169	AZD1305	HERG blocker
cg23147443	chr7:150649655	KCNH2	CHEMBL240	CHEMBL473	DOFETILIDE	HERG blocker
				CHEMBL1700	SOTALOL HYDROCHLORIDE	HERG blocker
				CHEMBL1083993	AMIODARONE HYDROCHLORIDE	HERG blocker
				CHEMBL1200564	IBUTILIDE FUMARATE	HERG blocker
				CHEMBL3545040	AZD7009	HERG blocker
				CHEMBL3545169	AZD1305	HERG blocker
cg18666454	chr7:150651937	KCNH2	CHEMBL240	CHEMBL473	DOFETILIDE	HERG blocker
				CHEMBL1700	SOTALOL HYDROCHLORIDE	HERG blocker
				CHEMBL1083993	AMIODARONE HYDROCHLORIDE	HERG blocker
				CHEMBL1200564	IBUTILIDE FUMARATE	HERG blocker
				CHEMBL3545040	AZD7009	HERG blocker
				CHEMBL3545169	AZD1305	HERG blocker
cg03131767	chr12:123446272	ABCB9	CHEMBL1293189	No	No	
cg11266582	chr15:64275853	DAPK2	CHEMBL3123	No	No	
cg20315954	chr17:15137304	PMP22	CHEMBL1293298	No	No	
cg21073212	chr20:30866501	KIF3B	CHEMBL6109	No	No	

*UCSC Known Gene used to map to drug target database

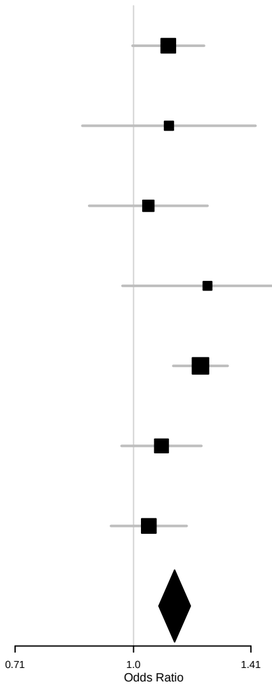
Table E12 *Druggable targets of genes to which the 35 DMRs annotated in analysis of school-aged asthma in relation to older child DNA methylation.*

chr:pos	GeneName*	ChEMBL Target ID	Approved drugs and clinical candidates [ChEMBL ID]	Approved drugs and clinical candidates [Name]	Mechanism of Action
chr2:149639612-149640260	KIF5C	CHEMBL2029194	No	No	
chr3:3151795-3152917	IL5RA	CHEMBL3580483	CHEMBL1742991	BENRALIZUMAB	Interleukin-5 receptor subunit alpha inhibitor
chr15:64275810-64275854	DAPK2	CHEMBL3123	No	No	
chr15:99443213-99443667	IGF1R	CHEMBL1957	CHEMBL1201717	MECASERMIN RINFABATE	Insulin-like growth factor I receptor agonist
			CHEMBL1201716	MECASERMIN	Insulin-like growth factor I receptor agonist
			CHEMBL1091644	LINSITINIB	Insulin-like growth factor I receptor inhibitor
			CHEMBL1743019	FIGITUMUMAB	Insulin-like growth factor I receptor antagonist
			CHEMBL1743024	GANITUMAB	Insulin-like growth factor I receptor antagonist
			CHEMBL283120	PICROPODOPHYLLOTOXIN	Insulin-like growth factor I receptor inhibitor
			CHEMBL575448	BMS-754807	Insulin-like growth factor I receptor inhibitor
			CHEMBL1743001	CIXUTUMUMAB	Insulin-like growth factor I receptor antagonist
			CHEMBL1743006	DALOTUZUMAB	Insulin-like growth factor I receptor antagonist
			CHEMBL1743064	ROBATUMUMAB	Insulin-like growth factor I receptor antagonist
			CHEMBL1743079	TEPROTUMUMAB	Insulin-like growth factor I receptor antagonist
			CHEMBL2109357	AVE-1642	Insulin-like growth factor I receptor antagonist
			CHEMBL3545025	INSM-18	Insulin-like growth factor I receptor inhibitor
			CHEMBL3545156	KW-2450	Insulin-like growth factor I receptor inhibitor
			CHEMBL551064	AEW-541	Insulin-like growth factor I receptor inhibitor
			CHEMBL3545004	PL-225B	Insulin-like growth factor I receptor inhibitor
			CHEMBL3545085	XL-228	Insulin-like growth factor I receptor inhibitor
chr17:78682785-78683458	RPTOR	CHEMBL3120040	No	No	

* Based on DMRCate annotation to RefGene from Illumina annotation file

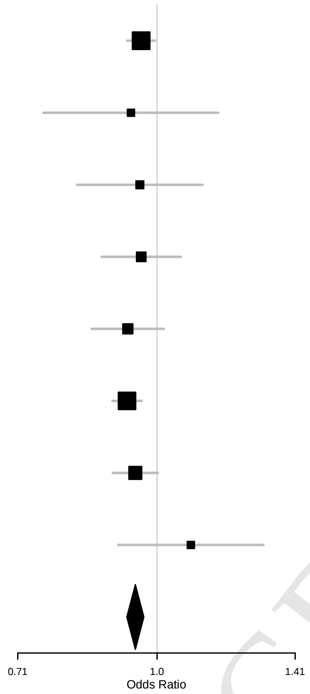
cg21486411

Cohort	N cases:controls	OR
ALSPAC	88:600	1.11
EDEN	34:116	1.11
GENR	37:624	1.04
GOYA	37:470	1.24
MOBA1	146:515	1.22
MOBA2	237:219	1.09
NEST	45:168	1.05
META−ANALYSIS	**624:2712**	**1.13**



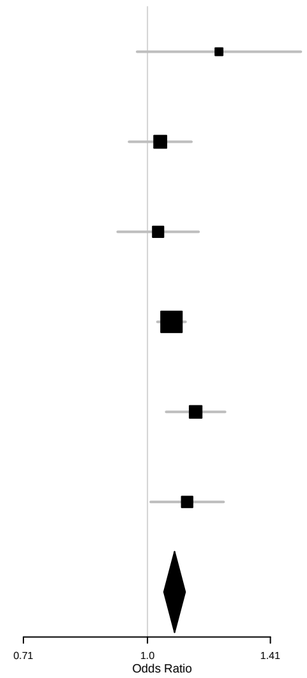
cg16792002

Cohort	N cases:controls	OR
ALSPAC	88:600	0.96
CHS	39:190	0.94
EDEN	34:116	0.96
GENR	37:624	0.96
GOYA	37:470	0.93
MOBA1	146:515	0.93
MOBA2	237:219	0.95
NEST	45:168	1.09
META−ANALYSIS	**663:2902**	**0.95**



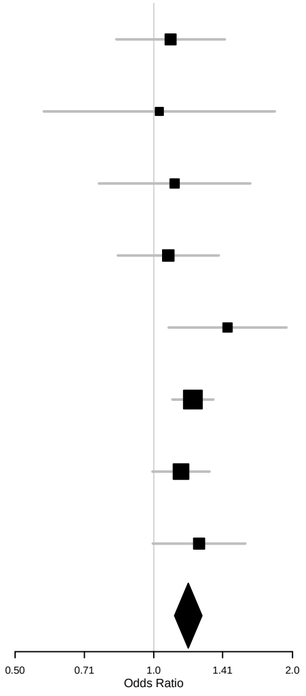
ch.11.109687686R

Cohort	N cases:controls	OR
ALSPAC	88:600	1.22
GENR	37:624	1.04
GOYA	37:470	1.03
MOBA1	146:515	1.07
MOBA2	237:219	1.14
NEST	45:168	1.12
META−ANALYSIS	**590:2596**	**1.08**



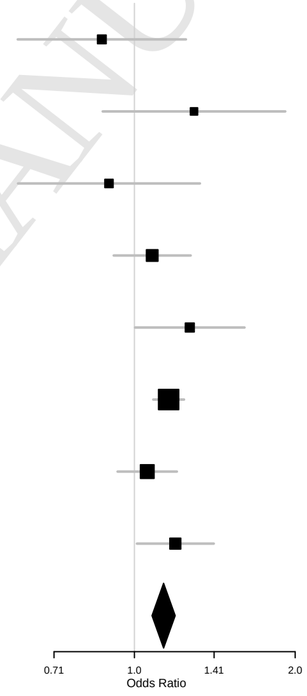
cg13427149

Cohort	N cases:controls	OR
ALSPAC	88:600	1.09
CHS	39:190	1.03
EDEN	34:116	1.11
GENR	37:624	1.08
GOYA	37:470	1.45
MOBA1	146:515	1.22
MOBA2	237:219	1.15
NEST	45:168	1.25
META−ANALYSIS	**663:2902**	**1.19**



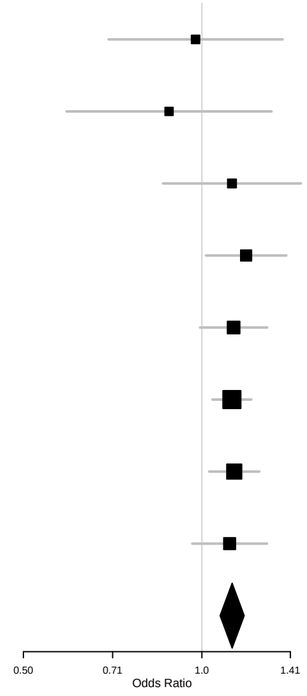
cg17333211

Cohort	N cases:controls	OR
ALSPAC	88:600	0.87
CHS	39:190	1.29
EDEN	34:116	0.90
GENR	37:624	1.08
GOYA	37:470	1.27
MOBA1	146:515	1.16
MOBA2	237:219	1.06
NEST	45:168	1.19
META−ANALYSIS	**663:2902**	**1.13**



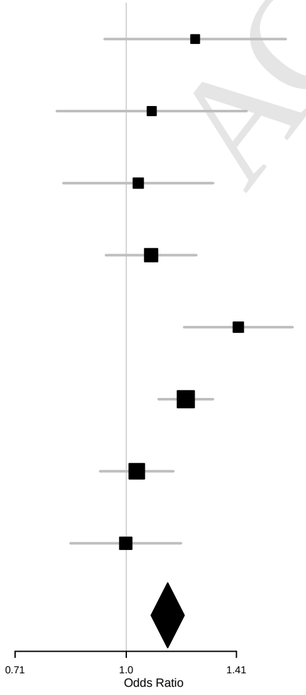
cg02331902

Cohort	N cases:controls	OR
ALSPAC	88:600	0.98
CHS	39:190	0.88
EDEN	34:116	1.12
GENR	37:624	1.19
GOYA	37:470	1.13
MOBA1	146:515	1.12
MOBA2	237:219	1.13
NEST	45:168	1.11
META−ANALYSIS	**663:2902**	**1.12**



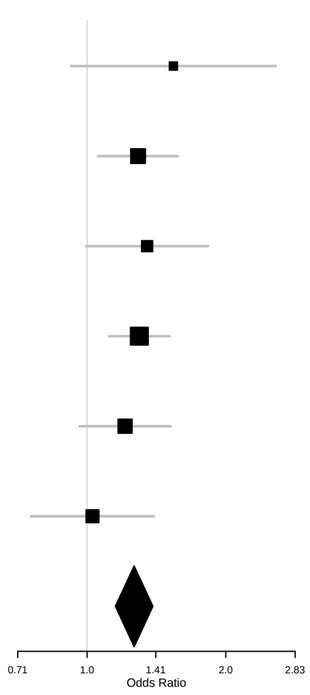
cg13289553

Cohort	N cases:controls	OR
ALSPAC	88:600	1.24
CHS	39:190	1.08
EDEN	34:116	1.04
GENR	37:624	1.08
GOYA	37:470	1.42
MOBA1	146:515	1.20
MOBA2	237:219	1.03
NEST	45:168	1.00
META−ANALYSIS	**663:2902**	**1.14**



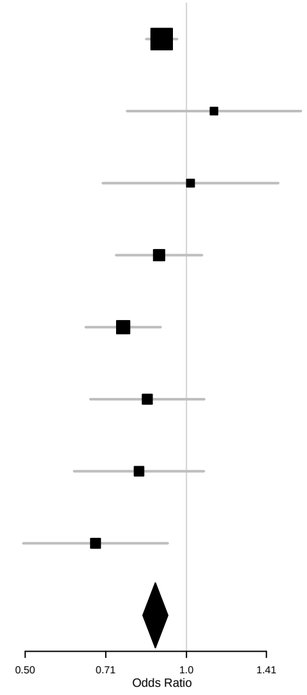
ch.6.1218502R

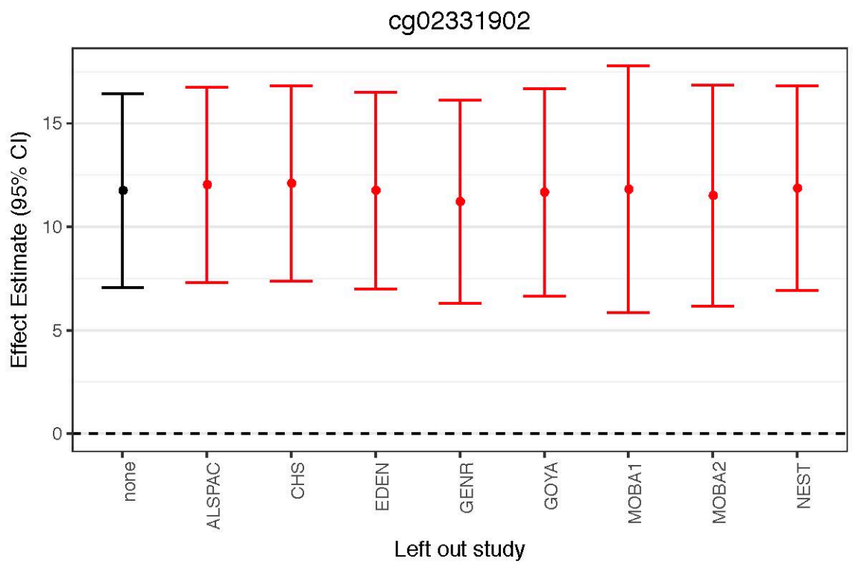
Cohort	N cases:controls	OR
ALSPAC	88:600	1.54
GENR	37:624	1.29
GOYA	37:470	1.35
MOBA1	146:515	1.30
MOBA2	237:219	1.21
NEST	45:168	1.03
META−ANALYSIS	**590:2596**	**1.27**

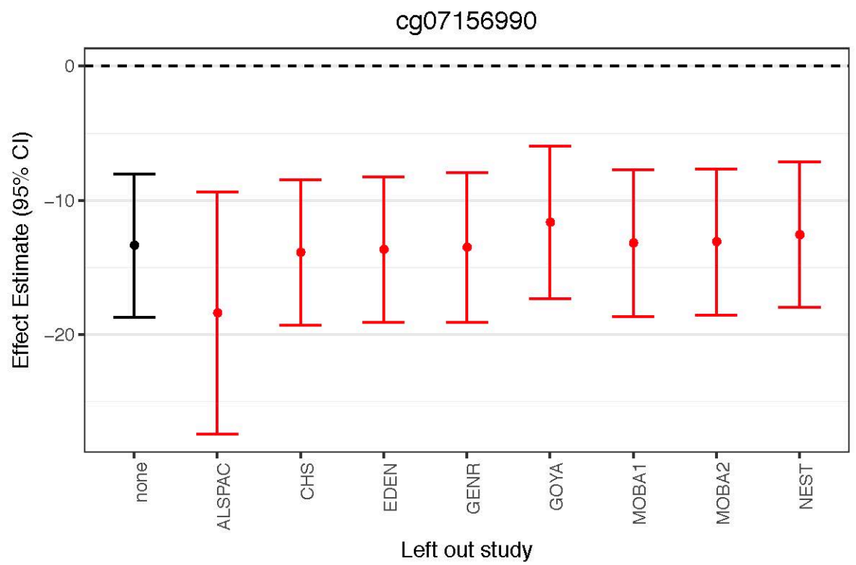


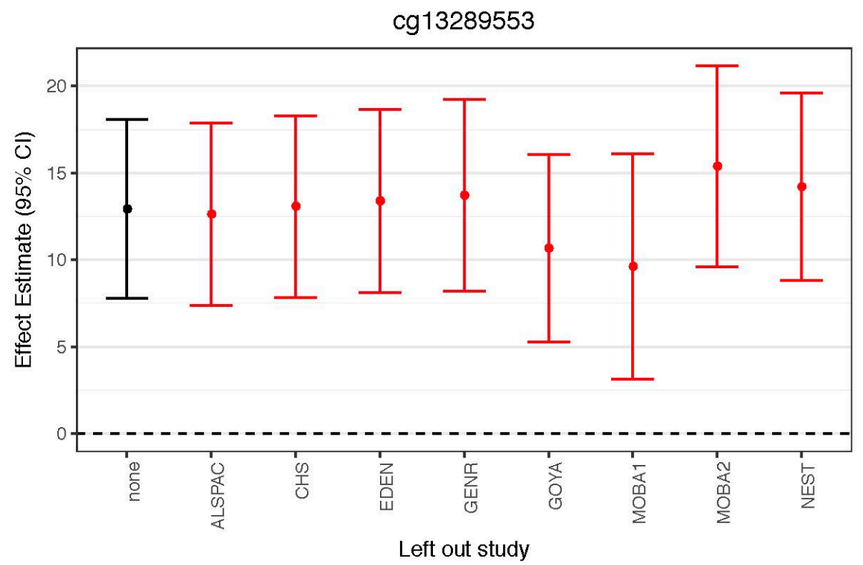
cg07156990

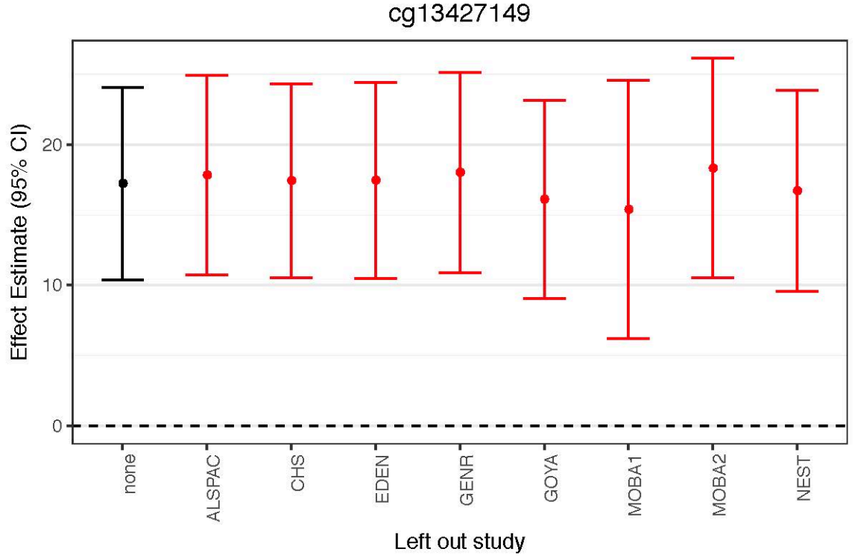
Cohort	N cases:controls	OR
ALSPAC	88:600	0.90
CHS	39:190	1.13
EDEN	34:116	1.02
GENR	37:624	0.89
GOYA	37:470	0.76
MOBA1	146:515	0.85
MOBA2	237:219	0.82
NEST	45:168	0.68
META−ANALYSIS	**663:2902**	**0.87**

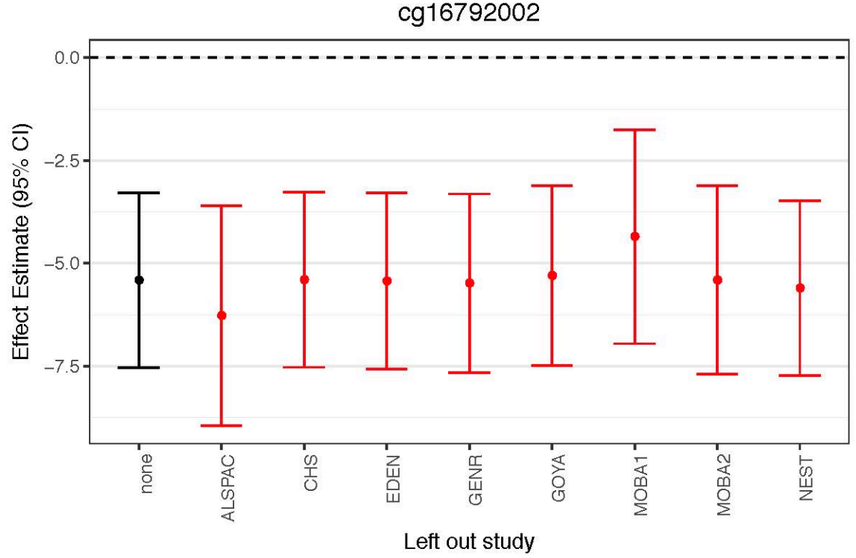


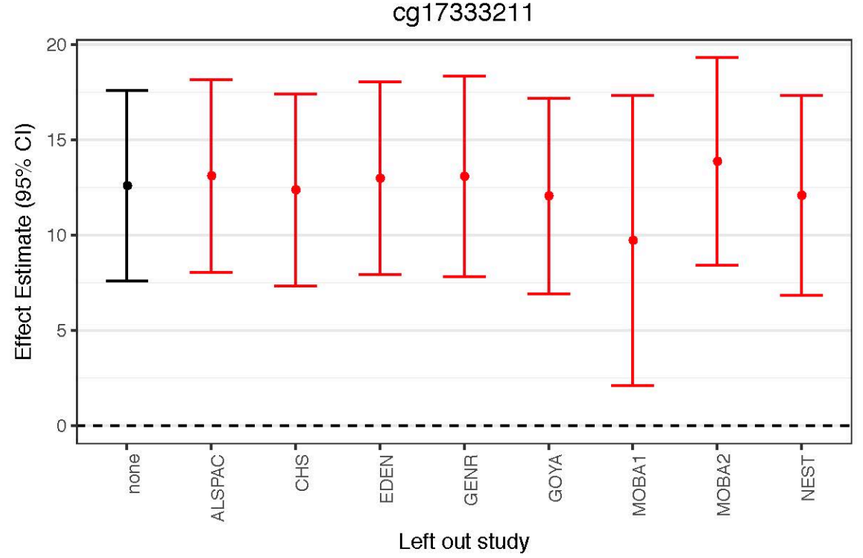

cg02331902
Effect Estimate (95% CI)
0
5
10
15
none
ALSPAC
CHS
EDEN
GENR
GOYA
MOBA1
MOBA2
NEST
Left out study

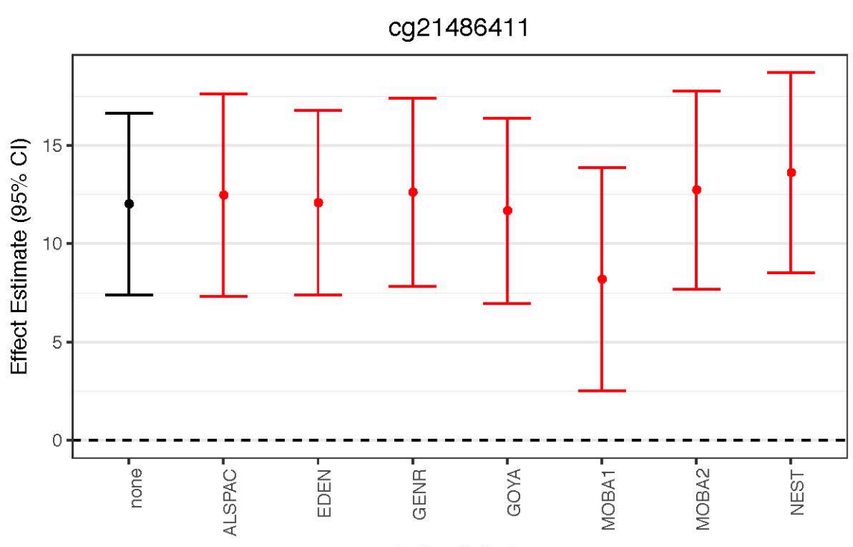

cg07156990
Effect Estimate (95% CI)
0
−10
−20
none
ALSPAC
CHS
EDEN
GENR
GOYA
MOBA1
MOBA2
NEST
Left out study

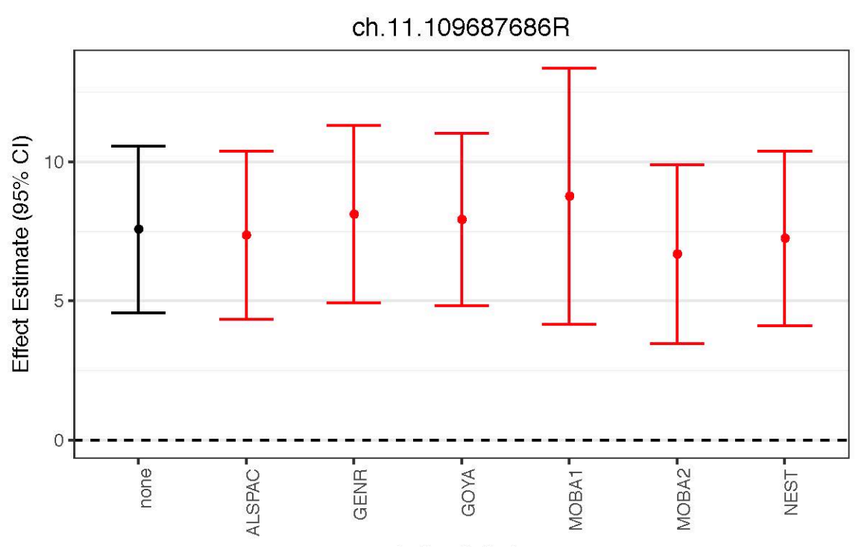

cg13289553
Effect Estimate (95% CI)
0
5
10
15
20
none
ALSPAC
CHS
EDEN
GENR
GOYA
MOBA1
MOBA2
NEST
Left out study

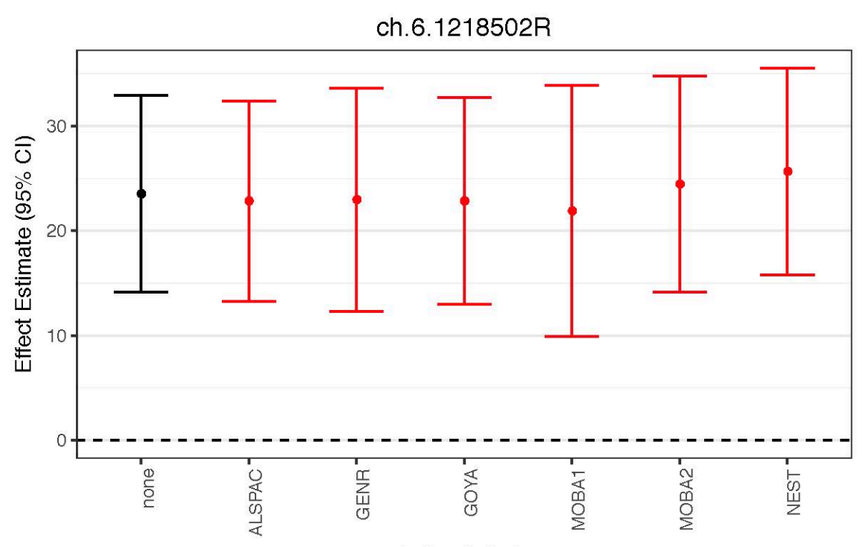

cg13427149
Effect Estimate (95% CI)
0
10
20
none
ALSPAC
CHS
EDEN
GENR
GOYA
MOBA1
MOBA2
NEST
Left out study


cg16792002
Effect Estimate (95% CI)
0.0
−2.5
−5.0
−7.5
none
ALSPAC
CHS
EDEN
GENR
GOYA
MOBA1
MOBA2
NEST
Left out study


cg17333211
Effect Estimate (95% CI)
0
5
10
15
20
none
ALSPAC
CHS
EDEN
GENR
GOYA
MOBA1
MOBA2
NEST
Left out study

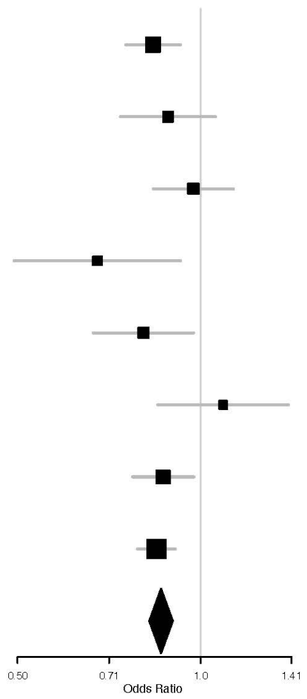

cg21486411
Effect Estimate (95% CI)
0
5
10
15
none
ALSPAC
EDEN
GENR
GOYA
MOBA1
MOBA2
NEST
Left out study


ch.11.109687686R
Effect Estimate (95% CI)
0
5
10
none
ALSPAC
GENR
GOYA
MOBA1
MOBA2
NEST
Left out study


ch.6.1218502R
Effect Estimate (95% CI)
0
10
20
30
none
ALSPAC
GENR
GOYA
MOBA1
MOBA2
NEST
Left out study

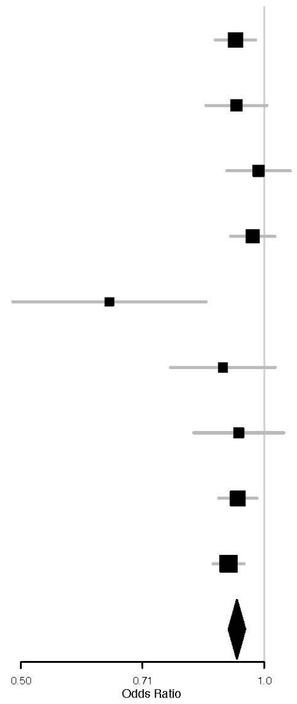
cg10644885

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.84
BAMSE_MEDALL	47:167	0.88
CHOP	19:363	0.97
ICAC	97:97	0.68
NFBC	29:343	0.81
PIAMA	15:182	1.09
RAINE	114:405	0.87
STOPPA	137:323	0.85
META−ANALYSIS	**551:2094**	**0.86**



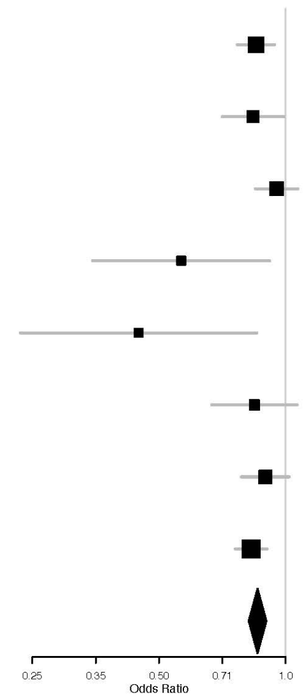
cg04983687

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.92
BAMSE_MEDALL	47:167	0.92
CHOP	19:363	0.98
GALA	106:87	0.97
ICAC	97:97	0.64
NFBC	29:343	0.89
PIAMA	15:182	0.93
RAINE	114:405	0.93
STOPPA	137:323	0.90
META−ANALYSIS	**657:2181**	**0.93**



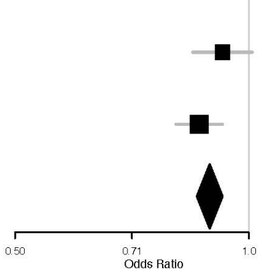
cg05300717

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.85
BAMSE_MEDALL	47:167	0.84
CHOP	19:363	0.95
ICAC	97:97	0.56
NFBC	29:343	0.45
PIAMA	15:182	0.84
RAINE	114:405	0.89
STOPPA	137:323	0.83
META−ANALYSIS	**551:2094**	**0.86**



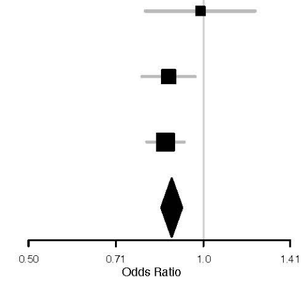
cg11699125

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.88
BAMSE_MEDALL	47:167	0.89
CHOP	19:363	1.00
GALA	106:87	0.93
ICAC	97:97	0.79
NFBC	29:343	0.73
PIAMA	15:182	0.96
RAINE	114:405	0.88
STOPPA	137:323	0.89
META−ANALYSIS	**657:2181**	**0.90**



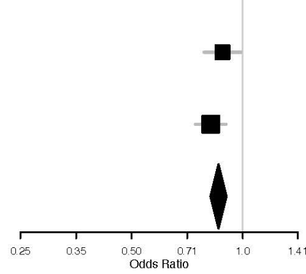
cg14084609

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.87
BAMSE_MEDALL	47:167	0.95
CHOP	19:363	0.98
GALA	106:87	0.90
ICAC	97:97	0.86
NFBC	29:343	0.83
PIAMA	15:182	0.82
RAINE	114:405	0.92
STOPPA	137:323	0.84
META−ANALYSIS	**657:2181**	**0.89**



cg06391412

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.83
BAMSE_MEDALL	47:167	0.85
CHOP	19:363	1.02
GALA	106:87	0.89
ICAC	97:97	0.86
NFBC	29:343	0.79
PIAMA	15:182	0.95
RAINE	114:405	0.91
STOPPA	137:323	0.83
META−ANALYSIS	**657:2181**	**0.87**



cg13835688

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.84
BAMSE_MEDALL	47:167	0.89
CHOP	19:363	1.03
ICAC	97:97	0.68
NFBC	29:343	0.86
PIAMA	15:182	0.90
RAINE	114:405	0.92
STOPPA	137:323	0.86
META−ANALYSIS	**551:2094**	**0.89**

cg06558622

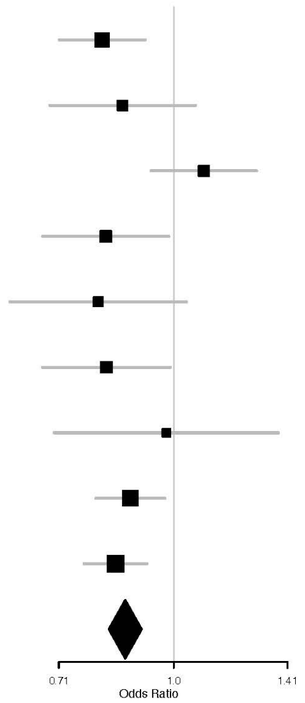
Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.86
BAMSE_MEDALL	47:167	0.87
CHOP	19:363	0.97
GALA	106:87	0.95
ICAC	97:97	0.81
NFBC	29:343	0.75
PIAMA	15:182	0.99
RAINE	114:405	0.87
STOPPA	137:323	0.86
META−ANALYSIS	**657:2181**	**0.88**

cg14011077

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.89
BAMSE_MEDALL	47:167	0.86
CHOP	19:363	0.98
ICAC	97:97	0.89
NFBC	29:343	0.62
PIAMA	15:182	0.77
RAINE	114:405	0.88
STOPPA	137:323	0.82
META−ANALYSIS	**551:2094**	**0.86**

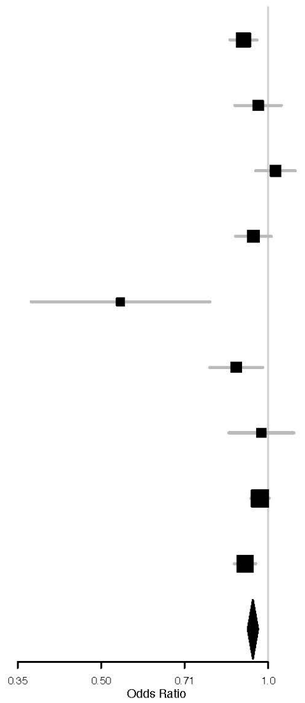
cg17971251

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.81
BAMSE_MEDALL	47:167	0.86
CHOP	19:363	1.10
GALA	106:87	0.81
ICAC	97:97	0.80
NFBC	29:343	0.82
PIAMA	15:182	0.98
RAINE	114:405	0.88
STOPPA	137:323	0.84
META−ANALYSIS	**657:2181**	**0.86**



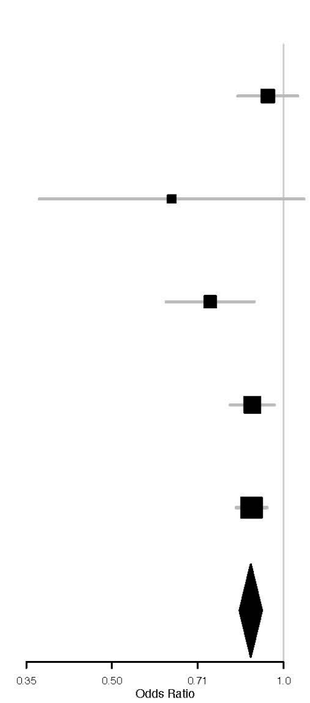
cg21220721

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.90
BAMSE_MEDALL	47:167	0.96
CHOP	19:363	1.03
GALA	106:87	0.94
ICAC	97:97	0.54
NFBC	29:343	0.88
PIAMA	15:182	0.97
RAINE	114:405	0.97
STOPPA	137:323	0.91
META−ANALYSIS	**657:2181**	**0.94**



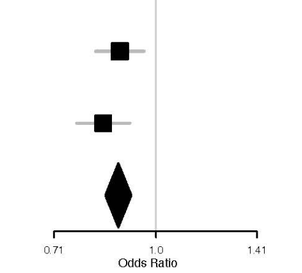
cg09249800

Cohort	N cases:controls	OR
GALA	106:87	0.94
ICAC	97:97	0.64
NFBC	29:343	0.74
RAINE	114:405	0.88
STOPPA	137:323	0.88
META−ANALYSIS	**483:1255**	**0.88**



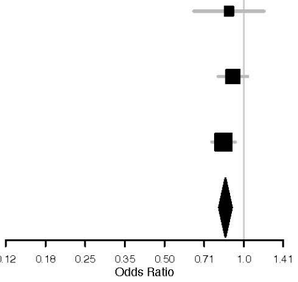
cg13054523

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.85
BAMSE_MEDALL	47:167	0.88
CHOP	19:363	1.06
GALA	106:87	0.84
ICAC	97:97	1.00
NFBC	29:343	0.38
PIAMA	15:182	0.95
RAINE	114:405	0.87
STOPPA	137:323	0.82
META−ANALYSIS	**657:2181**	**0.87**



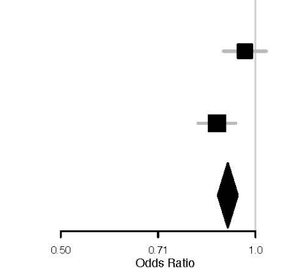
cg09377531

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.88
BAMSE_MEDALL	47:167	0.83
CHOP	19:363	1.08
ICAC	97:97	0.83
NFBC	29:343	0.82
PIAMA	15:182	0.89
RAINE	114:405	0.97
STOPPA	137:323	0.87
META−ANALYSIS	**551:2094**	**0.90**



cg25087851

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.84
BAMSE_MEDALL	47:167	0.82
CHOP	19:363	0.95
GALA	106:87	0.98
ICAC	97:97	0.75
NFBC	29:343	0.94
PIAMA	15:182	1.10
RAINE	114:405	0.87
STOPPA	137:323	0.86
META−ANALYSIS	**657:2181**	**0.89**



cg26252077

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.84
BAMSE_MEDALL	47:167	0.76
CHOP	19:363	1.06
ICAC	97:97	0.84
NFBC	29:343	0.86
PIAMA	15:182	1.13
RAINE	114:405	0.88
STOPPA	137:323	0.84
META−ANALYSIS	**551:2094**	**0.88**

cg05184016

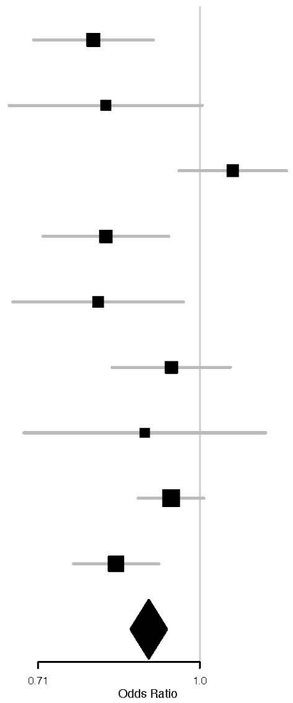
Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.77
BAMSE_MEDALL	47:167	0.80
CHOP	19:363	1.01
GALA	106:87	0.90
ICAC	97:97	0.86
NFBC	29:343	0.29
PIAMA	15:182	0.88
RAINE	114:405	0.91
STOPPA	137:323	0.84
META−ANALYSIS	**657:2181**	**0.85**

cg01000631

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.87
BAMSE_MEDALL	47:167	0.98
CHOP	19:363	0.96
ICAC	97:97	0.60
NFBC	29:343	0.82
PIAMA	15:182	0.97
RAINE	114:405	0.96
STOPPA	137:323	0.87
META−ANALYSIS	**551:2094**	**0.91**

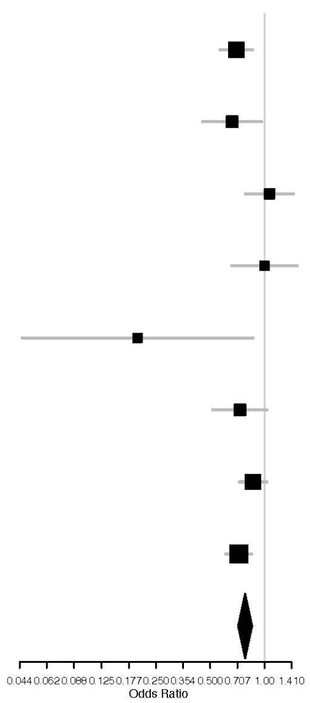
cg11683482

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.80
BAMSE_MEDALL	47:167	0.82
CHOP	19:363	1.07
GALA	106:87	0.82
ICAC	97:97	0.80
NFBC	29:343	0.94
PIAMA	15:182	0.89
RAINE	114:405	0.94
STOPPA	137:323	0.84
META−ANALYSIS	**657:2181**	**0.90**



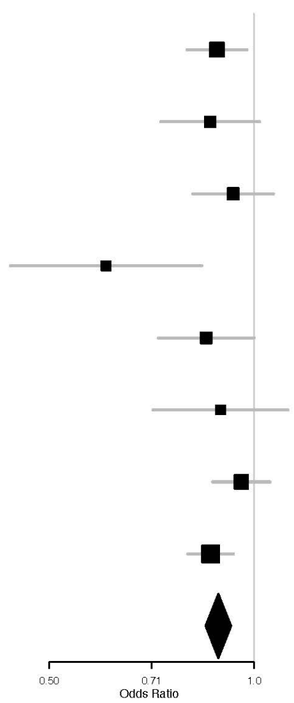
cg13850063

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.70
BAMSE_MEDALL	47:167	0.66
CHOP	19:363	1.07
ICAC	97:97	1.00
NFBC	29:343	0.20
PIAMA	15:182	0.73
RAINE	114:405	0.86
STOPPA	137:323	0.72
META−ANALYSIS	**551:2094**	**0.78**



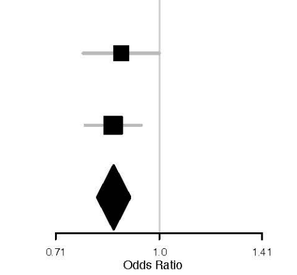
cg13458609

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.88
BAMSE_MEDALL	47:167	0.86
CHOP	19:363	0.93
ICAC	97:97	0.61
NFBC	29:343	0.85
PIAMA	15:182	0.89
RAINE	114:405	0.96
STOPPA	137:323	0.86
META−ANALYSIS	**551:2094**	**0.89**



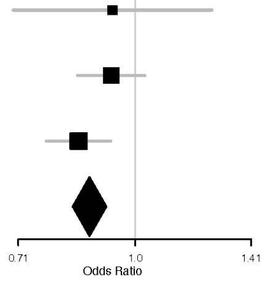
cg00170714

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.81
BAMSE_MEDALL	47:167	0.85
CHOP	19:363	0.92
GALA	106:87	0.88
ICAC	97:97	0.72
NFBC	29:343	0.90
PIAMA	15:182	1.15
RAINE	114:405	0.95
STOPPA	137:323	0.83
META−ANALYSIS	**657:2181**	**0.89**



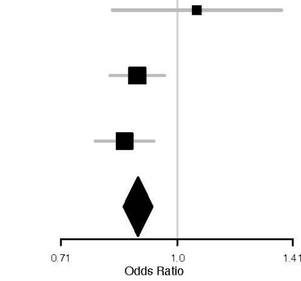
cg07970948

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.88
BAMSE_MEDALL	47:167	0.88
CHOP	19:363	0.99
GALA	106:87	1.01
ICAC	97:97	0.86
NFBC	29:343	0.76
PIAMA	15:182	1.00
RAINE	114:405	0.90
STOPPA	137:323	0.88
META−ANALYSIS	**657:2181**	**0.91**



cg18337287

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.86
BAMSE_MEDALL	47:167	0.89
CHOP	19:363	1.06
GALA	106:87	0.77
ICAC	97:97	0.67
NFBC	29:343	0.97
PIAMA	15:182	1.10
RAINE	114:405	0.88
STOPPA	137:323	0.82
META−ANALYSIS	**657:2181**	**0.86**



cg24459209

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.82
BAMSE_MEDALL	47:167	0.89
CHOP	19:363	0.82
ICAC	97:97	0.85
NFBC	29:343	0.82
PIAMA	15:182	1.12
RAINE	114:405	0.88
STOPPA	137:323	0.86
META−ANALYSIS	**551:2094**	**0.86**

cg06725287

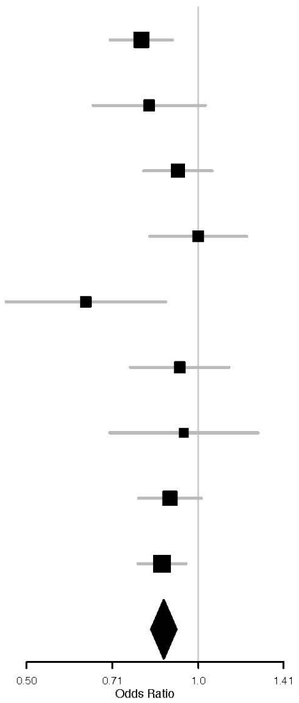
Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.81
BAMSE_MEDALL	47:167	0.77
CHOP	19:363	1.03
GALA	106:87	0.85
ICAC	97:97	0.87
NFBC	29:343	0.91
PIAMA	15:182	0.93
RAINE	114:405	0.93
STOPPA	137:323	0.85
META−ANALYSIS	**657:2181**	**0.87**

cg04933530

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.86
BAMSE_MEDALL	47:167	0.87
CHOP	19:363	0.96
GALA	106:87	0.84
ICAC	97:97	0.81
NFBC	29:343	1.01
PIAMA	15:182	1.06
RAINE	114:405	0.89
STOPPA	137:323	0.85
META−ANALYSIS	**657:2181**	**0.89**

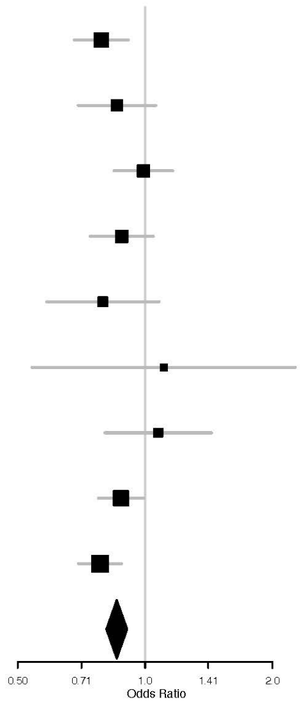
cg03437605

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.79
BAMSE_MEDALL	47:167	0.82
CHOP	19:363	0.92
GALA	106:87	1.00
ICAC	97:97	0.64
NFBC	29:343	0.93
PIAMA	15:182	0.94
RAINE	114:405	0.89
STOPPA	137:323	0.86
META−ANALYSIS	**657:2181**	**0.87**



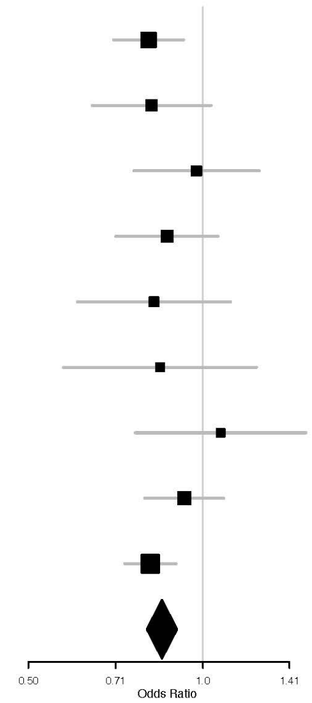
cg12104982

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.79
BAMSE_MEDALL	47:167	0.86
CHOP	19:363	0.99
GALA	106:87	0.88
ICAC	97:97	0.79
NFBC	29:343	1.11
PIAMA	15:182	1.07
RAINE	114:405	0.88
STOPPA	137:323	0.78
META−ANALYSIS	**657:2181**	**0.86**



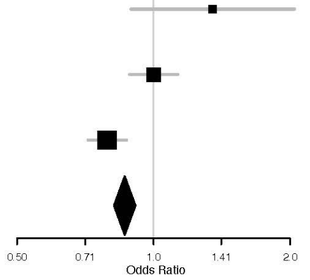
cg08077807

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.81
BAMSE_MEDALL	47:167	0.82
CHOP	19:363	0.97
GALA	106:87	0.87
ICAC	97:97	0.82
NFBC	29:343	0.84
PIAMA	15:182	1.07
RAINE	114:405	0.93
STOPPA	137:323	0.81
META−ANALYSIS	**657:2181**	**0.85**



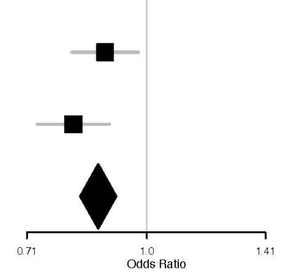
cg10065736

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.85
BAMSE_MEDALL	47:167	0.92
CHOP	19:363	1.01
GALA	106:87	0.97
ICAC	97:97	0.71
NFBC	29:343	0.88
PIAMA	15:182	1.02
RAINE	114:405	0.91
STOPPA	137:323	0.87
META−ANALYSIS	**657:2181**	**0.90**



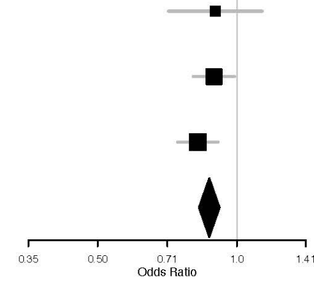
cg18666454

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.88
BAMSE_MEDALL	47:167	0.86
CHOP	19:363	0.91
GALA	106:87	0.86
ICAC	97:97	0.66
NFBC	29:343	0.82
PIAMA	15:182	0.93
RAINE	114:405	0.96
STOPPA	137:323	0.89
META−ANALYSIS	**657:2181**	**0.89**



cg09705784

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.86
BAMSE_MEDALL	47:167	0.82
CHOP	19:363	0.87
ICAC	97:97	0.75
NFBC	29:343	0.74
PIAMA	15:182	0.86
RAINE	114:405	0.96
STOPPA	137:323	0.93
META−ANALYSIS	**551:2094**	**0.91**



cg02494549

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.82
BAMSE_MEDALL	47:167	0.82
CHOP	19:363	0.77
GALA	106:87	1.04
ICAC	97:97	0.96
NFBC	29:343	0.82
PIAMA	15:182	1.35
RAINE	114:405	1.00
STOPPA	137:323	0.79
META−ANALYSIS	**657:2181**	**0.86**

cg21723861

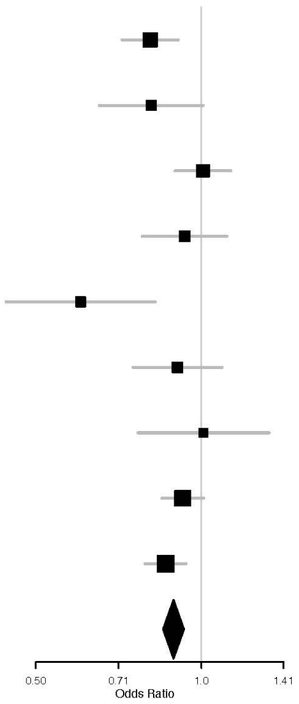
Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.81
BAMSE_MEDALL	47:167	0.89
CHOP	19:363	0.95
ICAC	97:97	0.93
NFBC	29:343	0.90
PIAMA	15:182	1.12
RAINE	114:405	0.89
STOPPA	137:323	0.81
META−ANALYSIS	**551:2094**	**0.87**

cg05875066

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.86
BAMSE_MEDALL	47:167	0.55
CHOP	19:363	0.97
GALA	106:87	0.92
ICAC	97:97	1.01
NFBC	29:343	0.95
PIAMA	15:182	0.90
RAINE	114:405	0.89
STOPPA	137:323	0.82
META−ANALYSIS	**657:2181**	**0.87**

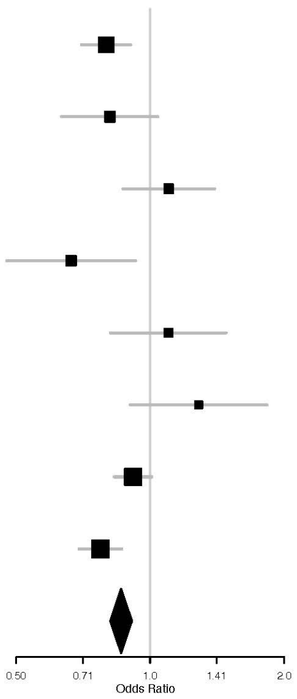
cg08773180

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.81
BAMSE_MEDALL	47:167	0.81
CHOP	19:363	1.01
GALA	106:87	0.93
ICAC	97:97	0.60
NFBC	29:343	0.90
PIAMA	15:182	1.01
RAINE	114:405	0.92
STOPPA	137:323	0.86
META−ANALYSIS	**657:2181**	**0.89**



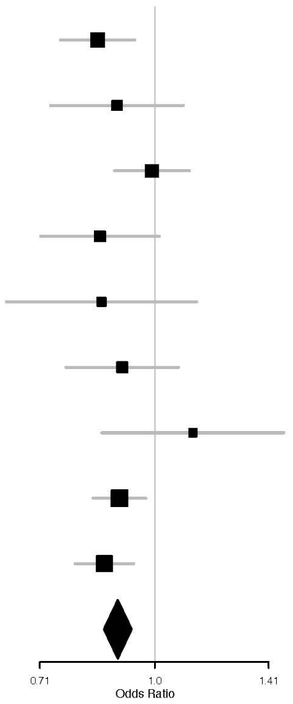
cg02596233

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.80
BAMSE_MEDALL	47:167	0.81
CHOP	19:363	1.10
ICAC	97:97	0.66
NFBC	29:343	1.10
PIAMA	15:182	1.29
RAINE	114:405	0.92
STOPPA	137:323	0.77
META−ANALYSIS	**551:2094**	**0.86**



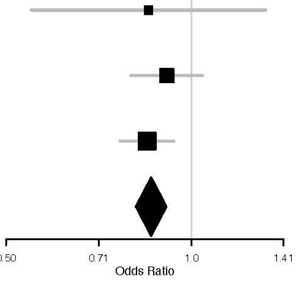
cg16263722

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.84
BAMSE_MEDALL	47:167	0.89
CHOP	19:363	0.99
GALA	106:87	0.85
ICAC	97:97	0.85
NFBC	29:343	0.91
PIAMA	15:182	1.12
RAINE	114:405	0.90
STOPPA	137:323	0.86
META−ANALYSIS	**657:2181**	**0.89**



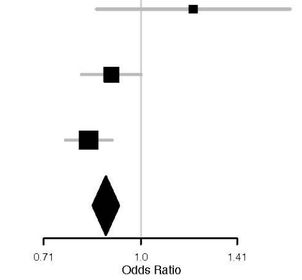
cg10704177

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.84
BAMSE_MEDALL	47:167	0.80
CHOP	19:363	1.04
GALA	106:87	0.93
ICAC	97:97	0.60
NFBC	29:343	0.90
PIAMA	15:182	1.07
RAINE	114:405	0.93
STOPPA	137:323	0.87
META−ANALYSIS	**657:2181**	**0.90**



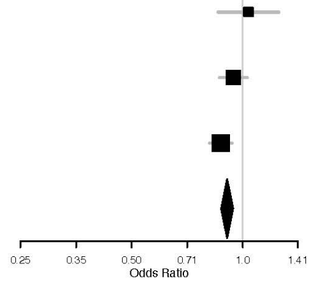
cg15700636

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.80
BAMSE_MEDALL	47:167	0.88
CHOP	19:363	1.10
GALA	106:87	0.94
ICAC	97:97	0.68
NFBC	29:343	0.82
PIAMA	15:182	1.00
RAINE	114:405	0.92
STOPPA	137:323	0.85
META−ANALYSIS	**657:2181**	**0.89**



cg07908654

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.83
BAMSE_MEDALL	47:167	0.91
CHOP	19:363	0.96
GALA	106:87	0.99
ICAC	97:97	0.67
NFBC	29:343	0.75
PIAMA	15:182	0.89
RAINE	114:405	0.91
STOPPA	137:323	0.88
META−ANALYSIS	**657:2181**	**0.89**



cg10815420

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.90
BAMSE_MEDALL	47:167	0.75
CHOP	19:363	0.83
GALA	106:87	0.86
ICAC	97:97	0.85
NFBC	29:343	0.73
PIAMA	15:182	0.85
RAINE	114:405	0.91
STOPPA	137:323	0.85
META−ANALYSIS	**657:2181**	**0.86**

cg07410597

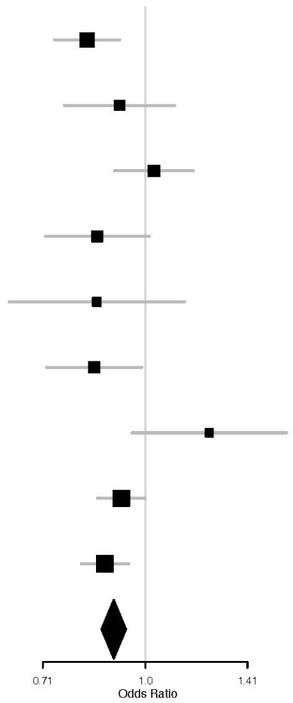
Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.85
BAMSE_MEDALL	47:167	0.84
CHOP	19:363	1.04
GALA	106:87	0.96
ICAC	97:97	0.87
NFBC	29:343	0.84
PIAMA	15:182	1.21
RAINE	114:405	0.90
STOPPA	137:323	0.83
META−ANALYSIS	**657:2181**	**0.88**

cg08940169

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.90
BAMSE_MEDALL	47:167	0.93
CHOP	19:363	0.96
GALA	106:87	0.89
ICAC	97:97	0.50
NFBC	29:343	0.76
PIAMA	15:182	1.04
RAINE	114:405	0.94
STOPPA	137:323	0.87
META−ANALYSIS	**657:2181**	**0.91**

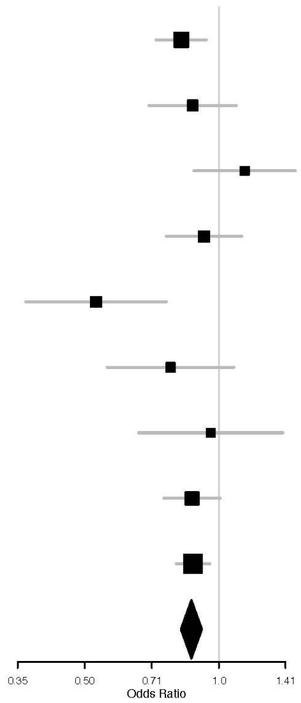
cg00944309

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.82
BAMSE_MEDALL	47:167	0.92
CHOP	19:363	1.03
GALA	106:87	0.85
ICAC	97:97	0.85
NFBC	29:343	0.84
PIAMA	15:182	1.24
RAINE	114:405	0.92
STOPPA	137:323	0.87
META−ANALYSIS	**657:2181**	**0.90**



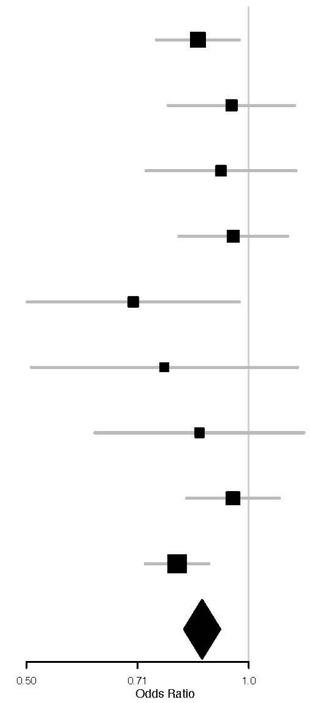
cg20263733

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.82
BAMSE_MEDALL	47:167	0.87
CHOP	19:363	1.14
GALA	106:87	0.93
ICAC	97:97	0.53
NFBC	29:343	0.78
PIAMA	15:182	0.96
RAINE	114:405	0.87
STOPPA	137:323	0.87
META−ANALYSIS	**657:2181**	**0.87**



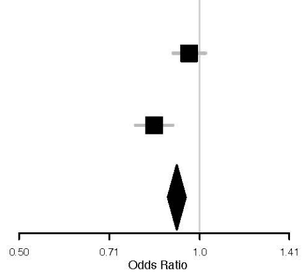
cg25270424

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.85
BAMSE_MEDALL	47:167	0.95
CHOP	19:363	0.92
GALA	106:87	0.95
ICAC	97:97	0.70
NFBC	29:343	0.77
PIAMA	15:182	0.86
RAINE	114:405	0.95
STOPPA	137:323	0.80
META−ANALYSIS	**657:2181**	**0.86**



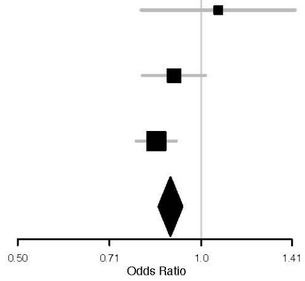
cg16409452

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.90
BAMSE_MEDALL	47:167	0.92
CHOP	19:363	1.01
GALA	106:87	0.87
ICAC	97:97	0.76
NFBC	29:343	0.91
PIAMA	15:182	0.88
RAINE	114:405	0.94
STOPPA	137:323	0.86
META−ANALYSIS	**657:2181**	**0.91**



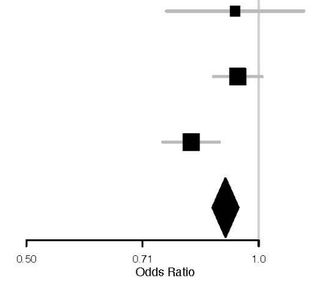
cg04077085

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.84
BAMSE_MEDALL	47:167	0.86
CHOP	19:363	0.96
GALA	106:87	0.85
ICAC	97:97	0.75
NFBC	29:343	1.01
PIAMA	15:182	0.99
RAINE	114:405	0.96
STOPPA	137:323	0.80
META−ANALYSIS	**657:2181**	**0.86**



cg05477517

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.80
BAMSE_MEDALL	47:167	0.78
CHOP	19:363	0.90
GALA	106:87	0.99
ICAC	97:97	0.64
NFBC	29:343	0.91
PIAMA	15:182	1.23
RAINE	114:405	0.99
STOPPA	137:323	0.80
META−ANALYSIS	**657:2181**	**0.88**



cg23706836

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.90
BAMSE_MEDALL	47:167	0.91
CHOP	19:363	1.01
ICAC	97:97	0.71
NFBC	29:343	0.88
PIAMA	15:182	1.14
RAINE	114:405	0.96
STOPPA	137:323	0.84
META−ANALYSIS	**551:2094**	**0.92**

cg18460809

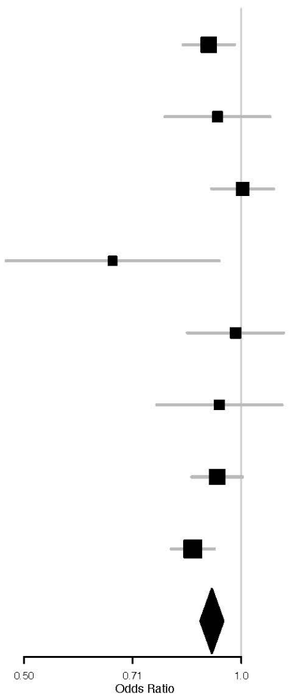
Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.97
BAMSE_MEDALL	47:167	0.84
CHOP	19:363	0.98
GALA	106:87	0.79
ICAC	97:97	0.67
NFBC	29:343	1.00
PIAMA	15:182	1.07
RAINE	114:405	0.90
STOPPA	137:323	0.84
META−ANALYSIS	**657:2181**	**0.89**

cg01998785

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.88
BAMSE_MEDALL	47:167	0.88
CHOP	19:363	1.03
GALA	106:87	0.87
ICAC	97:97	0.77
NFBC	29:343	0.95
PIAMA	15:182	0.93
RAINE	114:405	0.94
STOPPA	137:323	0.82
META−ANALYSIS	**657:2181**	**0.91**

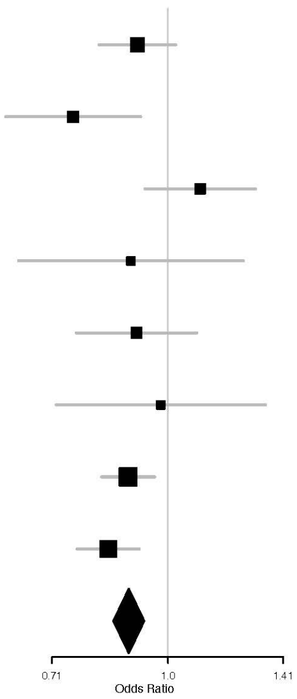
cg18550847

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.90
BAMSE_MEDALL	47:167	0.93
CHOP	19:363	1.00
ICAC	97:97	0.66
NFBC	29:343	0.98
PIAMA	15:182	0.93
RAINE	114:405	0.93
STOPPA	137:323	0.86
META−ANALYSIS	**551:2094**	**0.91**



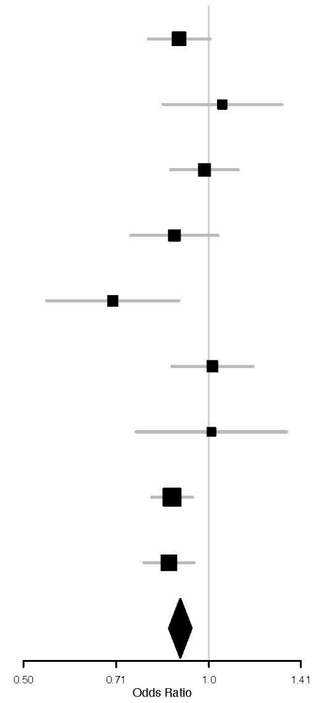
cg03131767

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.91
BAMSE_MEDALL	47:167	0.75
CHOP	19:363	1.10
ICAC	97:97	0.90
NFBC	29:343	0.91
PIAMA	15:182	0.98
RAINE	114:405	0.89
STOPPA	137:323	0.84
META−ANALYSIS	**551:2094**	**0.89**



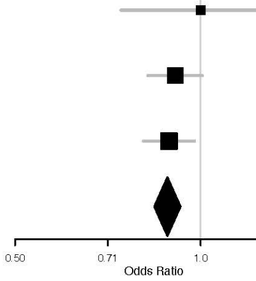
cg02435538

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.89
BAMSE_MEDALL	47:167	1.05
CHOP	19:363	0.98
GALA	106:87	0.88
ICAC	97:97	0.70
NFBC	29:343	1.01
PIAMA	15:182	1.01
RAINE	114:405	0.87
STOPPA	137:323	0.86
META−ANALYSIS	**657:2181**	**0.90**



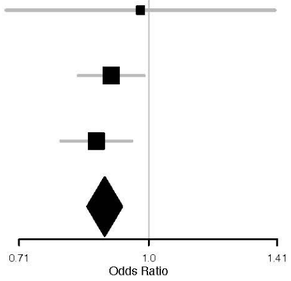
cg11987455

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.86
BAMSE_MEDALL	47:167	0.90
CHOP	19:363	0.86
GALA	106:87	0.86
ICAC	97:97	0.93
NFBC	29:343	0.83
PIAMA	15:182	1.24
RAINE	114:405	0.92
STOPPA	137:323	0.87
META−ANALYSIS	**657:2181**	**0.89**



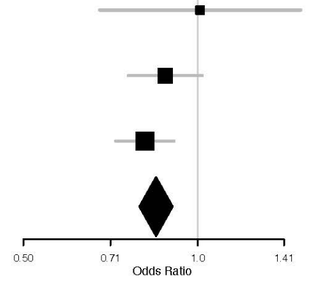
cg09447105

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.74
BAMSE_MEDALL	47:167	0.80
CHOP	19:363	1.19
GALA	106:87	0.90
ICAC	97:97	0.89
NFBC	29:343	0.87
PIAMA	15:182	1.03
RAINE	114:405	0.86
STOPPA	137:323	0.85
META−ANALYSIS	**657:2181**	**0.88**



cg13628444

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.79
BAMSE_MEDALL	47:167	0.80
CHOP	19:363	0.99
ICAC	97:97	0.82
NFBC	29:343	0.89
PIAMA	15:182	0.99
RAINE	114:405	0.94
STOPPA	137:323	0.85
META−ANALYSIS	**551:2094**	**0.89**



cg25173129

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.79
BAMSE_MEDALL	47:167	0.85
CHOP	19:363	1.06
GALA	106:87	0.84
ICAC	97:97	0.77
NFBC	29:343	0.78
PIAMA	15:182	1.00
RAINE	114:405	0.91
STOPPA	137:323	0.89
META−ANALYSIS	**657:2181**	**0.88**

cg14025883

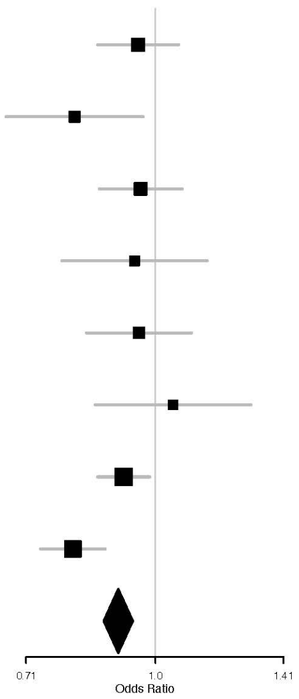
Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.80
BAMSE_MEDALL	47:167	0.97
CHOP	19:363	1.11
GALA	106:87	0.84
ICAC	97:97	1.00
NFBC	29:343	0.81
PIAMA	15:182	0.98
RAINE	114:405	0.90
STOPPA	137:323	0.87
META−ANALYSIS	**657:2181**	**0.89**

cg02133716

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.78
BAMSE_MEDALL	47:167	0.89
CHOP	19:363	1.11
GALA	106:87	0.93
ICAC	97:97	0.75
NFBC	29:343	0.76
PIAMA	15:182	1.01
RAINE	114:405	0.88
STOPPA	137:323	0.81
META−ANALYSIS	**657:2181**	**0.85**

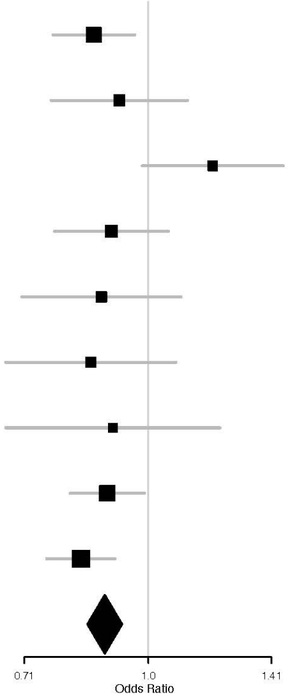
cg17890764

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.96
BAMSE_MEDALL	47:167	0.81
CHOP	19:363	0.96
ICAC	97:97	0.95
NFBC	29:343	0.96
PIAMA	15:182	1.05
RAINE	114:405	0.92
STOPPA	137:323	0.80
META−ANALYSIS	**551:2094**	**0.91**



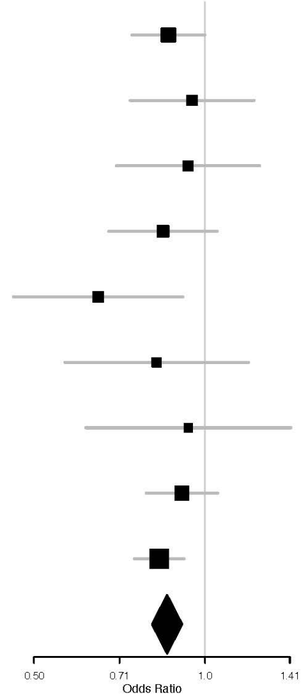
cg25479097

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.86
BAMSE_MEDALL	47:167	0.92
CHOP	19:363	1.20
GALA	106:87	0.90
ICAC	97:97	0.88
NFBC	29:343	0.85
PIAMA	15:182	0.91
RAINE	114:405	0.89
STOPPA	137:323	0.83
META−ANALYSIS	**657:2181**	**0.89**



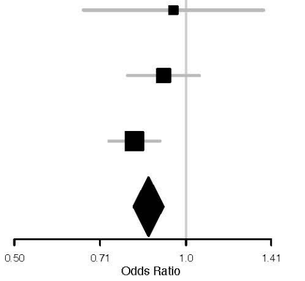
cg13197551

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.86
BAMSE_MEDALL	47:167	0.95
CHOP	19:363	0.93
GALA	106:87	0.84
ICAC	97:97	0.65
NFBC	29:343	0.82
PIAMA	15:182	0.93
RAINE	114:405	0.91
STOPPA	137:323	0.83
META−ANALYSIS	**657:2181**	**0.86**



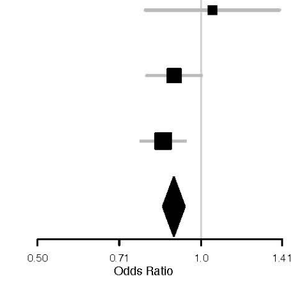
cg02803925

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.85
BAMSE_MEDALL	47:167	0.87
CHOP	19:363	1.14
ICAC	97:97	0.75
NFBC	29:343	0.64
PIAMA	15:182	0.93
RAINE	114:405	0.89
STOPPA	137:323	0.83
META−ANALYSIS	**551:2094**	**0.86**



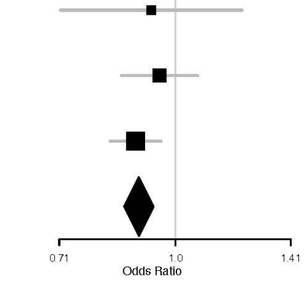
cg02970679

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.82
BAMSE_MEDALL	47:167	0.93
CHOP	19:363	0.96
GALA	106:87	0.91
ICAC	97:97	0.60
NFBC	29:343	0.84
PIAMA	15:182	1.08
RAINE	114:405	0.95
STOPPA	137:323	0.83
META−ANALYSIS	**657:2181**	**0.88**



cg07386061

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.89
BAMSE_MEDALL	47:167	0.80
CHOP	19:363	0.97
GALA	106:87	0.97
ICAC	97:97	0.90
NFBC	29:343	0.84
PIAMA	15:182	1.01
RAINE	114:405	0.94
STOPPA	137:323	0.87
META−ANALYSIS	**657:2181**	**0.91**



cg09332506

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.87
BAMSE_MEDALL	47:167	0.82
CHOP	19:363	1.11
GALA	106:87	0.91
ICAC	97:97	0.69
NFBC	29:343	0.86
PIAMA	15:182	0.95
RAINE	114:405	0.91
STOPPA	137:323	0.81
META−ANALYSIS	**657:2181**	**0.86**

cg10142874

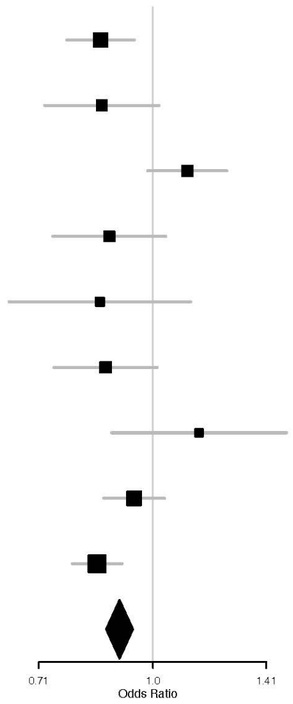
Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.82
BAMSE_MEDALL	47:167	0.89
CHOP	19:363	1.01
GALA	106:87	0.96
ICAC	97:97	0.63
NFBC	29:343	0.74
PIAMA	15:182	1.05
RAINE	114:405	0.89
STOPPA	137:323	0.85
META−ANALYSIS	**657:2181**	**0.89**

cg20885063

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.81
BAMSE_MEDALL	47:167	0.92
CHOP	19:363	1.05
GALA	106:87	0.92
ICAC	97:97	0.81
NFBC	29:343	0.78
PIAMA	15:182	0.93
RAINE	114:405	0.95
STOPPA	137:323	0.89
META−ANALYSIS	**657:2181**	**0.90**

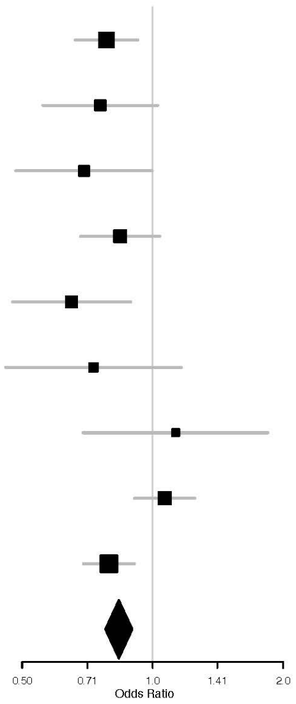
cg16362140

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.85
BAMSE_MEDALL	47:167	0.86
CHOP	19:363	1.11
GALA	106:87	0.88
ICAC	97:97	0.85
NFBC	29:343	0.87
PIAMA	15:182	1.15
RAINE	114:405	0.94
STOPPA	137:323	0.84
META−ANALYSIS	**657:2181**	**0.90**



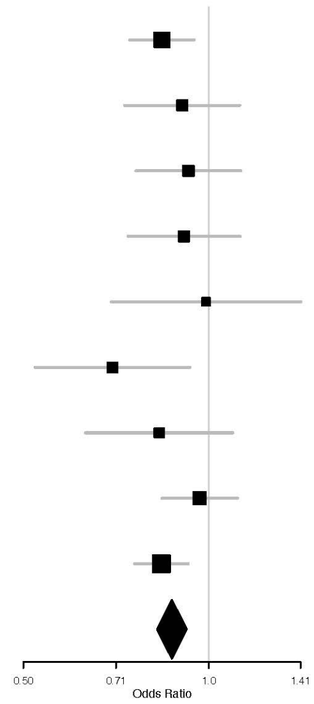
cg14678084

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.78
BAMSE_MEDALL	47:167	0.76
CHOP	19:363	0.69
GALA	106:87	0.84
ICAC	97:97	0.65
NFBC	29:343	0.73
PIAMA	15:182	1.13
RAINE	114:405	1.07
STOPPA	137:323	0.79
META−ANALYSIS	**657:2181**	**0.84**



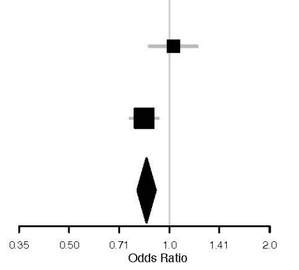
cg18879389

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.84
BAMSE_MEDALL	47:167	0.91
CHOP	19:363	0.93
GALA	106:87	0.91
ICAC	97:97	0.99
NFBC	29:343	0.70
PIAMA	15:182	0.83
RAINE	114:405	0.97
STOPPA	137:323	0.84
META−ANALYSIS	**657:2181**	**0.87**



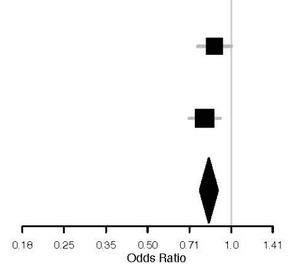
cg17988187

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.89
BAMSE_MEDALL	47:167	0.95
CHOP	19:363	1.01
ICAC	97:97	0.70
NFBC	29:343	0.80
PIAMA	15:182	1.10
RAINE	114:405	0.92
STOPPA	137:323	0.84
META−ANALYSIS	**551:2094**	**0.90**



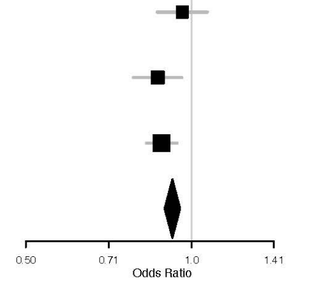
cg18912470

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.88
BAMSE_MEDALL	47:167	0.78
CHOP	19:363	0.97
GALA	106:87	0.93
ICAC	97:97	1.03
NFBC	29:343	0.86
PIAMA	15:182	0.78
RAINE	114:405	0.92
STOPPA	137:323	0.88
META−ANALYSIS	**657:2181**	**0.91**



cg00213281

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.82
BAMSE_MEDALL	47:167	0.73
CHOP	19:363	1.02
GALA	106:87	0.93
ICAC	97:97	0.67
NFBC	29:343	0.75
PIAMA	15:182	0.92
RAINE	114:405	0.95
STOPPA	137:323	0.87
META−ANALYSIS	**657:2181**	**0.88**



cg24368962

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.80
BAMSE_MEDALL	47:167	0.83
CHOP	19:363	1.09
ICAC	97:97	0.54
NFBC	29:343	0.62
PIAMA	15:182	1.54
RAINE	114:405	1.03
STOPPA	137:323	0.84
META−ANALYSIS	**551:2094**	**0.85**

cg26979537

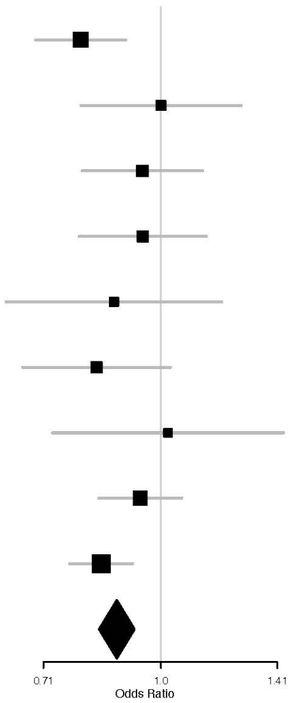
Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.76
BAMSE_MEDALL	47:167	0.89
CHOP	19:363	0.93
ICAC	97:97	1.06
NFBC	29:343	0.54
PIAMA	15:182	0.67
RAINE	114:405	0.87
STOPPA	137:323	0.80
META−ANALYSIS	**551:2094**	**0.83**

cg10099827

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.94
BAMSE_MEDALL	47:167	0.99
CHOP	19:363	0.98
GALA	106:87	0.94
ICAC	97:97	0.73
NFBC	29:343	0.88
PIAMA	15:182	0.96
RAINE	114:405	0.87
STOPPA	137:323	0.88
META−ANALYSIS	**657:2181**	**0.92**

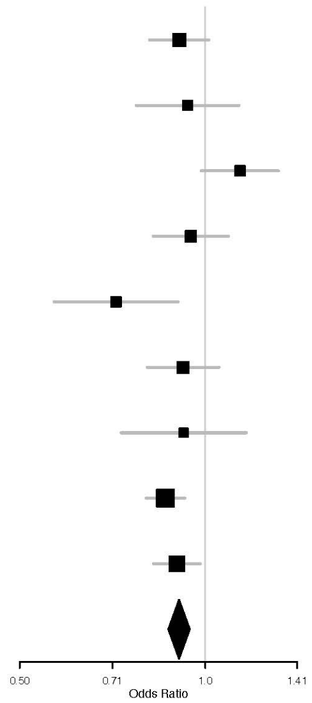
cg01942646

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.79
BAMSE_MEDALL	47:167	1.00
CHOP	19:363	0.95
GALA	106:87	0.95
ICAC	97:97	0.87
NFBC	29:343	0.83
PIAMA	15:182	1.02
RAINE	114:405	0.94
STOPPA	137:323	0.84
META−ANALYSIS	**657:2181**	**0.88**



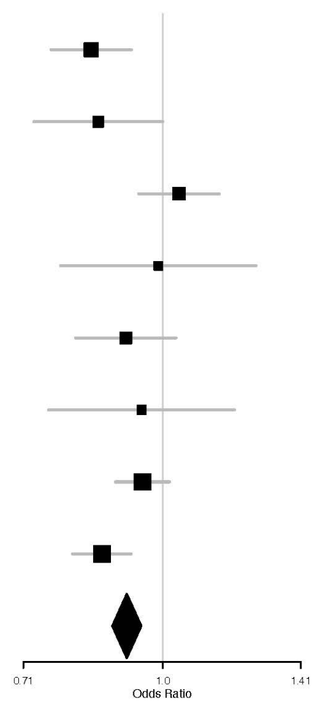
cg23387863

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.91
BAMSE_MEDALL	47:167	0.94
CHOP	19:363	1.14
GALA	106:87	0.95
ICAC	97:97	0.72
NFBC	29:343	0.92
PIAMA	15:182	0.92
RAINE	114:405	0.86
STOPPA	137:323	0.90
META−ANALYSIS	**657:2181**	**0.91**



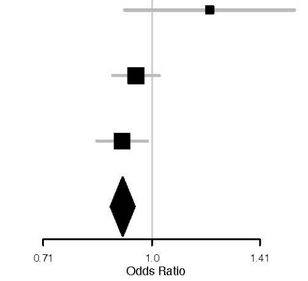
cg19434937

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.84
BAMSE_MEDALL	47:167	0.85
CHOP	19:363	1.04
ICAC	97:97	0.99
NFBC	29:343	0.91
PIAMA	15:182	0.95
RAINE	114:405	0.95
STOPPA	137:323	0.86
META−ANALYSIS	**551:2094**	**0.91**



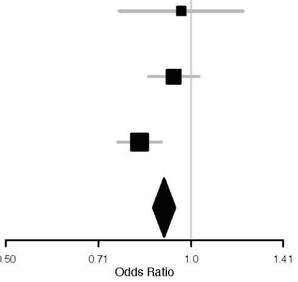
cg26752663

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	1.09
BAMSE_MEDALL	47:167	1.27
CHOP	19:363	1.11
GALA	106:87	1.16
ICAC	97:97	1.55
NFBC	29:343	1.09
PIAMA	15:182	1.32
RAINE	114:405	1.03
STOPPA	137:323	1.20
META−ANALYSIS	**657:2181**	**1.12**



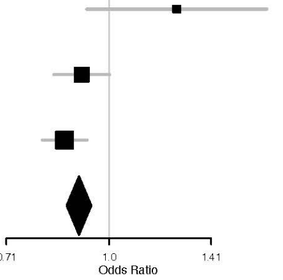
cg23147443

Cohort	N cases:controls	OR
GALA	106:87	0.93
ICAC	97:97	0.70
NFBC	29:343	0.91
RAINE	114:405	0.91
STOPPA	137:323	0.88
META−ANALYSIS	**483:1255**	**0.89**



cg18042632

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.89
BAMSE_MEDALL	47:167	1.00
CHOP	19:363	0.93
GALA	106:87	0.88
ICAC	97:97	0.76
NFBC	29:343	0.96
PIAMA	15:182	0.96
RAINE	114:405	0.94
STOPPA	137:323	0.90
META−ANALYSIS	**657:2181**	**0.92**



cg25939647

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.82
BAMSE_MEDALL	47:167	0.79
CHOP	19:363	0.98
GALA	106:87	0.91
ICAC	97:97	0.81
NFBC	29:343	0.87
PIAMA	15:182	1.20
RAINE	114:405	0.95
STOPPA	137:323	0.91
META−ANALYSIS	**657:2181**	**0.91**

cg04497992

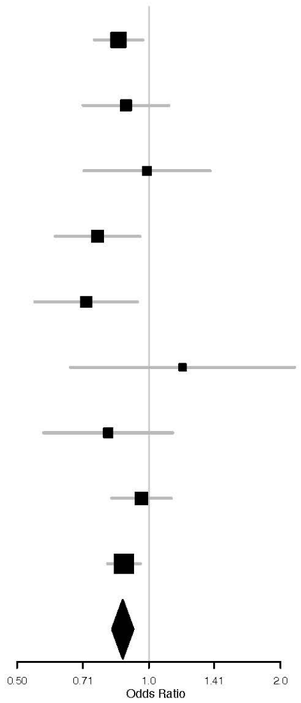
Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.90
BAMSE_MEDALL	47:167	0.90
CHOP	19:363	1.03
GALA	106:87	0.95
ICAC	97:97	0.77
NFBC	29:343	0.89
PIAMA	15:182	0.96
RAINE	114:405	0.94
STOPPA	137:323	0.82
META−ANALYSIS	**657:2181**	**0.90**

cg00736681

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.88
BAMSE_MEDALL	47:167	0.88
CHOP	19:363	1.03
GALA	106:87	0.93
ICAC	97:97	0.89
NFBC	29:343	0.81
PIAMA	15:182	1.26
RAINE	114:405	0.91
STOPPA	137:323	0.86
META−ANALYSIS	**657:2181**	**0.90**

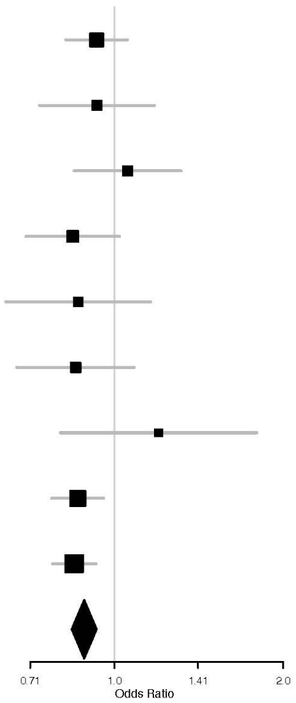
cg24028828

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.85
BAMSE_MEDALL	47:167	0.89
CHOP	19:363	0.99
GALA	106:87	0.76
ICAC	97:97	0.72
NFBC	29:343	1.19
PIAMA	15:182	0.81
RAINE	114:405	0.96
STOPPA	137:323	0.88
META−ANALYSIS	**657:2181**	**0.87**



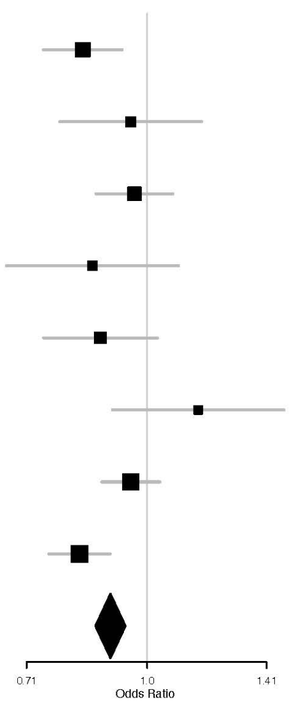
cg01499988

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.93
BAMSE_MEDALL	47:167	0.93
CHOP	19:363	1.06
GALA	106:87	0.84
ICAC	97:97	0.86
NFBC	29:343	0.85
PIAMA	15:182	1.20
RAINE	114:405	0.86
STOPPA	137:323	0.85
META−ANALYSIS	**657:2181**	**0.88**



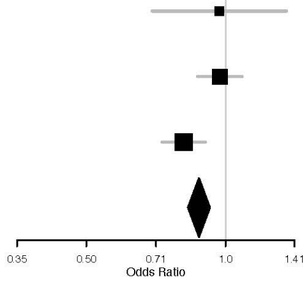
cg17374802

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.83
BAMSE_MEDALL	47:167	0.95
CHOP	19:363	0.96
ICAC	97:97	0.85
NFBC	29:343	0.87
PIAMA	15:182	1.16
RAINE	114:405	0.95
STOPPA	137:323	0.82
META−ANALYSIS	**551:2094**	**0.90**



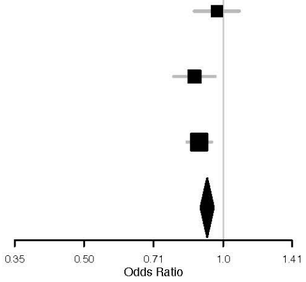
cg22816343

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.83
BAMSE_MEDALL	47:167	0.73
CHOP	19:363	0.99
GALA	106:87	0.99
ICAC	97:97	0.75
NFBC	29:343	0.88
PIAMA	15:182	0.66
RAINE	114:405	0.95
STOPPA	137:323	0.87
META−ANALYSIS	**657:2181**	**0.89**



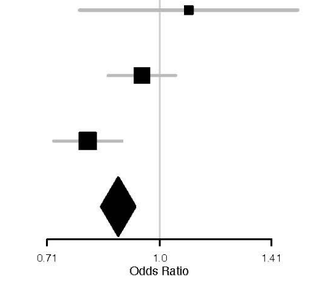
cg03014680

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.92
BAMSE_MEDALL	47:167	0.98
CHOP	19:363	0.97
ICAC	97:97	0.76
NFBC	29:343	1.03
PIAMA	15:182	1.10
RAINE	114:405	0.89
STOPPA	137:323	0.91
META−ANALYSIS	**551:2094**	**0.92**



cg06426027

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.79
BAMSE_MEDALL	47:167	0.91
CHOP	19:363	1.11
ICAC	97:97	0.80
NFBC	29:343	0.72
PIAMA	15:182	0.91
RAINE	114:405	0.84
STOPPA	137:323	0.81
META−ANALYSIS	**551:2094**	**0.83**



cg04217850

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.78
BAMSE_MEDALL	47:167	0.78
CHOP	19:363	1.15
GALA	106:87	0.81
ICAC	97:97	0.52
NFBC	29:343	0.90
PIAMA	15:182	0.97
RAINE	114:405	0.97
STOPPA	137:323	0.81
META−ANALYSIS	**657:2181**	**0.88**

cg08640475

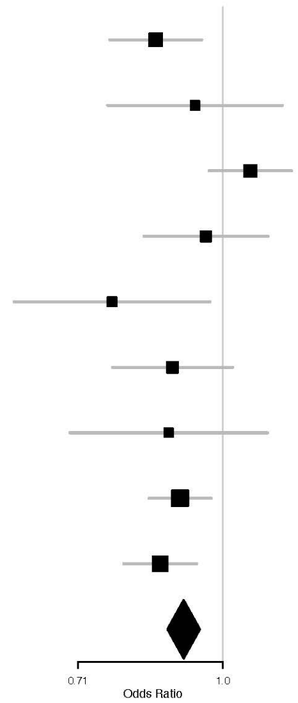
Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.94
BAMSE_MEDALL	47:167	0.97
CHOP	19:363	1.04
GALA	106:87	0.91
ICAC	97:97	0.59
NFBC	29:343	0.78
PIAMA	15:182	0.97
RAINE	114:405	0.87
STOPPA	137:323	0.89
META−ANALYSIS	**657:2181**	**0.92**

cg02359181

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.75
BAMSE_MEDALL	47:167	0.85
CHOP	19:363	1.10
GALA	106:87	0.86
ICAC	97:97	0.94
NFBC	29:343	0.91
PIAMA	15:182	1.09
RAINE	114:405	0.95
STOPPA	137:323	0.80
META−ANALYSIS	**657:2181**	**0.88**

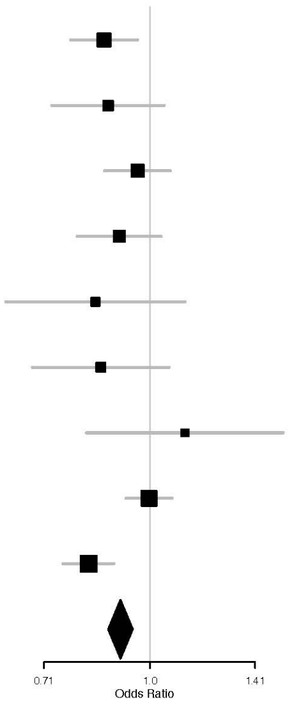
cg04321303

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.85
BAMSE_MEDALL	47:167	0.94
CHOP	19:363	1.07
GALA	106:87	0.96
ICAC	97:97	0.77
NFBC	29:343	0.89
PIAMA	15:182	0.88
RAINE	114:405	0.90
STOPPA	137:323	0.86
META−ANALYSIS	**657:2181**	**0.91**



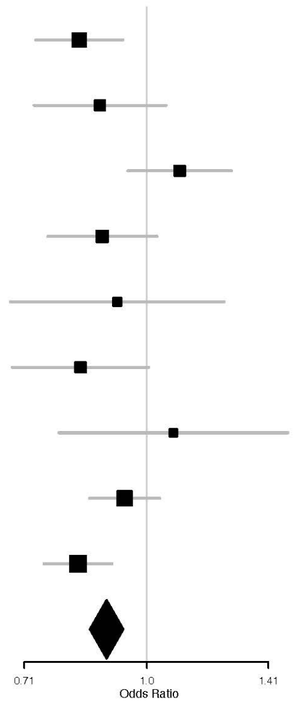
cg10387956

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.86
BAMSE_MEDALL	47:167	0.87
CHOP	19:363	0.96
GALA	106:87	0.90
ICAC	97:97	0.84
NFBC	29:343	0.85
PIAMA	15:182	1.12
RAINE	114:405	1.00
STOPPA	137:323	0.82
META−ANALYSIS	**657:2181**	**0.91**



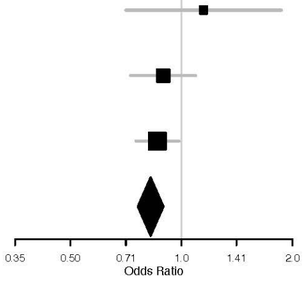
cg19805160

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.83
BAMSE_MEDALL	47:167	0.88
CHOP	19:363	1.10
GALA	106:87	0.88
ICAC	97:97	0.92
NFBC	29:343	0.83
PIAMA	15:182	1.08
RAINE	114:405	0.94
STOPPA	137:323	0.82
META−ANALYSIS	**657:2181**	**0.89**



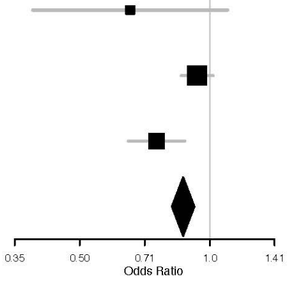
cg06958964

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.84
BAMSE_MEDALL	47:167	0.73
CHOP	19:363	0.95
GALA	106:87	0.76
ICAC	97:97	0.87
NFBC	29:343	0.75
PIAMA	15:182	1.02
RAINE	114:405	0.92
STOPPA	137:323	0.86
META−ANALYSIS	**657:2181**	**0.85**



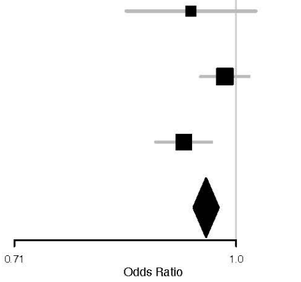
cg21919729

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.89
BAMSE_MEDALL	47:167	0.92
CHOP	19:363	1.06
ICAC	97:97	0.90
NFBC	29:343	0.90
PIAMA	15:182	0.96
RAINE	114:405	0.95
STOPPA	137:323	0.88
META−ANALYSIS	**551:2094**	**0.92**



cg09565310

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.79
BAMSE_MEDALL	47:167	0.85
CHOP	19:363	1.07
ICAC	97:97	0.96
NFBC	29:343	0.84
PIAMA	15:182	1.01
RAINE	114:405	0.94
STOPPA	137:323	0.86
META−ANALYSIS	**551:2094**	**0.89**



cg20503329

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.67
BAMSE_MEDALL	47:167	0.60
CHOP	19:363	1.22
GALA	106:87	0.99
ICAC	97:97	0.75
NFBC	29:343	0.69
PIAMA	15:182	1.15
RAINE	114:405	0.89
STOPPA	137:323	0.86
META−ANALYSIS	**657:2181**	**0.82**

cg18817654

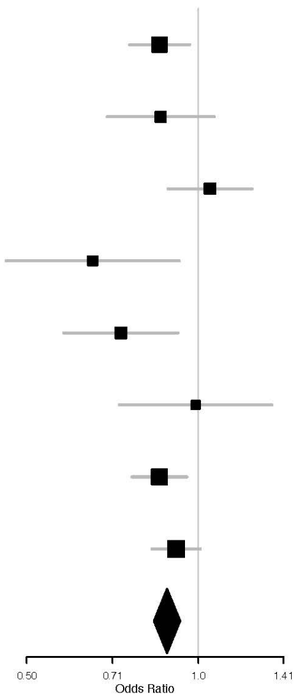
Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.77
BAMSE_MEDALL	47:167	0.82
CHOP	19:363	1.09
GALA	106:87	0.97
ICAC	97:97	0.78
NFBC	29:343	0.80
PIAMA	15:182	0.65
RAINE	114:405	0.93
STOPPA	137:323	0.75
META−ANALYSIS	**657:2181**	**0.87**

cg19851574

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.92
BAMSE_MEDALL	47:167	0.94
CHOP	19:363	1.02
GALA	106:87	0.97
ICAC	97:97	0.95
NFBC	29:343	0.91
PIAMA	15:182	0.93
RAINE	114:405	0.98
STOPPA	137:323	0.92
META−ANALYSIS	**657:2181**	**0.95**

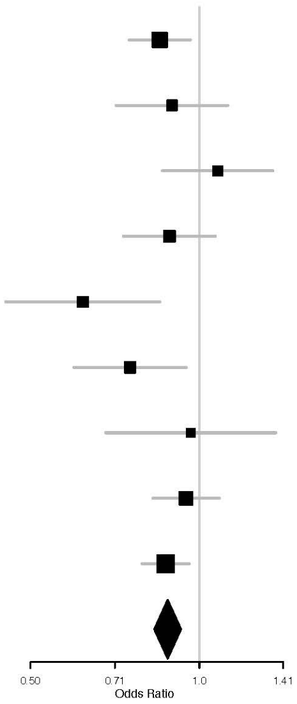
cg20315954

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.86
BAMSE_MEDALL	47:167	0.86
CHOP	19:363	1.05
ICAC	97:97	0.65
NFBC	29:343	0.73
PIAMA	15:182	0.99
RAINE	114:405	0.85
STOPPA	137:323	0.91
META−ANALYSIS	**551:2094**	**0.88**



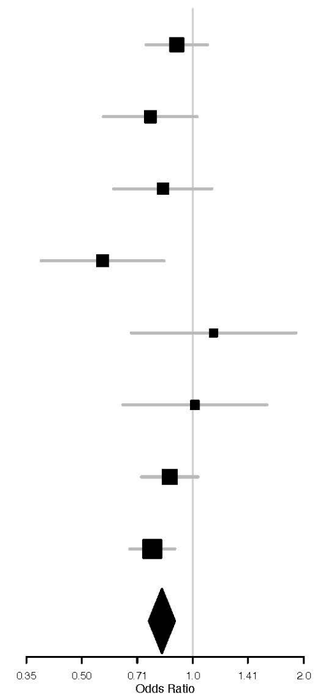
cg13233042

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.85
BAMSE_MEDALL	47:167	0.89
CHOP	19:363	1.08
GALA	106:87	0.88
ICAC	97:97	0.62
NFBC	29:343	0.75
PIAMA	15:182	0.97
RAINE	114:405	0.95
STOPPA	137:323	0.87
META−ANALYSIS	**657:2181**	**0.88**



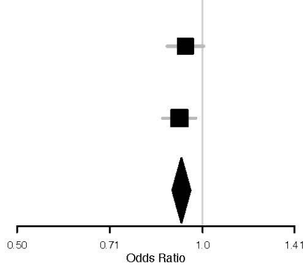
cg27533472

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.90
BAMSE_MEDALL	47:167	0.77
CHOP	19:363	0.83
ICAC	97:97	0.57
NFBC	29:343	1.14
PIAMA	15:182	1.01
RAINE	114:405	0.87
STOPPA	137:323	0.78
META−ANALYSIS	**551:2094**	**0.82**



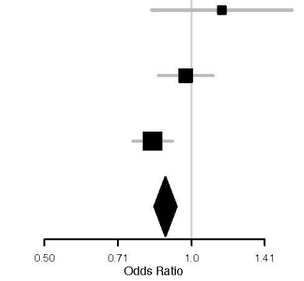
cg01310029

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.85
BAMSE_MEDALL	47:167	0.91
CHOP	19:363	0.98
ICAC	97:97	0.80
NFBC	29:343	0.80
PIAMA	15:182	1.13
RAINE	114:405	0.94
STOPPA	137:323	0.86
META−ANALYSIS	**551:2094**	**0.89**



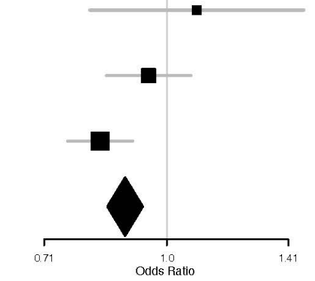
cg09597192

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.82
BAMSE_MEDALL	47:167	0.84
CHOP	19:363	1.15
GALA	106:87	0.84
ICAC	97:97	0.55
NFBC	29:343	0.85
PIAMA	15:182	1.12
RAINE	114:405	0.90
STOPPA	137:323	0.89
META−ANALYSIS	**657:2181**	**0.88**



cg10159529

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.83
BAMSE_MEDALL	47:167	0.81
CHOP	19:363	0.97
ICAC	97:97	0.74
NFBC	29:343	0.87
PIAMA	15:182	0.92
RAINE	114:405	0.99
STOPPA	137:323	0.86
META−ANALYSIS	**551:2094**	**0.90**



cg12077754

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.90
BAMSE_MEDALL	47:167	0.89
CHOP	19:363	1.00
ICAC	97:97	0.77
NFBC	29:343	0.85
PIAMA	15:182	1.02
RAINE	114:405	0.94
STOPPA	137:323	0.92
META−ANALYSIS	**551:2094**	**0.92**

cg13482814

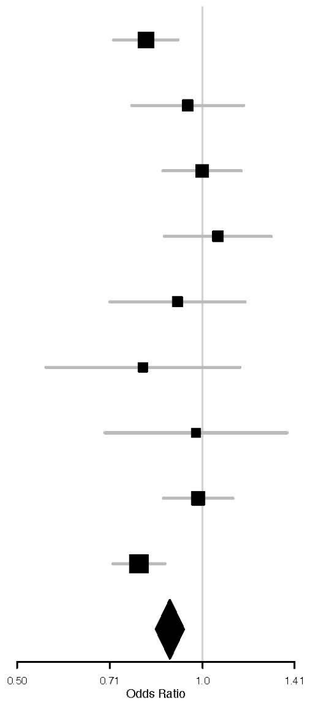
Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.90
BAMSE_MEDALL	47:167	0.88
CHOP	19:363	0.96
GALA	106:87	0.93
ICAC	97:97	0.59
NFBC	29:343	0.79
PIAMA	15:182	1.15
RAINE	114:405	0.97
STOPPA	137:323	0.83
META−ANALYSIS	**657:2181**	**0.88**

cg18368116

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.85
BAMSE_MEDALL	47:167	0.91
CHOP	19:363	1.04
GALA	106:87	0.90
ICAC	97:97	1.03
NFBC	29:343	0.81
PIAMA	15:182	1.09
RAINE	114:405	0.95
STOPPA	137:323	0.83
META−ANALYSIS	**657:2181**	**0.89**

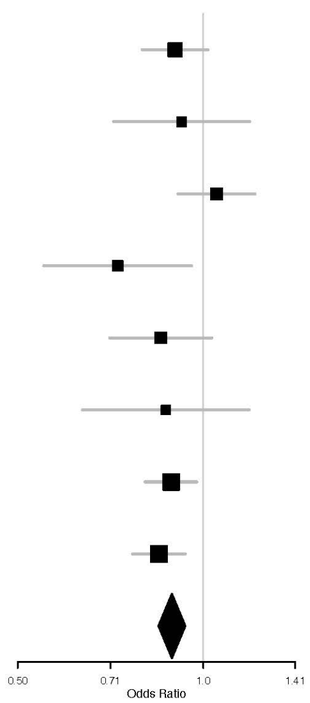
cg04895895

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.81
BAMSE_MEDALL	47:167	0.95
CHOP	19:363	1.00
GALA	106:87	1.06
ICAC	97:97	0.91
NFBC	29:343	0.80
PIAMA	15:182	0.98
RAINE	114:405	0.98
STOPPA	137:323	0.79
META−ANALYSIS	**657:2181**	**0.89**



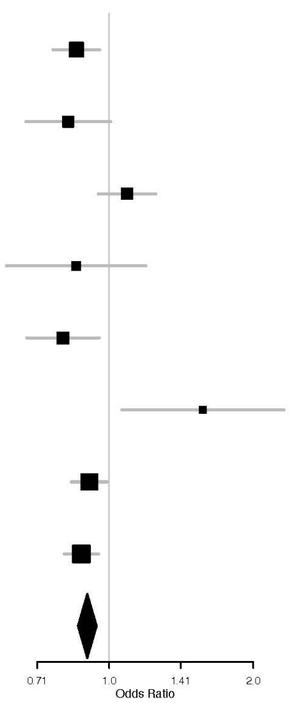
cg21045547

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.90
BAMSE_MEDALL	47:167	0.92
CHOP	19:363	1.05
ICAC	97:97	0.73
NFBC	29:343	0.85
PIAMA	15:182	0.87
RAINE	114:405	0.89
STOPPA	137:323	0.85
META−ANALYSIS	**551:2094**	**0.89**



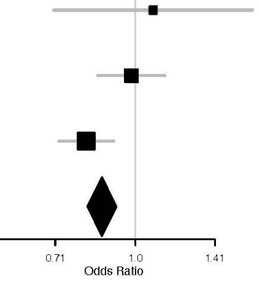
cg06070625

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.85
BAMSE_MEDALL	47:167	0.82
CHOP	19:363	1.09
ICAC	97:97	0.85
NFBC	29:343	0.80
PIAMA	15:182	1.57
RAINE	114:405	0.91
STOPPA	137:323	0.87
META−ANALYSIS	**551:2094**	**0.90**



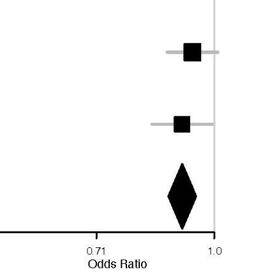
cg21498475

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.84
BAMSE_MEDALL	47:167	0.80
CHOP	19:363	1.06
GALA	106:87	0.92
ICAC	97:97	0.83
NFBC	29:343	0.96
PIAMA	15:182	1.07
RAINE	114:405	0.92
STOPPA	137:323	0.82
META−ANALYSIS	**657:2181**	**0.90**



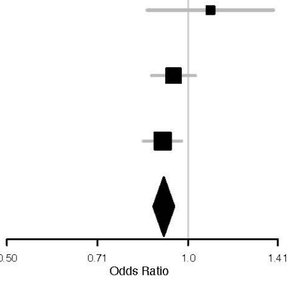
cg08698681

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.85
BAMSE_MEDALL	47:167	1.02
CHOP	19:363	1.09
GALA	106:87	0.94
ICAC	97:97	0.88
NFBC	29:343	0.84
PIAMA	15:182	0.93
RAINE	114:405	0.90
STOPPA	137:323	0.83
META−ANALYSIS	**657:2181**	**0.89**



cg20673965

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.78
BAMSE_MEDALL	47:167	1.02
CHOP	19:363	0.99
ICAC	97:97	0.90
NFBC	29:343	0.84
PIAMA	15:182	0.94
RAINE	114:405	0.91
STOPPA	137:323	0.87
META−ANALYSIS	**551:2094**	**0.90**



cg25636075

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.78
BAMSE_MEDALL	47:167	0.85
CHOP	19:363	0.96
GALA	106:87	0.88
ICAC	97:97	0.80
NFBC	29:343	0.89
PIAMA	15:182	1.08
RAINE	114:405	0.98
STOPPA	137:323	0.81
META−ANALYSIS	**657:2181**	**0.87**

cg11770323

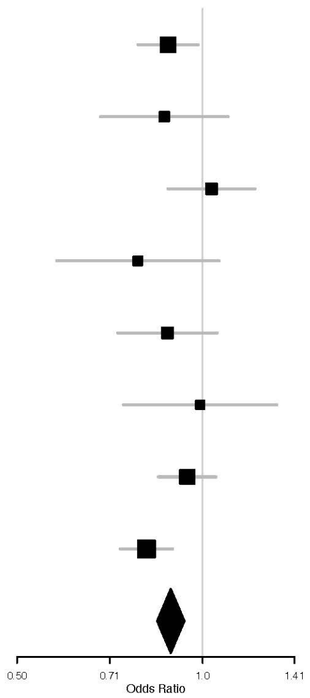
Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.90
BAMSE_MEDALL	47:167	0.73
CHOP	19:363	1.01
ICAC	97:97	0.76
NFBC	29:343	0.84
PIAMA	15:182	0.90
RAINE	114:405	0.94
STOPPA	137:323	0.91
META−ANALYSIS	**551:2094**	**0.91**

cg01901579

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.81
BAMSE_MEDALL	47:167	0.83
CHOP	19:363	1.08
GALA	106:87	0.89
ICAC	97:97	0.70
NFBC	29:343	0.90
PIAMA	15:182	1.09
RAINE	114:405	0.95
STOPPA	137:323	0.91
META−ANALYSIS	**657:2181**	**0.91**

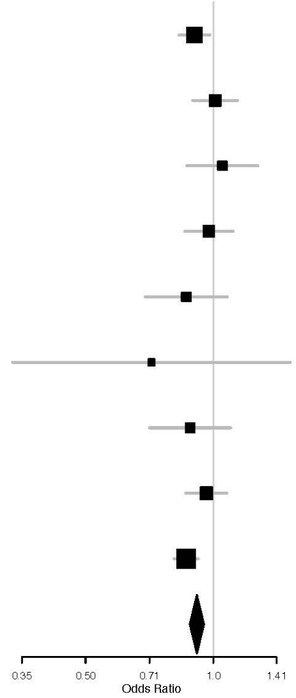
cg06315149

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.88
BAMSE_MEDALL	47:167	0.87
CHOP	19:363	1.03
ICAC	97:97	0.79
NFBC	29:343	0.88
PIAMA	15:182	0.99
RAINE	114:405	0.94
STOPPA	137:323	0.81
META−ANALYSIS	**551:2094**	**0.89**



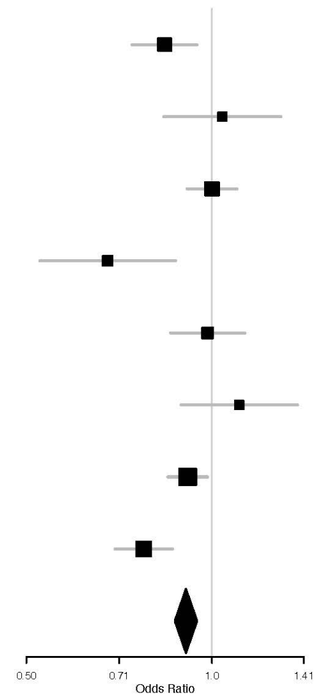
cg03329755

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.90
BAMSE_MEDALL	47:167	1.01
CHOP	19:363	1.05
GALA	106:87	0.98
ICAC	97:97	0.86
NFBC	29:343	0.71
PIAMA	15:182	0.88
RAINE	114:405	0.96
STOPPA	137:323	0.86
META−ANALYSIS	**657:2181**	**0.91**



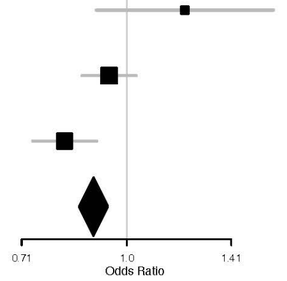
cg26033504

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.84
BAMSE_MEDALL	47:167	1.04
CHOP	19:363	1.00
ICAC	97:97	0.68
NFBC	29:343	0.98
PIAMA	15:182	1.11
RAINE	114:405	0.91
STOPPA	137:323	0.78
META−ANALYSIS	**551:2094**	**0.91**



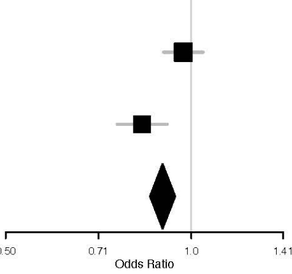
cg14611258

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.78
BAMSE_MEDALL	47:167	0.78
CHOP	19:363	1.04
GALA	106:87	0.82
ICAC	97:97	0.85
NFBC	29:343	0.91
PIAMA	15:182	1.19
RAINE	114:405	1.03
STOPPA	137:323	0.84
META−ANALYSIS	**657:2181**	**0.89**



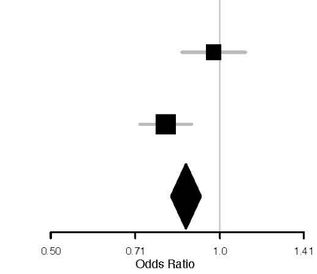
cg18783781

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.91
BAMSE_MEDALL	47:167	0.97
CHOP	19:363	1.10
GALA	106:87	0.78
ICAC	97:97	0.97
NFBC	29:343	0.81
PIAMA	15:182	1.14
RAINE	114:405	0.92
STOPPA	137:323	0.84
META−ANALYSIS	**657:2181**	**0.90**



cg25224369

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.85
BAMSE_MEDALL	47:167	0.77
CHOP	19:363	1.00
ICAC	97:97	0.76
NFBC	29:343	0.90
PIAMA	15:182	1.27
RAINE	114:405	0.94
STOPPA	137:323	0.82
META−ANALYSIS	**551:2094**	**0.90**



cg02473287

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.85
BAMSE_MEDALL	47:167	0.86
CHOP	19:363	1.06
GALA	106:87	0.87
ICAC	97:97	0.91
NFBC	29:343	0.78
PIAMA	15:182	1.21
RAINE	114:405	0.94
STOPPA	137:323	0.81
META−ANALYSIS	**657:2181**	**0.90**

cg00327263

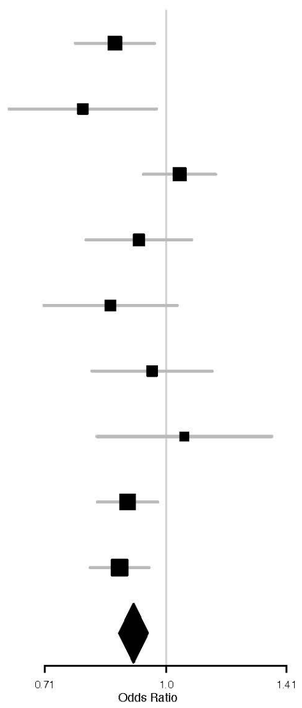
Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.89
BAMSE_MEDALL	47:167	0.87
CHOP	19:363	0.98
ICAC	97:97	0.84
NFBC	29:343	0.77
PIAMA	15:182	0.81
RAINE	114:405	0.97
STOPPA	137:323	0.83
META−ANALYSIS	**551:2094**	**0.90**

cg24818699

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.93
BAMSE_MEDALL	47:167	0.80
CHOP	19:363	0.82
ICAC	97:97	0.94
NFBC	29:343	0.92
PIAMA	15:182	0.70
RAINE	114:405	0.97
STOPPA	137:323	0.80
META−ANALYSIS	**551:2094**	**0.87**

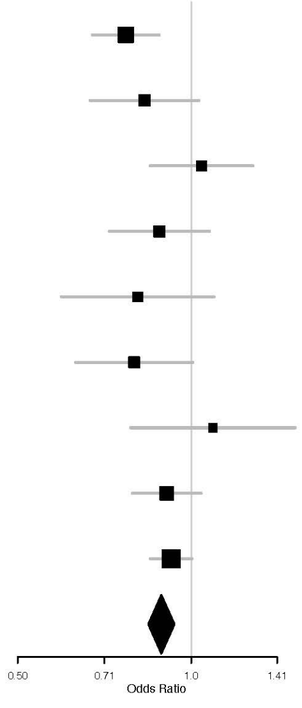
cg22312249

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.86
BAMSE_MEDALL	47:167	0.79
CHOP	19:363	1.04
GALA	106:87	0.93
ICAC	97:97	0.85
NFBC	29:343	0.96
PIAMA	15:182	1.05
RAINE	114:405	0.90
STOPPA	137:323	0.88
META−ANALYSIS	**657:2181**	**0.91**



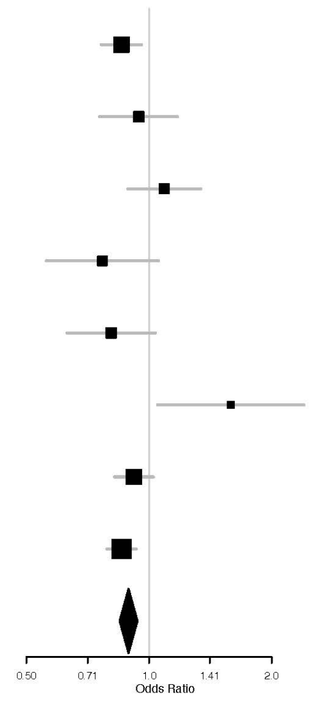
cg25854298

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.77
BAMSE_MEDALL	47:167	0.83
CHOP	19:363	1.04
GALA	106:87	0.88
ICAC	97:97	0.81
NFBC	29:343	0.80
PIAMA	15:182	1.09
RAINE	114:405	0.91
STOPPA	137:323	0.92
META−ANALYSIS	**657:2181**	**0.89**



cg09147843

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.86
BAMSE_MEDALL	47:167	0.94
CHOP	19:363	1.09
ICAC	97:97	0.77
NFBC	29:343	0.81
PIAMA	15:182	1.59
RAINE	114:405	0.92
STOPPA	137:323	0.86
META−ANALYSIS	**551:2094**	**0.89**



cg12643917

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.80
BAMSE_MEDALL	47:167	0.81
CHOP	19:363	0.95
GALA	106:87	0.95
ICAC	97:97	0.87
NFBC	29:343	0.82
PIAMA	15:182	0.95
RAINE	114:405	0.96
STOPPA	137:323	0.90
META−ANALYSIS	**657:2181**	**0.89**

cg02171825

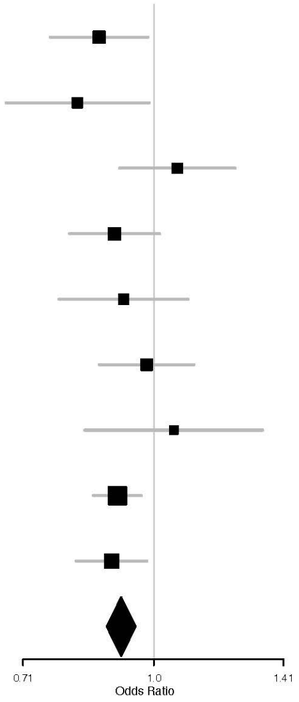
Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.88
BAMSE_MEDALL	47:167	0.90
CHOP	19:363	1.10
GALA	106:87	0.88
ICAC	97:97	0.70
NFBC	29:343	0.95
PIAMA	15:182	0.86
RAINE	114:405	0.89
STOPPA	137:323	0.84
META−ANALYSIS	**657:2181**	**0.88**

cg23205629

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.87
BAMSE_MEDALL	47:167	0.82
CHOP	19:363	1.08
ICAC	97:97	0.89
NFBC	29:343	0.89
PIAMA	15:182	1.09
RAINE	114:405	0.92
STOPPA	137:323	0.90
META−ANALYSIS	**551:2094**	**0.91**

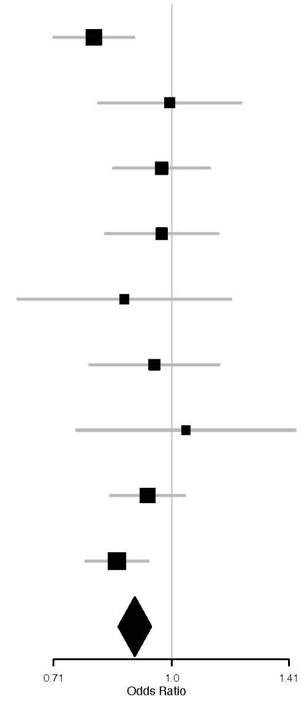
cg26134665

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.86
BAMSE_MEDALL	47:167	0.82
CHOP	19:363	1.06
GALA	106:87	0.90
ICAC	97:97	0.92
NFBC	29:343	0.98
PIAMA	15:182	1.05
RAINE	114:405	0.91
STOPPA	137:323	0.89
META−ANALYSIS	**657:2181**	**0.92**



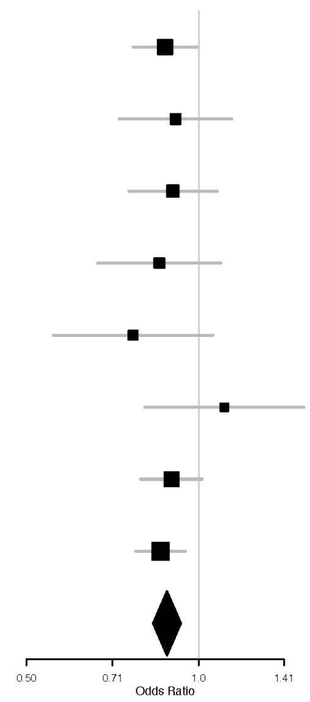
cg12819873

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.80
BAMSE_MEDALL	47:167	0.99
CHOP	19:363	0.97
GALA	106:87	0.97
ICAC	97:97	0.87
NFBC	29:343	0.95
PIAMA	15:182	1.04
RAINE	114:405	0.93
STOPPA	137:323	0.85
META−ANALYSIS	**657:2181**	**0.90**



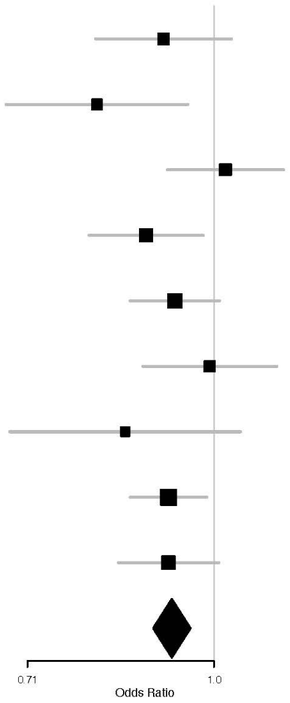
cg09423651

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.87
BAMSE_MEDALL	47:167	0.91
CHOP	19:363	0.90
ICAC	97:97	0.85
NFBC	29:343	0.77
PIAMA	15:182	1.11
RAINE	114:405	0.90
STOPPA	137:323	0.86
META−ANALYSIS	**551:2094**	**0.88**



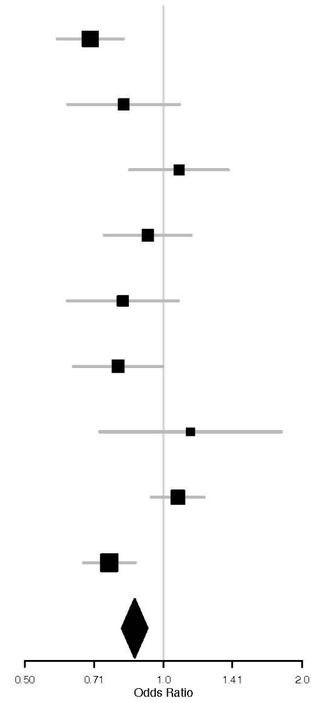
cg04973995

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.91
BAMSE_MEDALL	47:167	0.80
CHOP	19:363	1.02
GALA	106:87	0.88
ICAC	97:97	0.93
NFBC	29:343	0.99
PIAMA	15:182	0.85
RAINE	114:405	0.92
STOPPA	137:323	0.92
META−ANALYSIS	**657:2181**	**0.92**



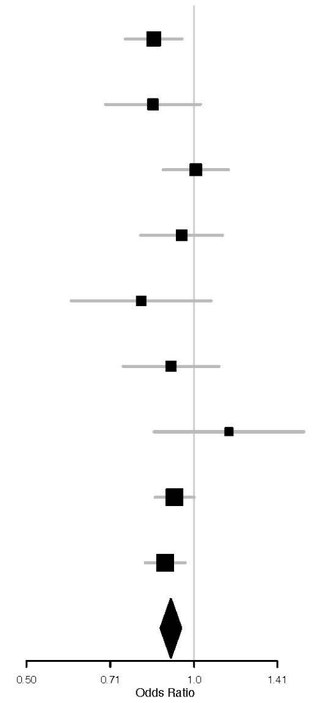
cg20226253

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.69
BAMSE_MEDALL	47:167	0.82
CHOP	19:363	1.08
GALA	106:87	0.92
ICAC	97:97	0.82
NFBC	29:343	0.80
PIAMA	15:182	1.15
RAINE	114:405	1.07
STOPPA	137:323	0.76
META−ANALYSIS	**657:2181**	**0.87**



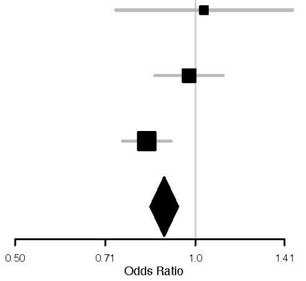
cg17041511

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.85
BAMSE_MEDALL	47:167	0.84
CHOP	19:363	1.01
GALA	106:87	0.95
ICAC	97:97	0.80
NFBC	29:343	0.91
PIAMA	15:182	1.15
RAINE	114:405	0.92
STOPPA	137:323	0.89
META−ANALYSIS	**657:2181**	**0.91**



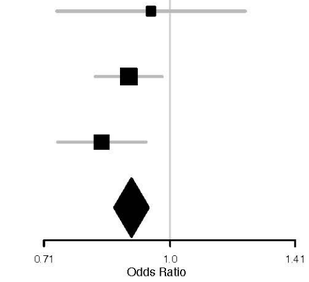
cg17947765

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.75
BAMSE_MEDALL	47:167	0.84
CHOP	19:363	1.06
GALA	106:87	0.83
ICAC	97:97	0.57
NFBC	29:343	0.96
PIAMA	15:182	1.17
RAINE	114:405	0.90
STOPPA	137:323	0.87
META−ANALYSIS	**657:2181**	**0.86**



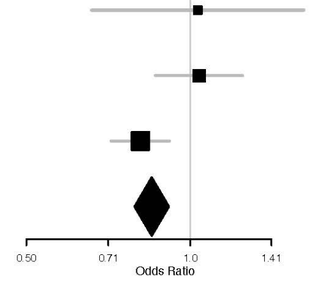
cg19928703

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.84
BAMSE_MEDALL	47:167	0.80
CHOP	19:363	1.06
GALA	106:87	0.89
ICAC	97:97	0.92
NFBC	29:343	0.74
PIAMA	15:182	0.94
RAINE	114:405	0.97
STOPPA	137:323	0.87
META−ANALYSIS	**657:2181**	**0.89**



cg15961693

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.90
BAMSE_MEDALL	47:167	0.75
CHOP	19:363	0.91
ICAC	97:97	0.66
NFBC	29:343	0.84
PIAMA	15:182	1.02
RAINE	114:405	0.97
STOPPA	137:323	0.89
META−ANALYSIS	**551:2094**	**0.89**



cg26396815

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.85
BAMSE_MEDALL	47:167	0.86
CHOP	19:363	1.00
GALA	106:87	1.00
ICAC	97:97	0.74
NFBC	29:343	0.87
PIAMA	15:182	1.03
RAINE	114:405	0.98
STOPPA	137:323	0.83
META−ANALYSIS	**657:2181**	**0.89**

cg07177867

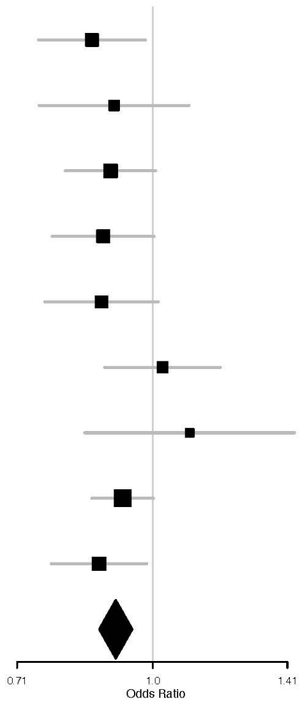
Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.87
BAMSE_MEDALL	47:167	0.83
CHOP	19:363	1.04
GALA	106:87	0.91
ICAC	97:97	0.99
NFBC	29:343	0.82
PIAMA	15:182	0.95
RAINE	114:405	0.89
STOPPA	137:323	0.83
META−ANALYSIS	**657:2181**	**0.90**

cg25950520

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.86
BAMSE_MEDALL	47:167	0.80
CHOP	19:363	0.72
GALA	106:87	0.82
ICAC	97:97	0.73
NFBC	29:343	0.84
PIAMA	15:182	1.03
RAINE	114:405	1.04
STOPPA	137:323	0.81
META−ANALYSIS	**657:2181**	**0.85**

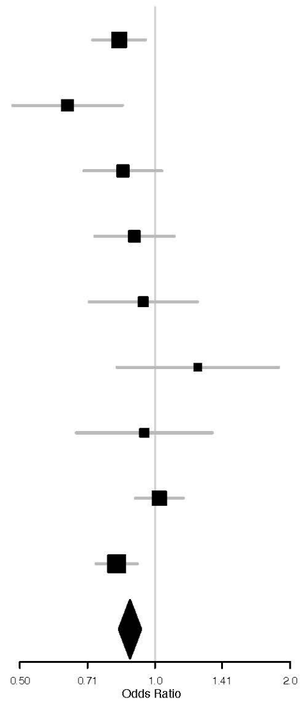
cg00043800

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.86
BAMSE_MEDALL	47:167	0.91
CHOP	19:363	0.90
GALA	106:87	0.88
ICAC	97:97	0.88
NFBC	29:343	1.03
PIAMA	15:182	1.10
RAINE	114:405	0.93
STOPPA	137:323	0.87
META−ANALYSIS	**657:2181**	**0.91**



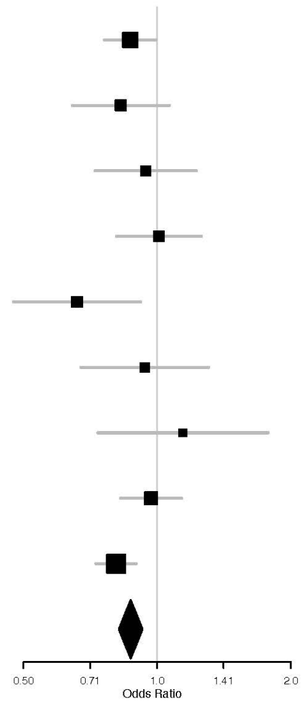
cg00045753

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.83
BAMSE_MEDALL	47:167	0.64
CHOP	19:363	0.85
GALA	106:87	0.90
ICAC	97:97	0.94
NFBC	29:343	1.25
PIAMA	15:182	0.95
RAINE	114:405	1.02
STOPPA	137:323	0.82
META−ANALYSIS	**657:2181**	**0.88**



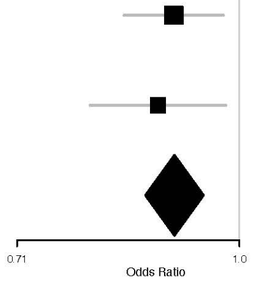
cg13792581

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.87
BAMSE_MEDALL	47:167	0.83
CHOP	19:363	0.94
GALA	106:87	1.01
ICAC	97:97	0.66
NFBC	29:343	0.94
PIAMA	15:182	1.14
RAINE	114:405	0.97
STOPPA	137:323	0.81
META−ANALYSIS	**657:2181**	**0.87**



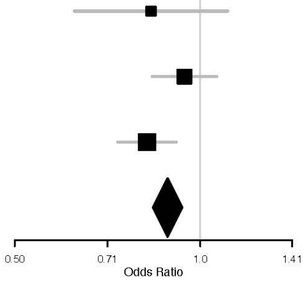
cg22588983

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.91
BAMSE_MEDALL	47:167	0.69
CHOP	19:363	1.03
GALA	106:87	0.90
ICAC	97:97	0.80
NFBC	29:343	0.77
PIAMA	15:182	1.05
RAINE	114:405	0.86
STOPPA	137:323	0.82
META−ANALYSIS	**657:2181**	**0.86**



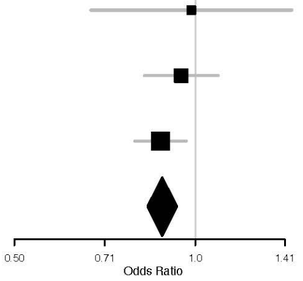
cg13576859

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.85
BAMSE_MEDALL	47:167	0.94
CHOP	19:363	1.06
GALA	106:87	0.90
ICAC	97:97	0.67
NFBC	29:343	0.99
PIAMA	15:182	0.88
RAINE	114:405	0.94
STOPPA	137:323	0.87
META−ANALYSIS	**657:2181**	**0.92**



cg08770358

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.84
BAMSE_MEDALL	47:167	0.84
CHOP	19:363	1.03
GALA	106:87	0.75
ICAC	97:97	0.89
NFBC	29:343	0.70
PIAMA	15:182	0.98
RAINE	114:405	0.92
STOPPA	137:323	0.82
META−ANALYSIS	**657:2181**	**0.84**



cg00222125

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.93
BAMSE_MEDALL	47:167	0.84
ICAC	97:97	0.95
PIAMA	15:182	0.90
RAINE	114:405	0.90
STOPPA	137:323	0.88
META−ANALYSIS	**503:1388**	**0.90**

cg22674082

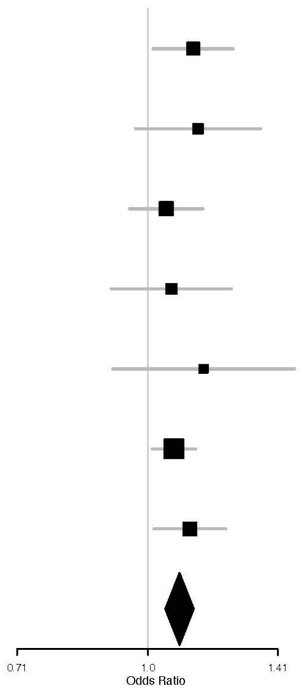
Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.86
BAMSE_MEDALL	47:167	1.10
CHOP	19:363	0.81
GALA	106:87	1.01
ICAC	97:97	0.74
NFBC	29:343	1.04
PIAMA	15:182	0.83
RAINE	114:405	0.94
STOPPA	137:323	0.82
META−ANALYSIS	**657:2181**	**0.89**

cg00366037

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.86
BAMSE_MEDALL	47:167	0.84
CHOP	19:363	0.87
GALA	106:87	0.93
ICAC	97:97	0.73
NFBC	29:343	0.83
PIAMA	15:182	0.99
RAINE	114:405	0.95
STOPPA	137:323	0.88
META−ANALYSIS	**657:2181**	**0.88**

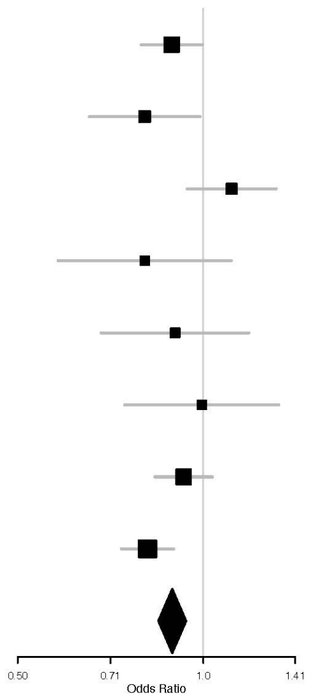
cg19468946

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	1.13
BAMSE_MEDALL	47:167	1.14
CHOP	19:363	1.05
ICAC	97:97	1.06
PIAMA	15:182	1.16
RAINE	114:405	1.07
STOPPA	137:323	1.12
META−ANALYSIS	**522:1751**	**1.09**



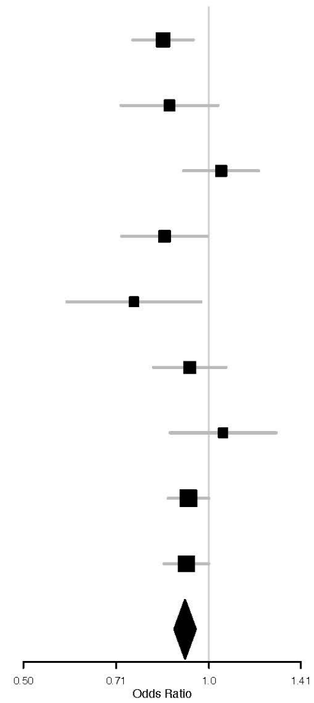
cg11266582

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.89
BAMSE_MEDALL	47:167	0.80
CHOP	19:363	1.11
ICAC	97:97	0.80
NFBC	29:343	0.90
PIAMA	15:182	0.99
RAINE	114:405	0.93
STOPPA	137:323	0.81
META−ANALYSIS	**551:2094**	**0.89**



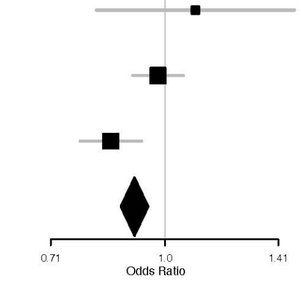
cg08969102

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.84
BAMSE_MEDALL	47:167	0.86
CHOP	19:363	1.05
GALA	106:87	0.85
ICAC	97:97	0.76
NFBC	29:343	0.93
PIAMA	15:182	1.05
RAINE	114:405	0.93
STOPPA	137:323	0.92
META−ANALYSIS	**657:2181**	**0.91**



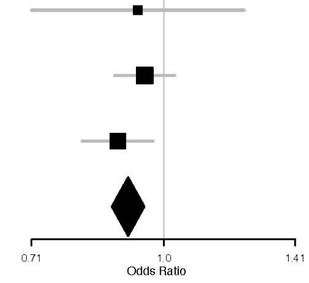
cg08067346

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.85
BAMSE_MEDALL	47:167	0.87
CHOP	19:363	1.03
GALA	106:87	0.98
ICAC	97:97	1.19
NFBC	29:343	0.65
PIAMA	15:182	1.13
RAINE	114:405	0.95
STOPPA	137:323	0.86
META−ANALYSIS	**657:2181**	**0.90**



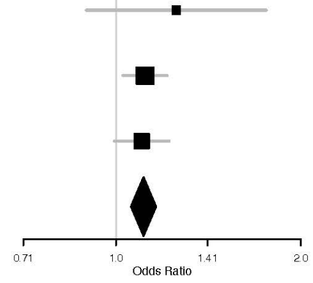
cg22235258

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.83
BAMSE_MEDALL	47:167	0.82
CHOP	19:363	1.07
GALA	106:87	1.08
ICAC	97:97	1.02
NFBC	29:343	0.82
PIAMA	15:182	1.01
RAINE	114:405	0.92
STOPPA	137:323	0.79
META−ANALYSIS	**657:2181**	**0.88**



cg13066938

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.84
BAMSE_MEDALL	47:167	0.96
CHOP	19:363	1.02
ICAC	97:97	0.91
NFBC	29:343	0.95
PIAMA	15:182	1.08
RAINE	114:405	0.93
STOPPA	137:323	0.82
META−ANALYSIS	**551:2094**	**0.91**



cg20866785

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.89
BAMSE_MEDALL	47:167	0.86
CHOP	19:363	0.99
GALA	106:87	0.87
ICAC	97:97	0.82
NFBC	29:343	0.84
PIAMA	15:182	1.10
RAINE	114:405	0.98
STOPPA	137:323	0.85
META−ANALYSIS	**657:2181**	**0.91**

cg01445399

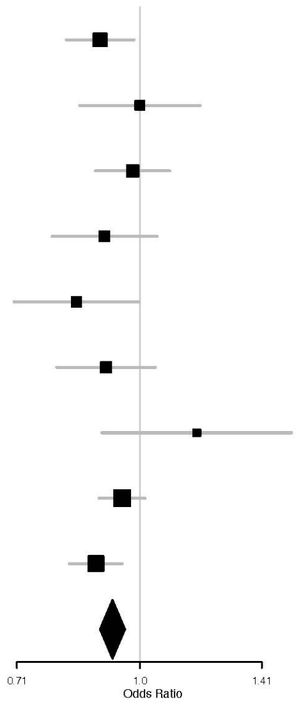
Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.82
BAMSE_MEDALL	47:167	0.85
CHOP	19:363	1.01
GALA	106:87	0.84
ICAC	97:97	0.85
NFBC	29:343	0.96
PIAMA	15:182	0.93
RAINE	114:405	0.95
STOPPA	137:323	0.89
META−ANALYSIS	**657:2181**	**0.91**

cg27383865

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	1.08
BAMSE_MEDALL	47:167	1.40
CHOP	19:363	1.16
GALA	106:87	1.47
ICAC	97:97	0.93
NFBC	29:343	0.94
PIAMA	15:182	1.25
RAINE	114:405	1.12
STOPPA	137:323	1.10
META−ANALYSIS	**657:2181**	**1.11**

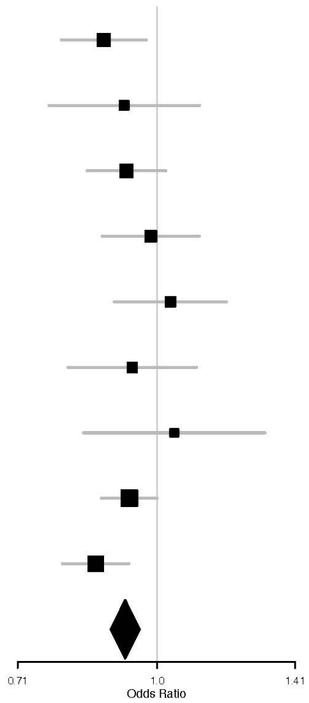
cg14978242

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.89
BAMSE_MEDALL	47:167	1.00
CHOP	19:363	0.98
GALA	106:87	0.90
ICAC	97:97	0.84
NFBC	29:343	0.91
PIAMA	15:182	1.17
RAINE	114:405	0.95
STOPPA	137:323	0.88
META−ANALYSIS	**657:2181**	**0.93**



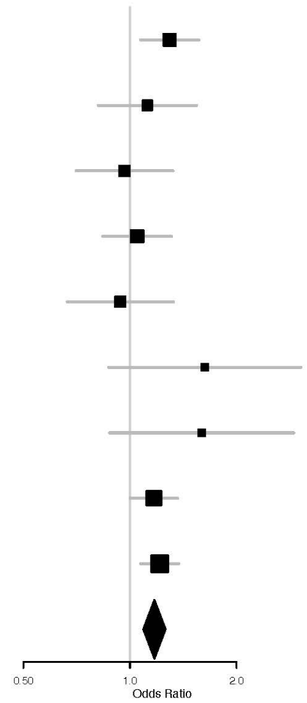
cg21073212

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.88
BAMSE_MEDALL	47:167	0.92
CHOP	19:363	0.93
GALA	106:87	0.98
ICAC	97:97	1.03
NFBC	29:343	0.94
PIAMA	15:182	1.04
RAINE	114:405	0.93
STOPPA	137:323	0.86
META−ANALYSIS	**657:2181**	**0.92**



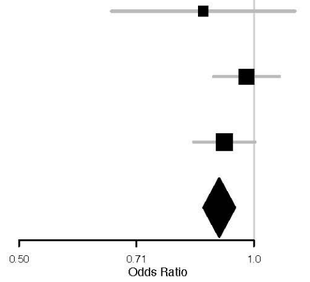
cg15219163

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	1.29
BAMSE_MEDALL	47:167	1.12
CHOP	19:363	0.97
GALA	106:87	1.05
ICAC	97:97	0.94
NFBC	29:343	1.63
PIAMA	15:182	1.59
RAINE	114:405	1.17
STOPPA	137:323	1.21
META−ANALYSIS	**657:2181**	**1.17**



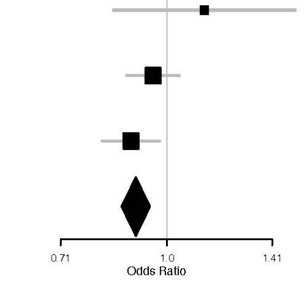
cg24576940

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.90
BAMSE_MEDALL	47:167	0.78
CHOP	19:363	0.82
GALA	106:87	0.79
ICAC	97:97	0.56
NFBC	29:343	0.14
PIAMA	15:182	0.90
RAINE	114:405	0.95
STOPPA	137:323	0.89
META−ANALYSIS	**657:2181**	**0.87**



cg15304012

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	1.12
BAMSE_MEDALL	47:167	1.37
CHOP	19:363	1.17
GALA	106:87	1.17
ICAC	97:97	1.16
NFBC	29:343	1.02
PIAMA	15:182	1.14
RAINE	114:405	1.04
STOPPA	137:323	1.05
META−ANALYSIS	**657:2181**	**1.08**



cg13007207

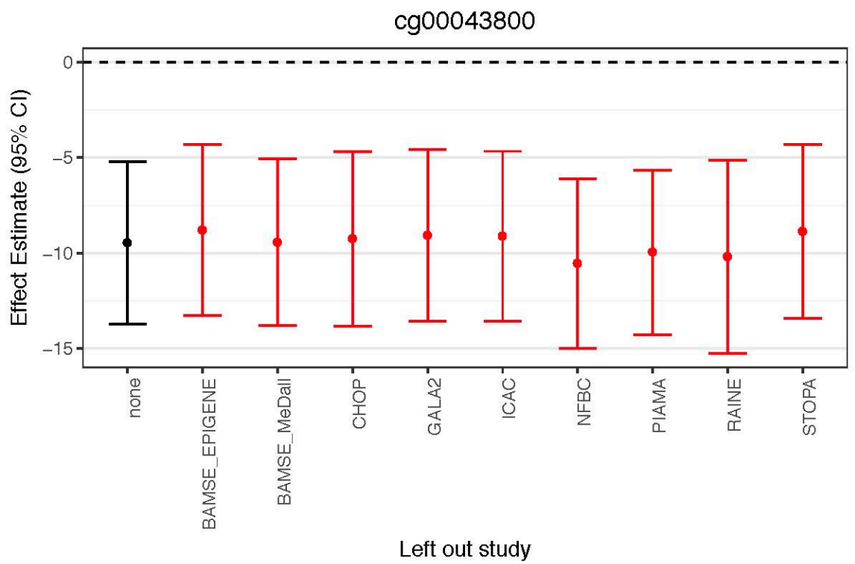
Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	1.41
BAMSE_MEDALL	47:167	1.25
CHOP	19:363	0.84
GALA	106:87	1.67
ICAC	97:97	1.20
NFBC	29:343	1.70
PIAMA	15:182	2.00
RAINE	114:405	1.35
STOPPA	137:323	1.06
META−ANALYSIS	**657:2181**	**1.26**

cg26774971

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.90
BAMSE_MEDALL	47:167	0.75
CHOP	19:363	0.97
GALA	106:87	0.90
ICAC	97:97	0.76
NFBC	29:343	0.66
PIAMA	15:182	0.86
RAINE	114:405	0.98
STOPPA	137:323	0.92
META−ANALYSIS	**657:2181**	**0.90**

cg21627181

Cohort	N cases:controls	OR
BAMSE_EPIGENE	93:214	0.80
BAMSE_MEDALL	47:167	0.78
CHOP	19:363	1.08
GALA	106:87	0.92
ICAC	97:97	0.87
NFBC	29:343	0.78
PIAMA	15:182	1.13
RAINE	114:405	0.96
STOPPA	137:323	0.89
META−ANALYSIS	**657:2181**	**0.90**


cg00043800
Effect Estimate (95% CI)
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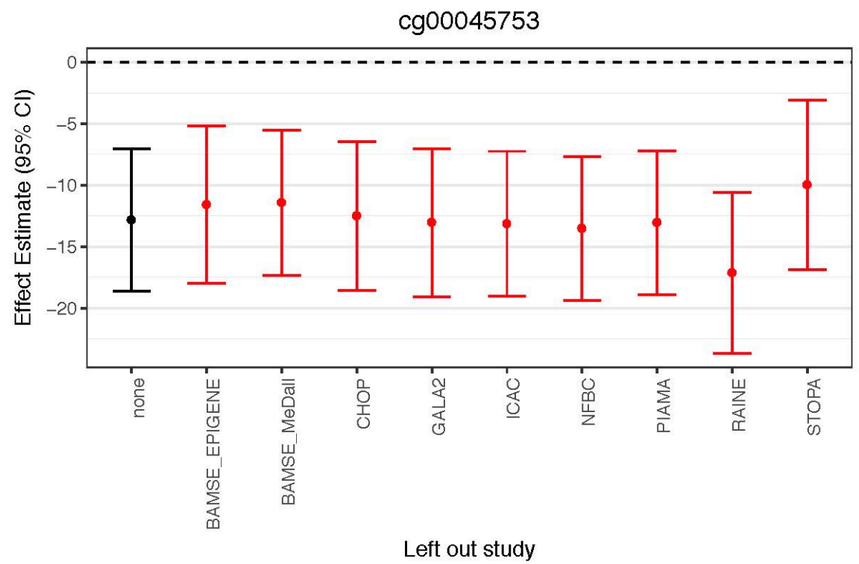
BAMSE_MeDall
CHOP
GALA2
ICAC
NFBC
PIAMA
RAINE
STOPA
Left out study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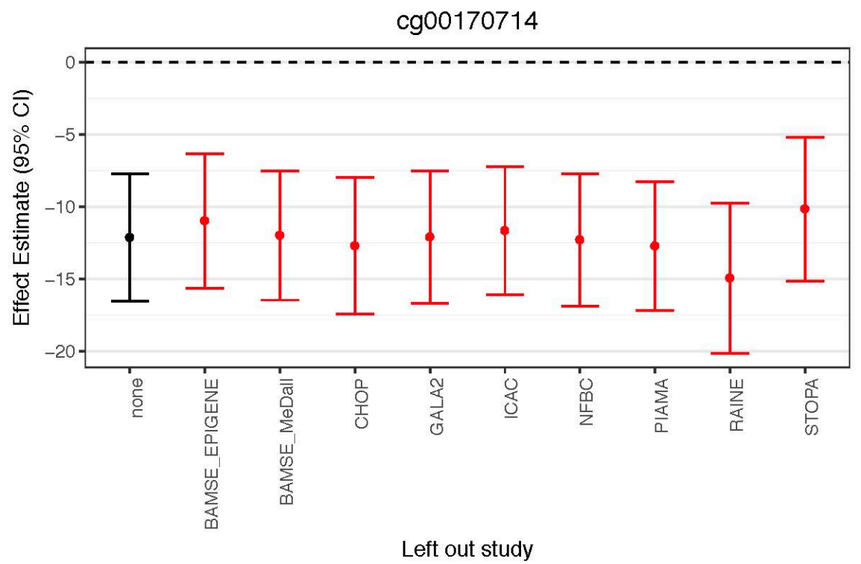
BAMSE_MeDall
CHOP
GALA2
ICAC
NFBC
PIAMA
RAINE
STOPA
Left out study


cg00170714
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BAMSE_MeDall
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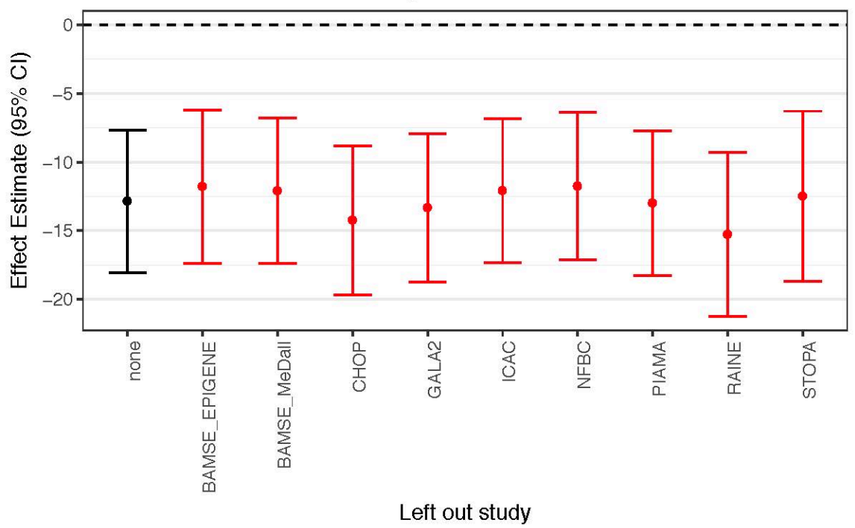
GALA2
ICAC
NFBC
PIAMA
RAINE
STOPA
Left out study


cg00213281
Effect Estimate (95% CI)
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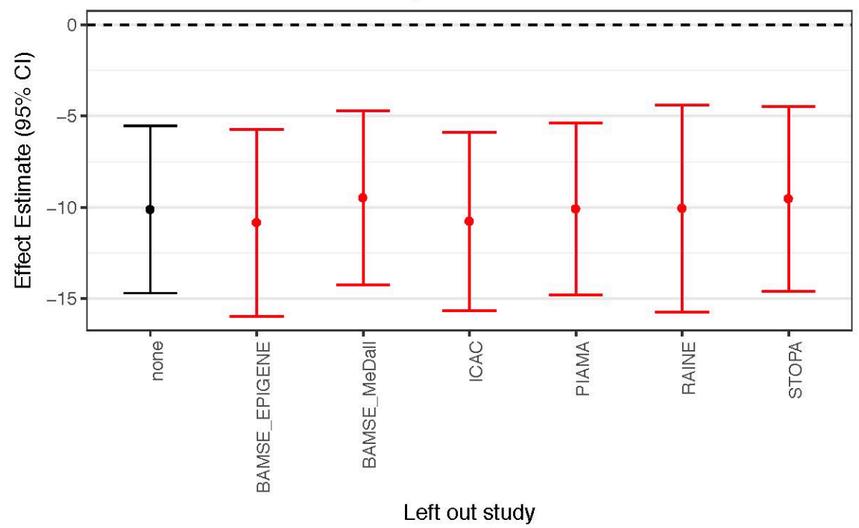
BAMSE_MeDall
CHOP
GALA2
ICAC
NFBC
PIAMA
RAINE
STOPA
Left out study


cg00222125
Effect Estimate (95% CI)
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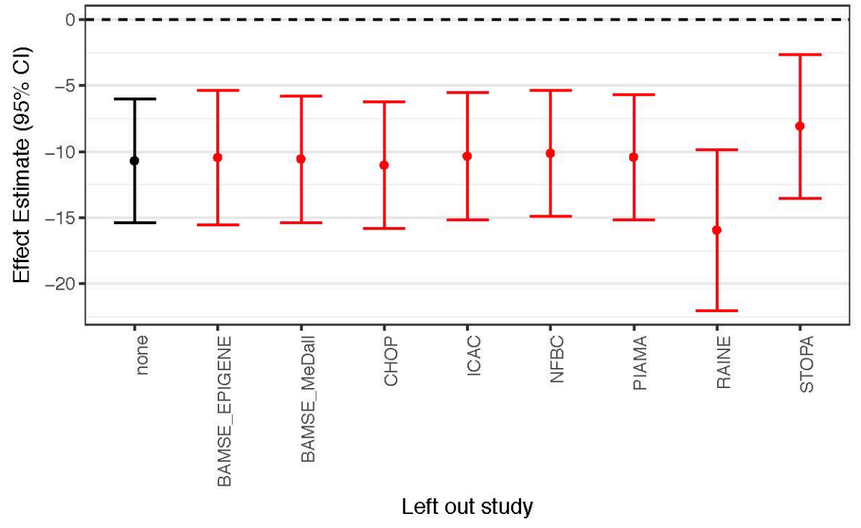
BAMSE_MeDall
ICAC
PIAMA
RAINE
STOPA
Left out study


cg00327263
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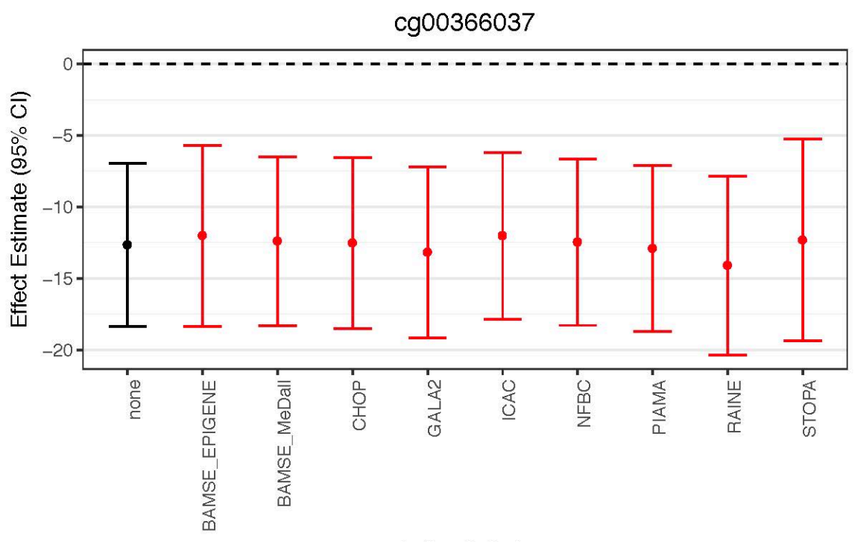
BAMSE_MeDall
CHOP
ICAC
NFBC
PIAMA
RAINE
STOPA
Left out study


cg00366037
Effect Estimate (95% CI)
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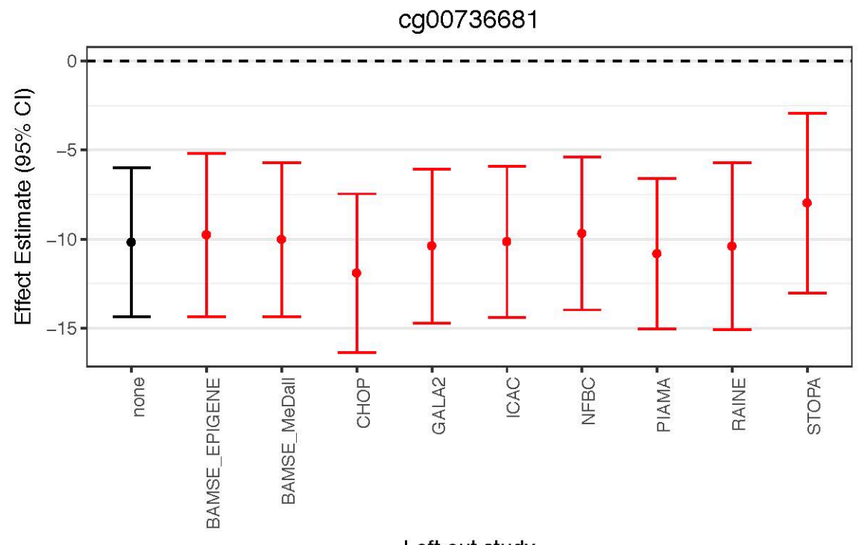
BAMSE_MeDall
CHOP
GALA2
ICAC
NFBC
PIAMA
RAINE
STOPA
Left out study


cg00736681
Effect Estimate (95% CI)
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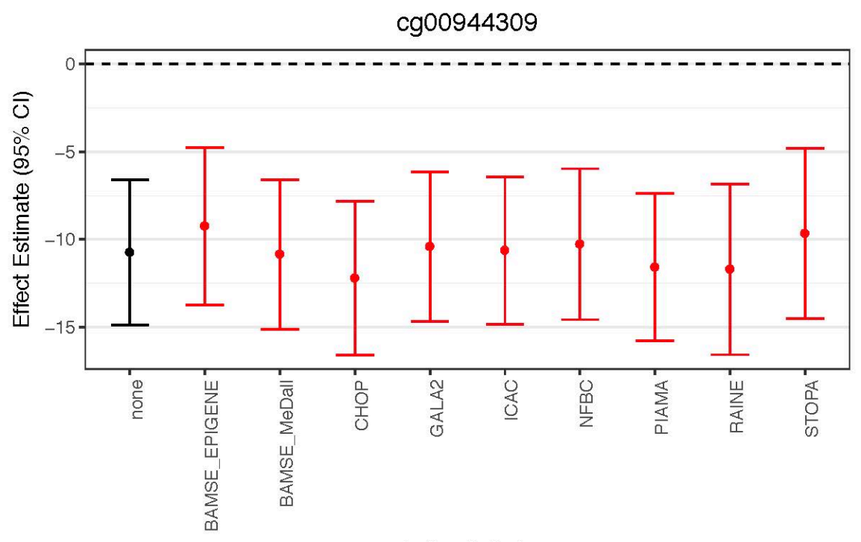
BAMSE_MeDall
CHOP
GALA2
ICAC
NFBC
PIAMA
RAINE
STOPA
Left out study


cg00944309
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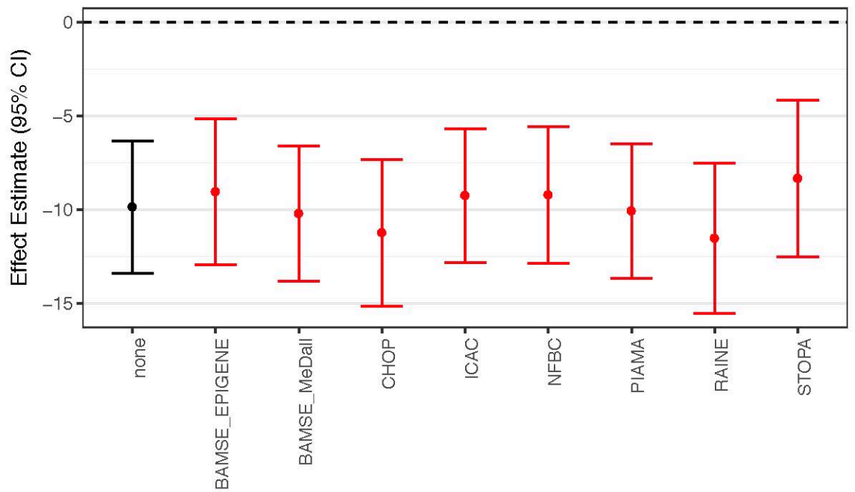
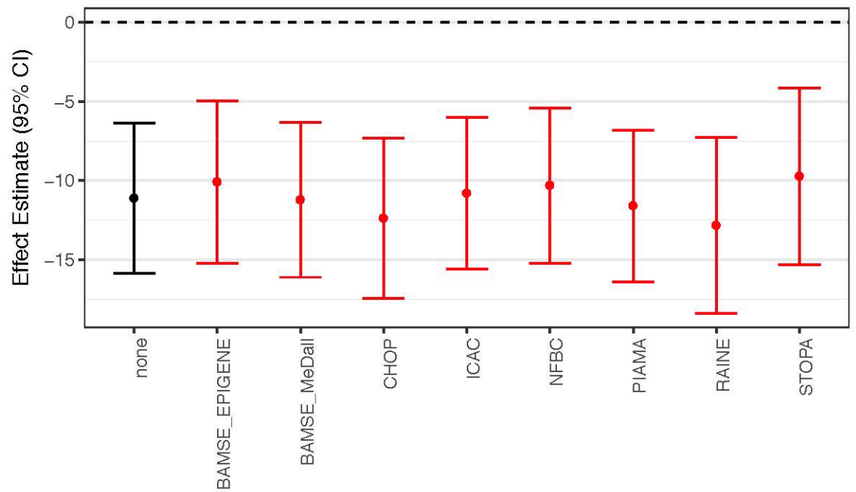
BAMSE_MeDall
CHOP
GALA2
ICAC
NFBC
PIAMA
RAINE
STOPA
Left out study

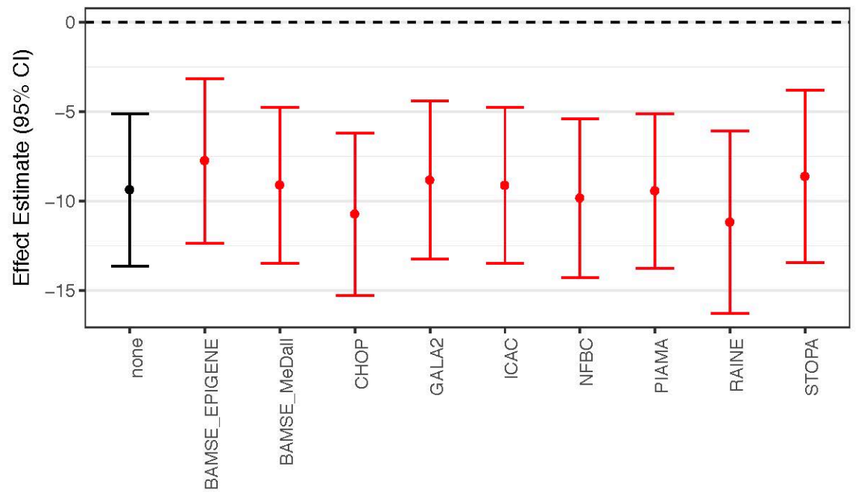
cg01000631



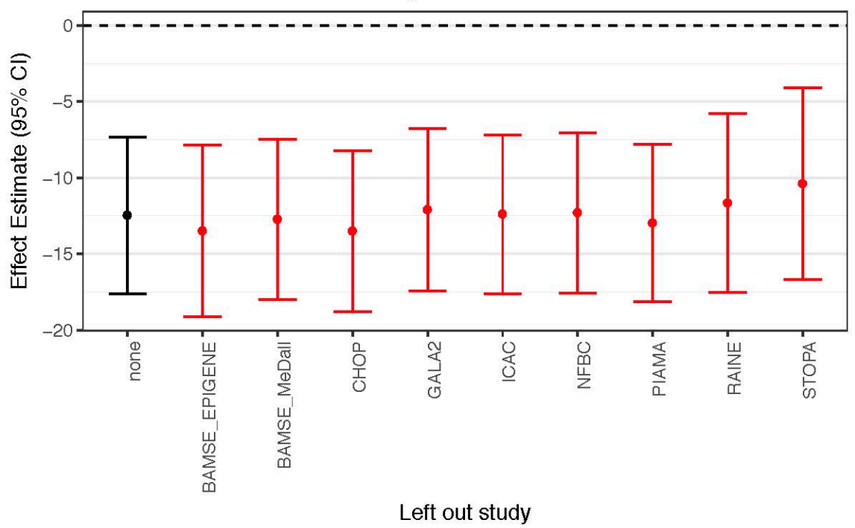
cg01310029



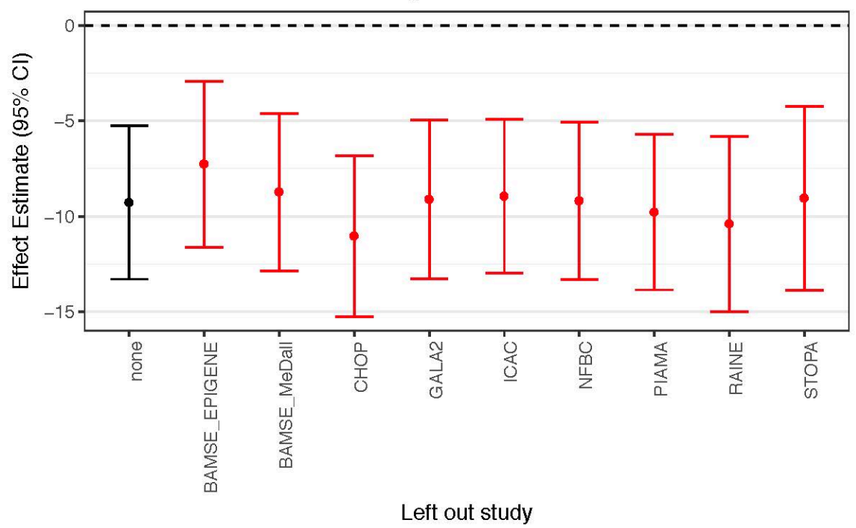
cg01445399



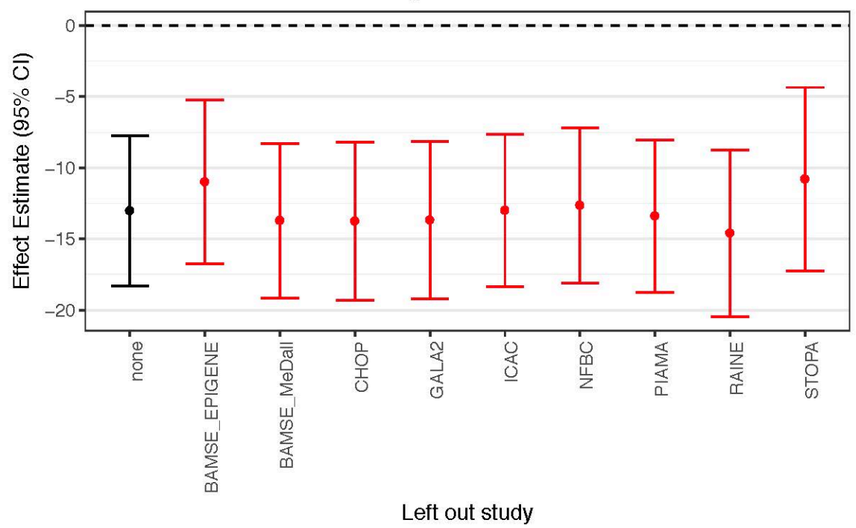
cg01499988



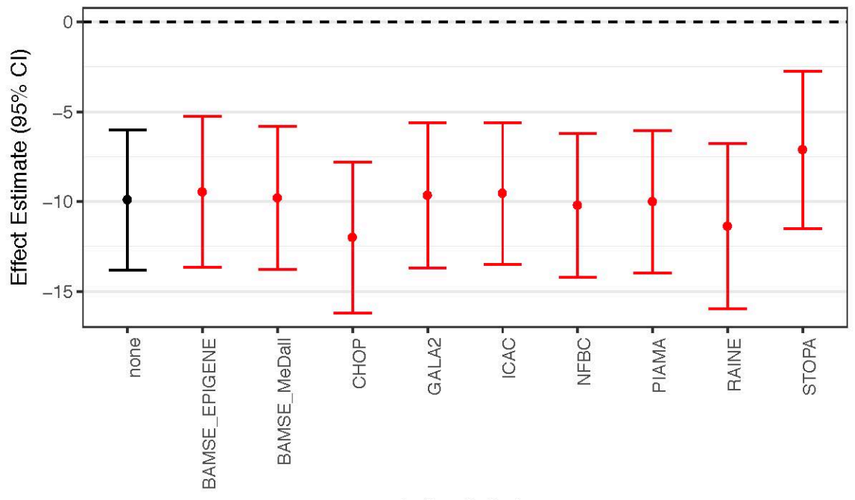
cg01901579



cg01942646



cg01998785



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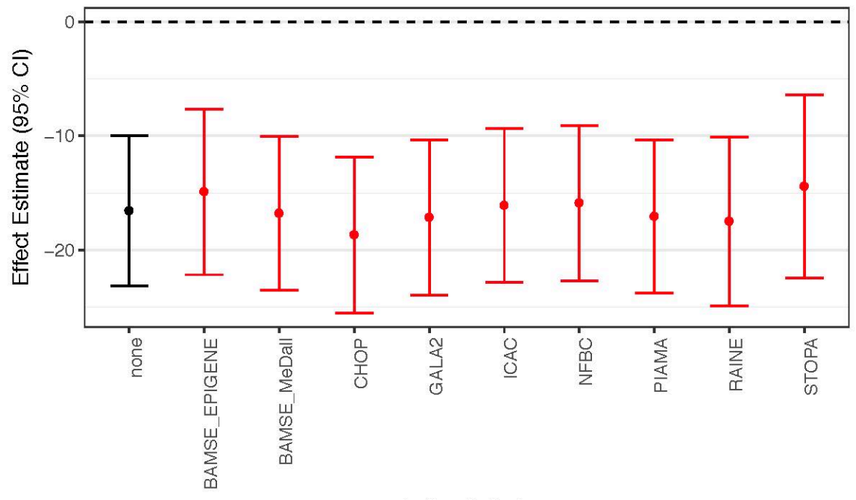

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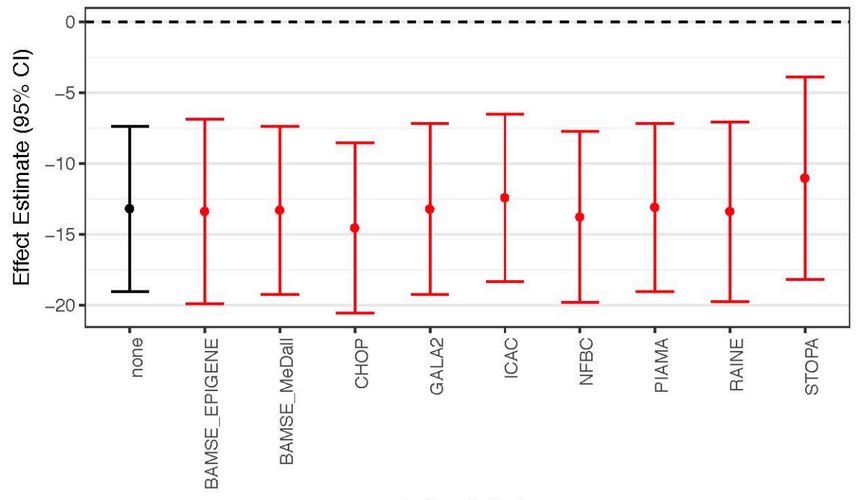

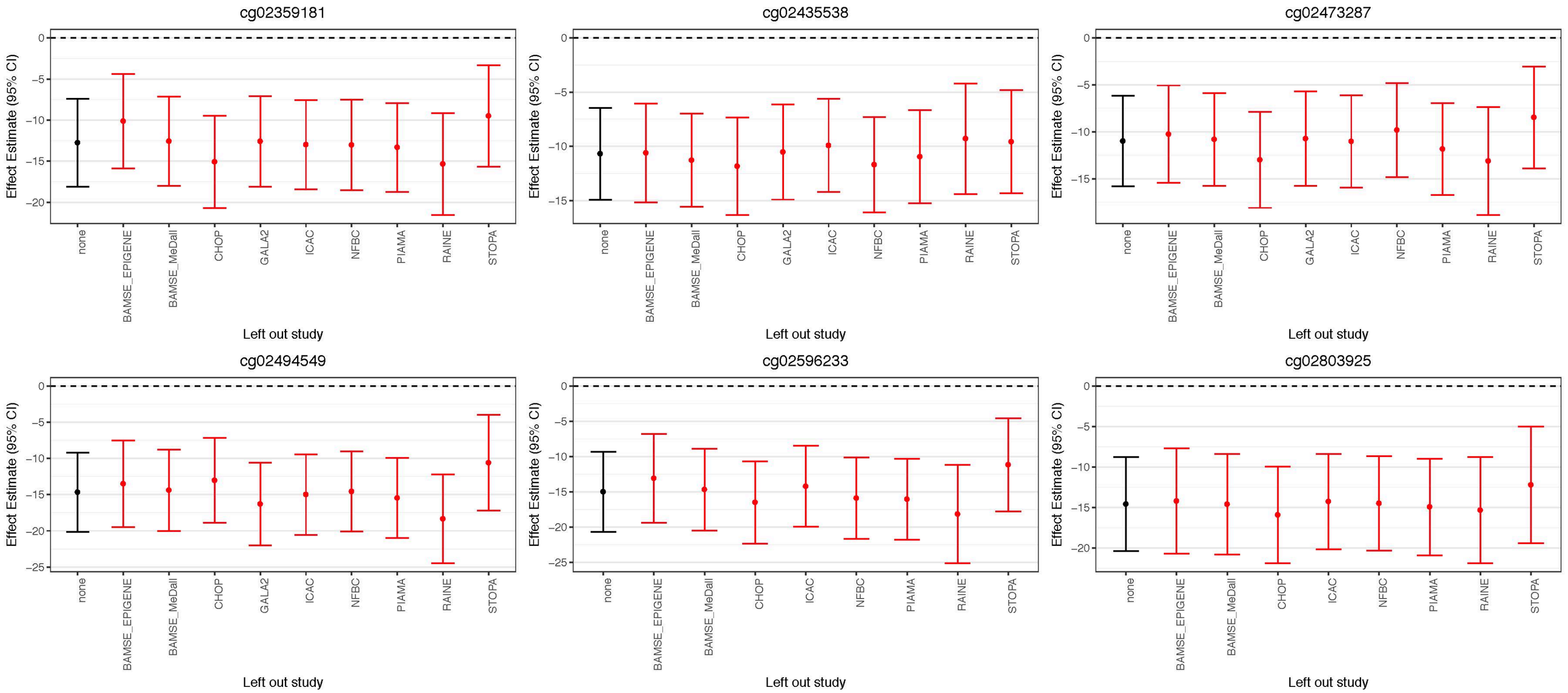
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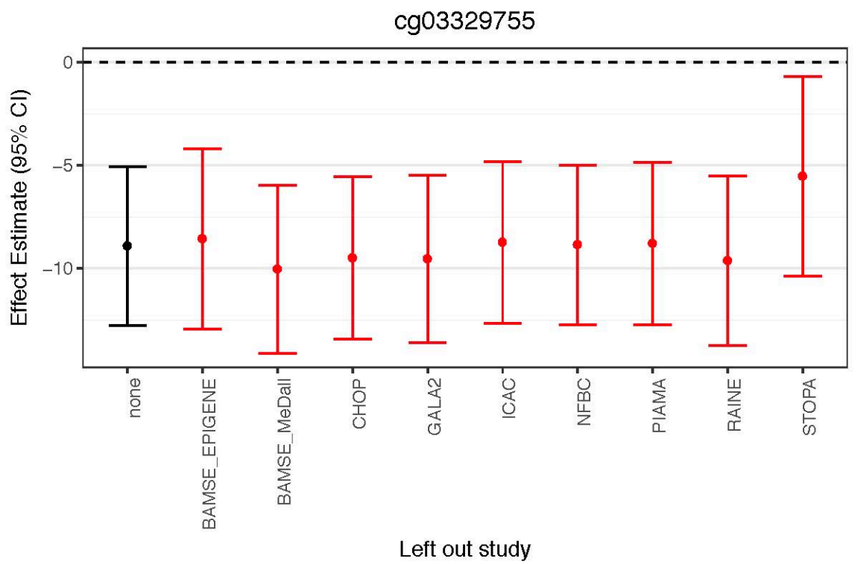
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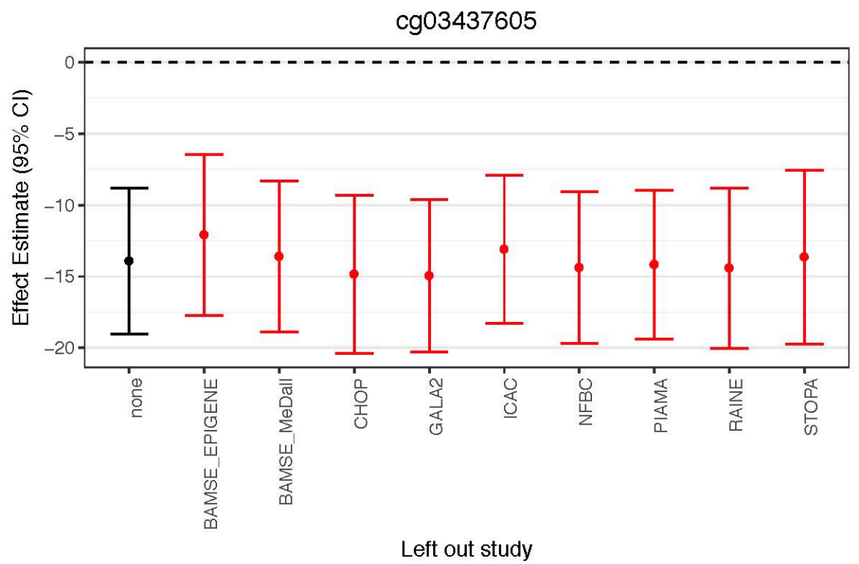
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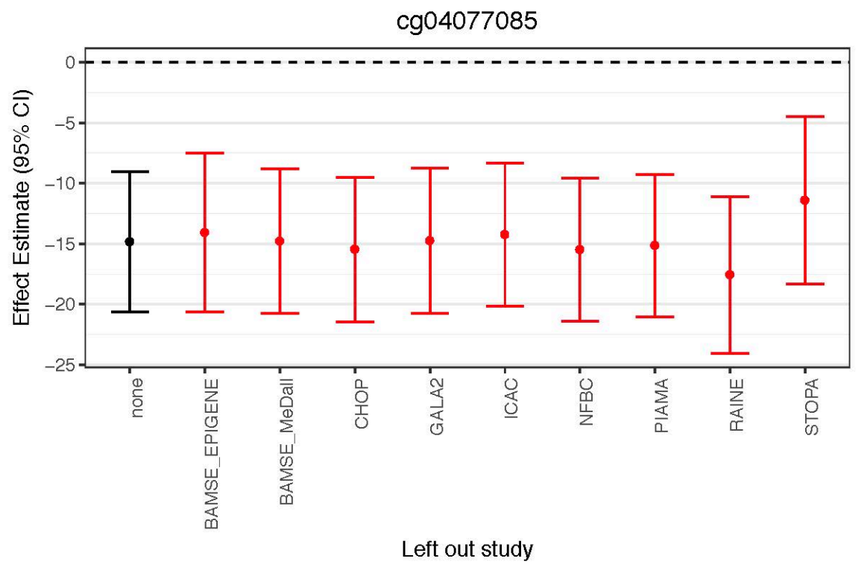
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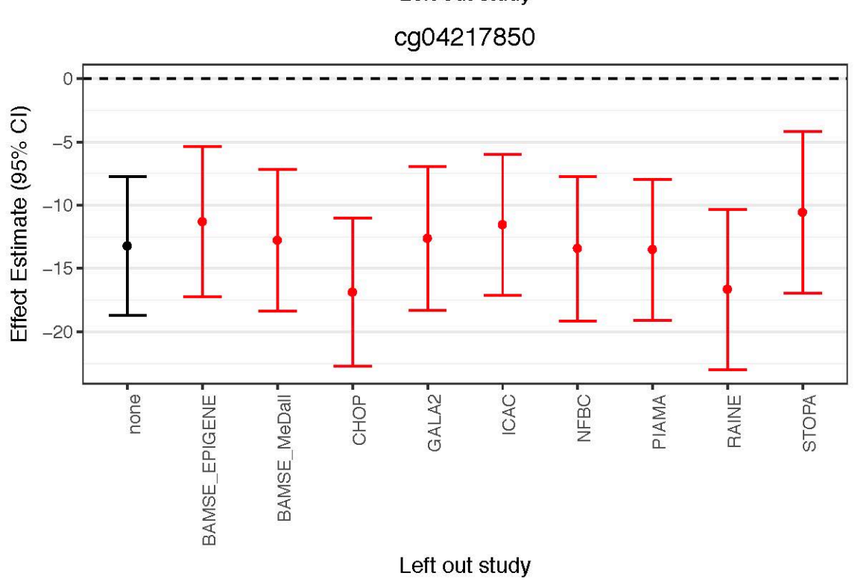
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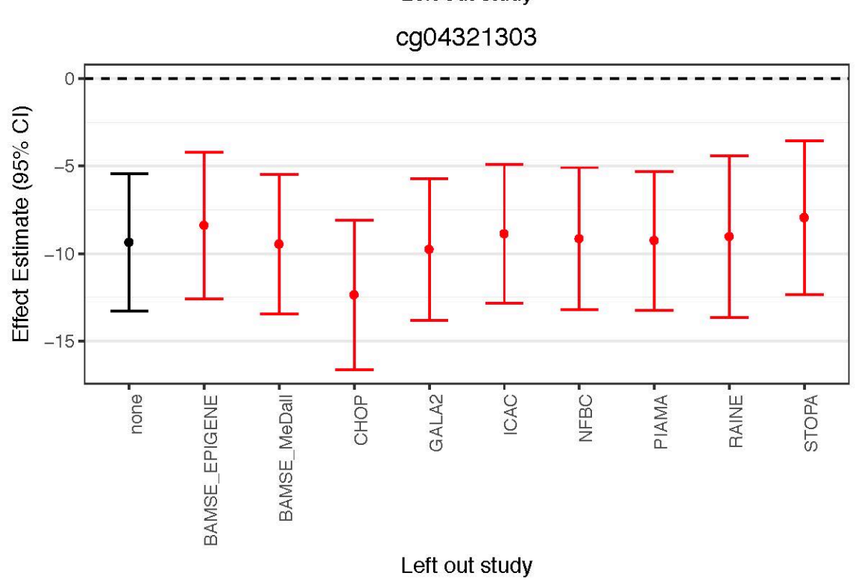
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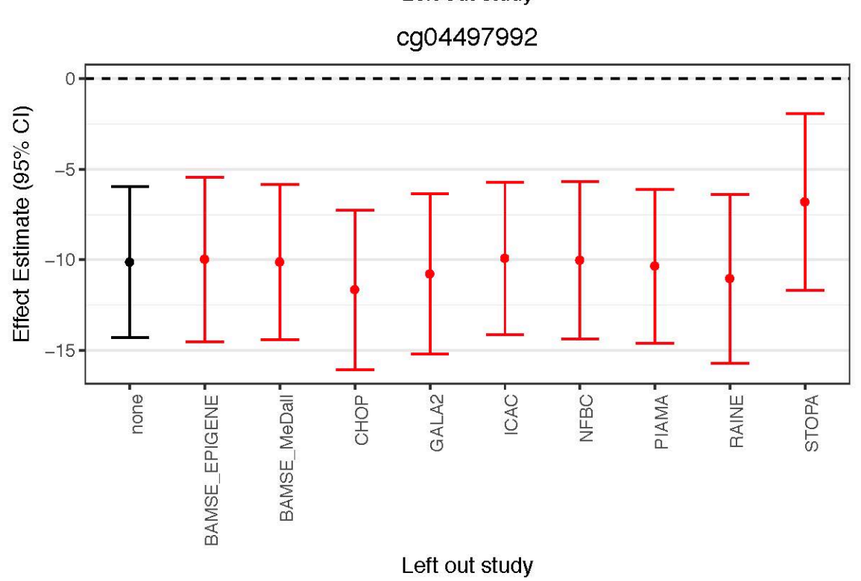
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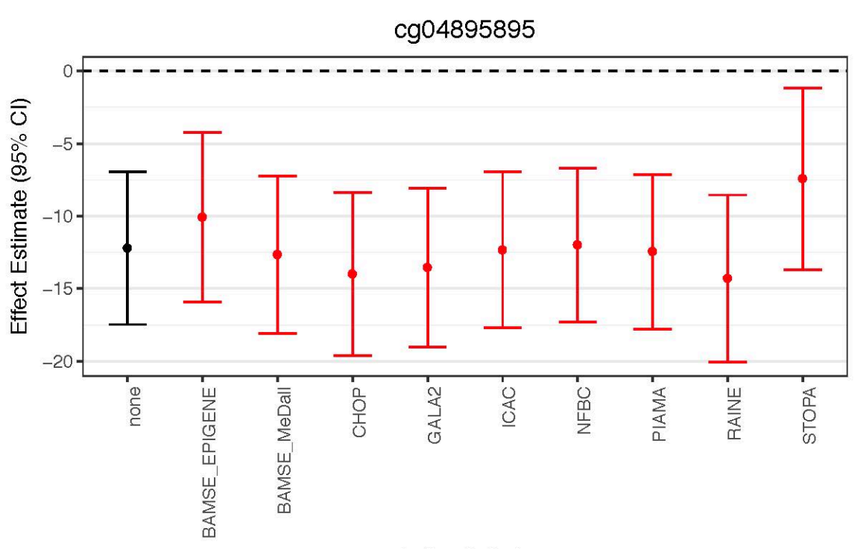
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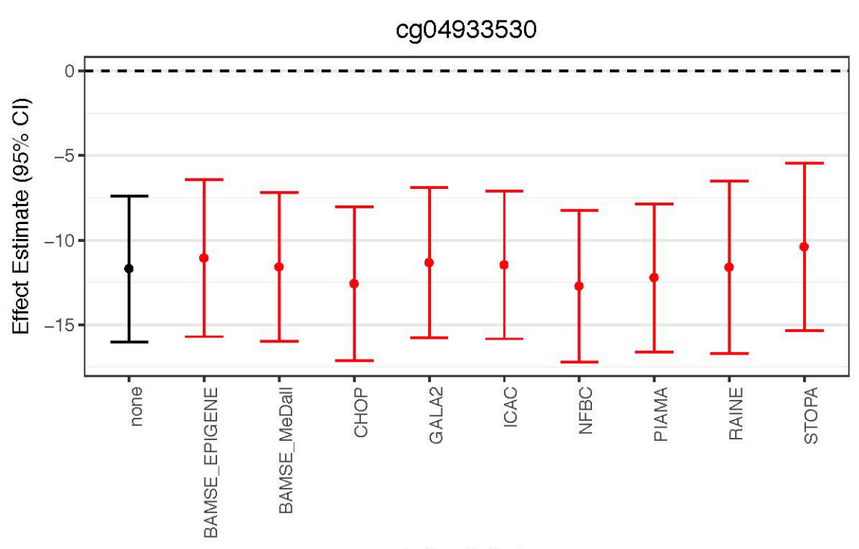
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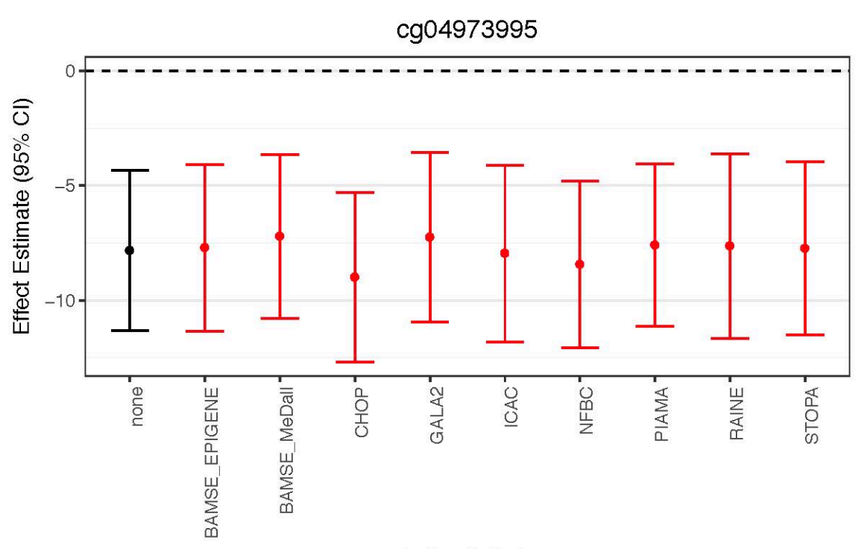
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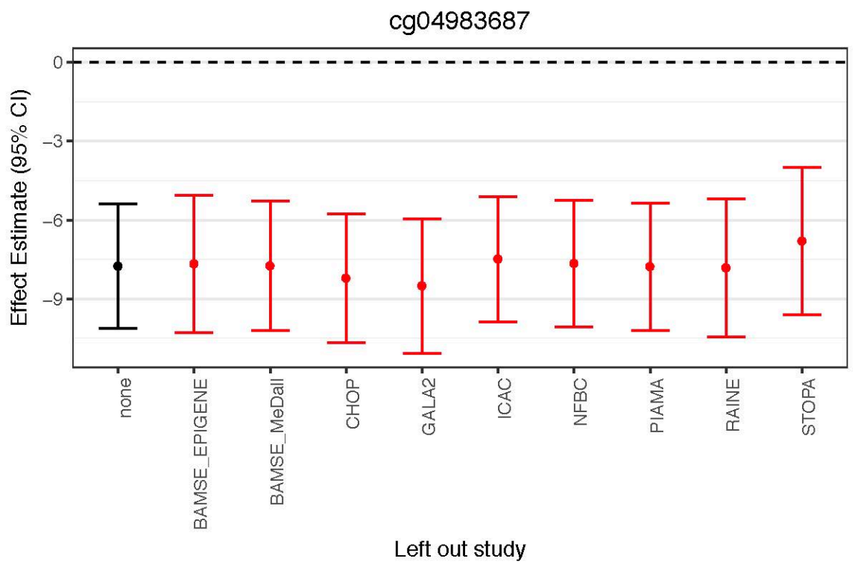
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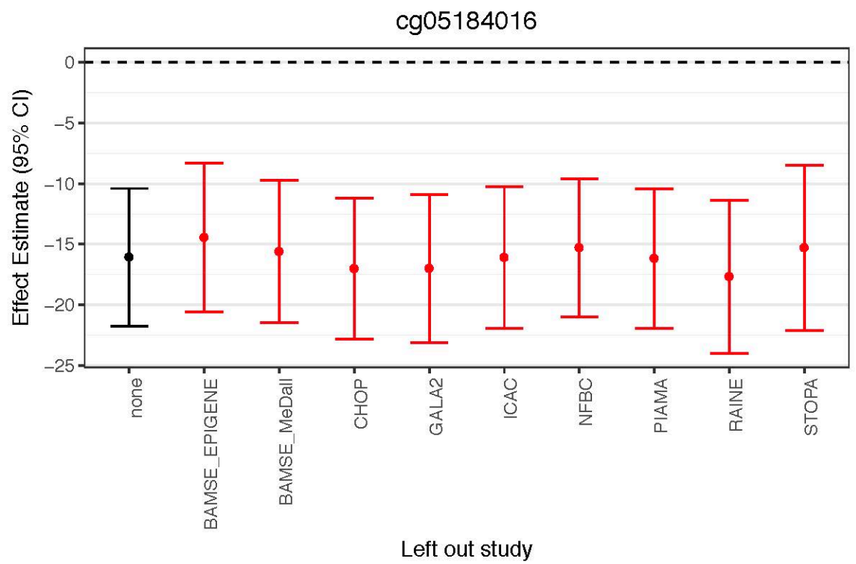
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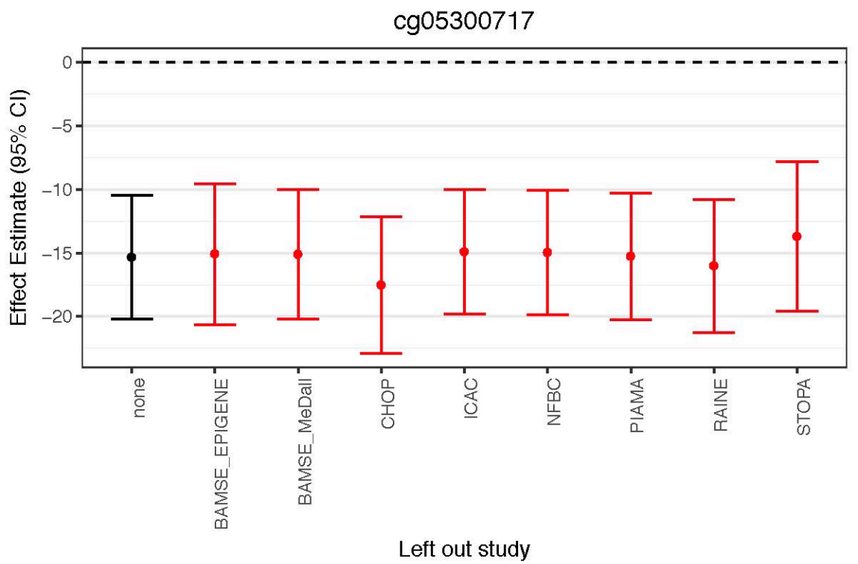
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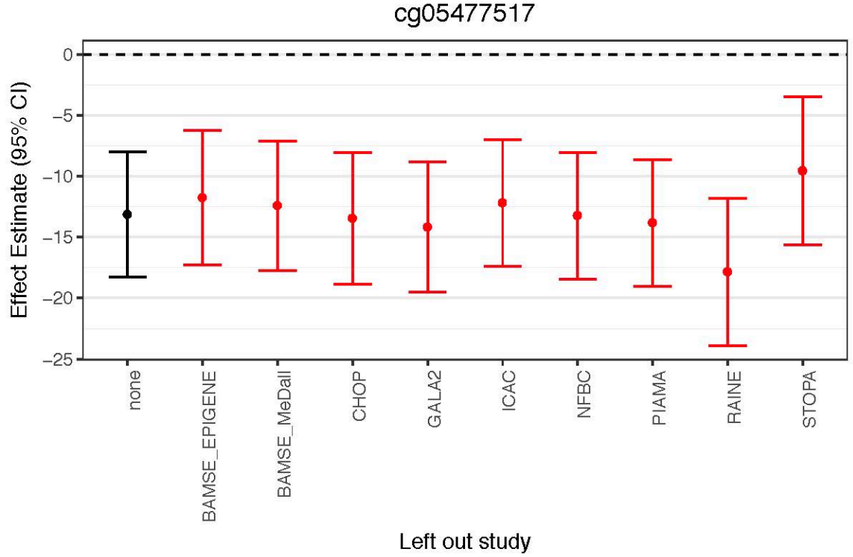
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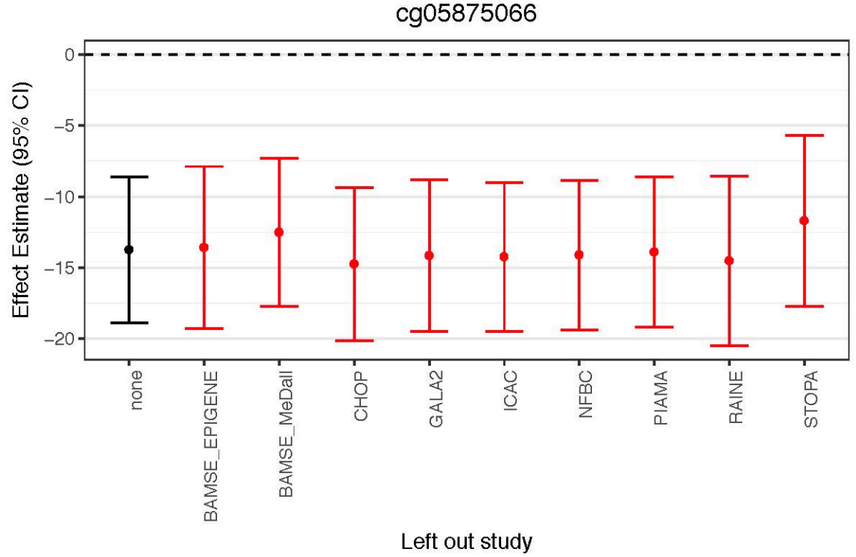
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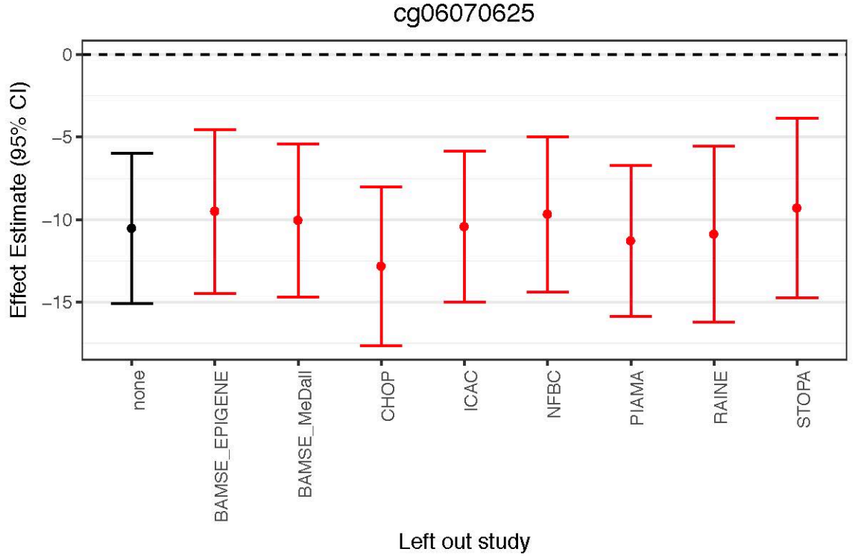
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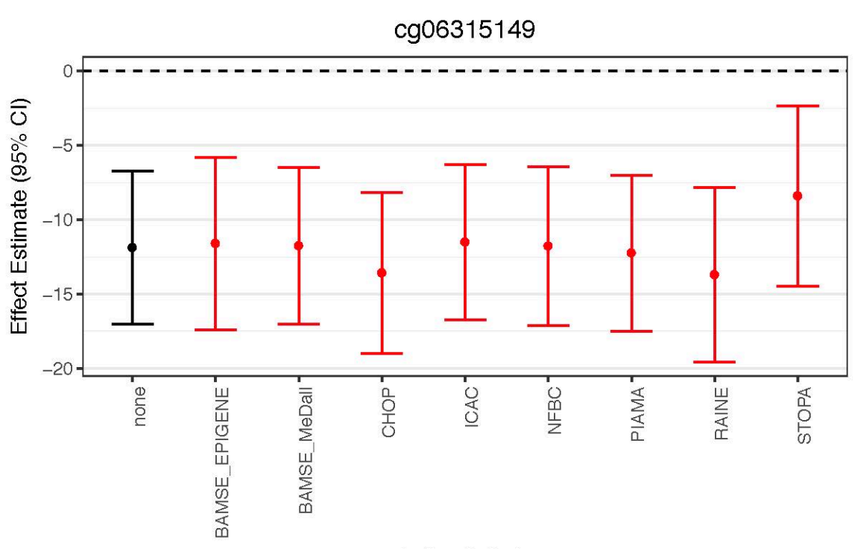
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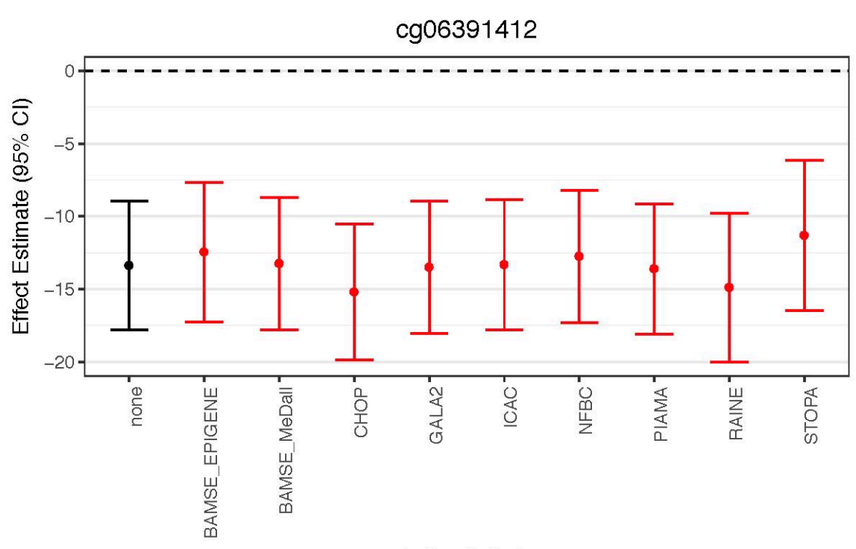
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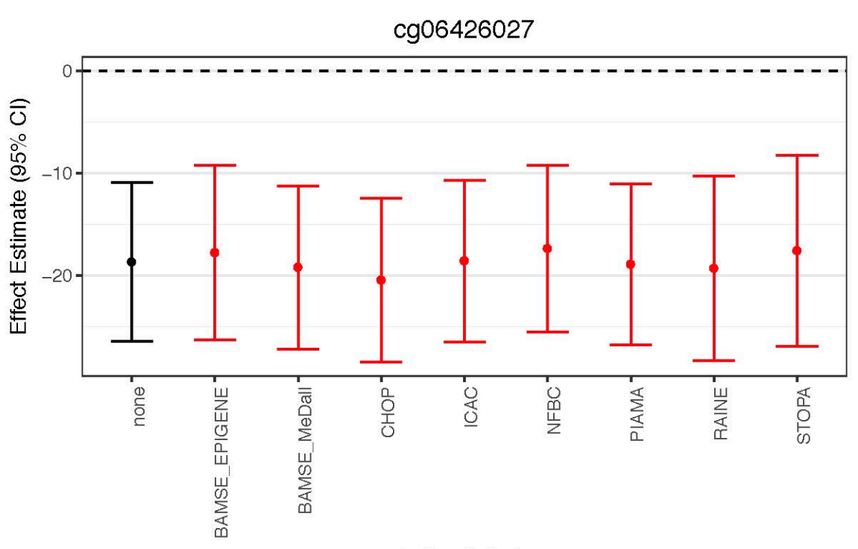
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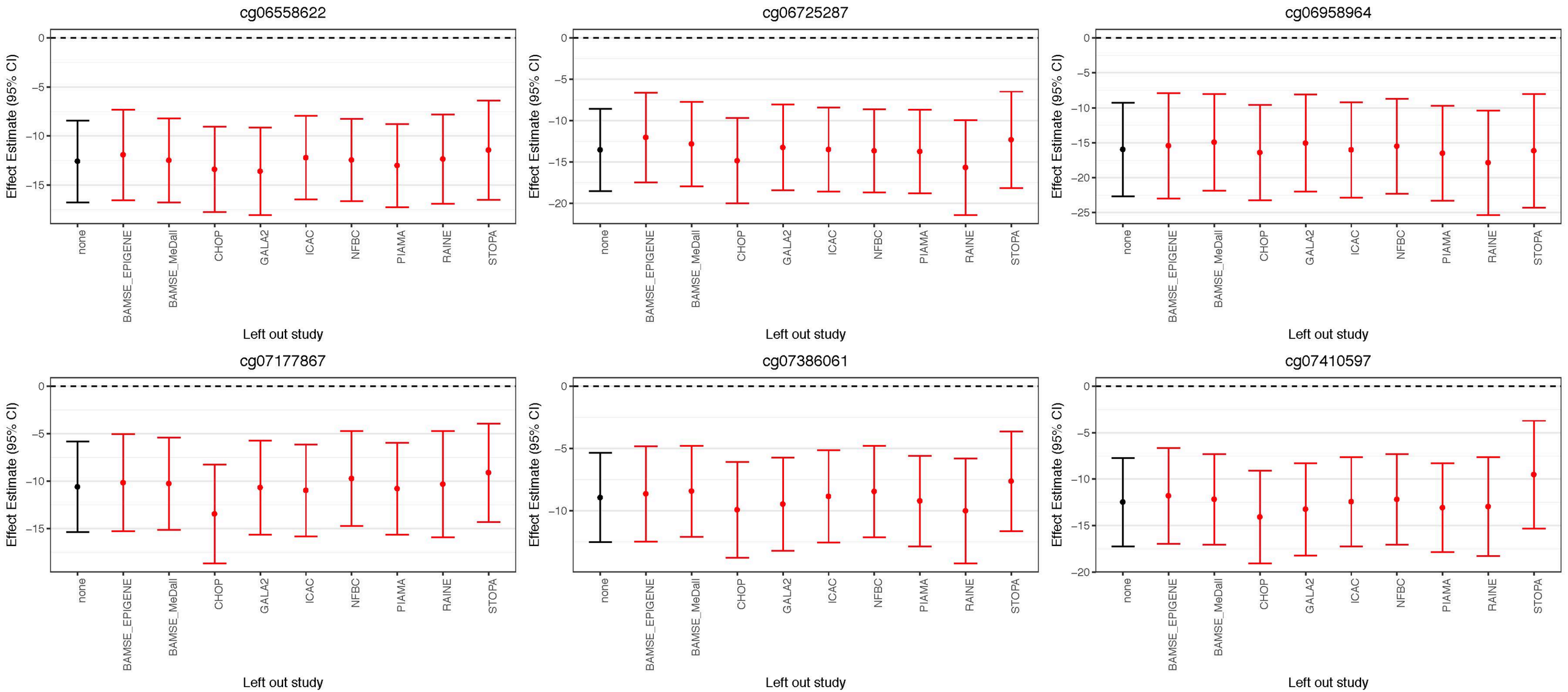
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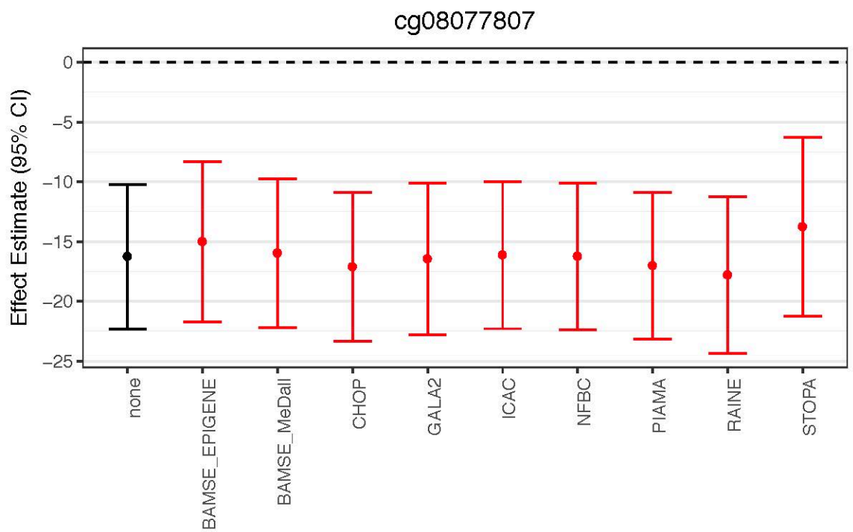
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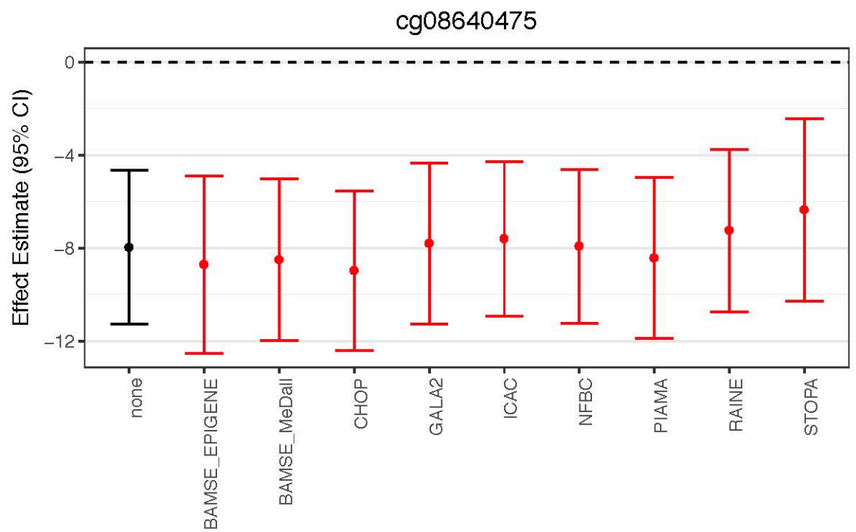
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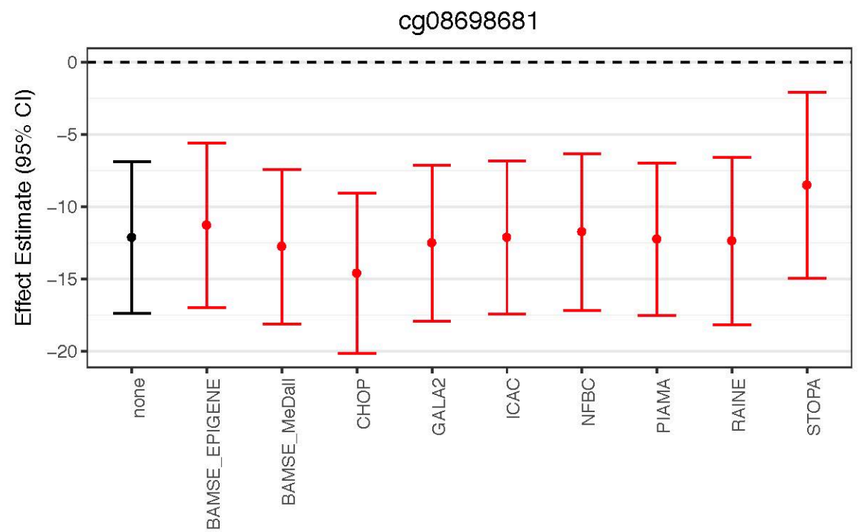
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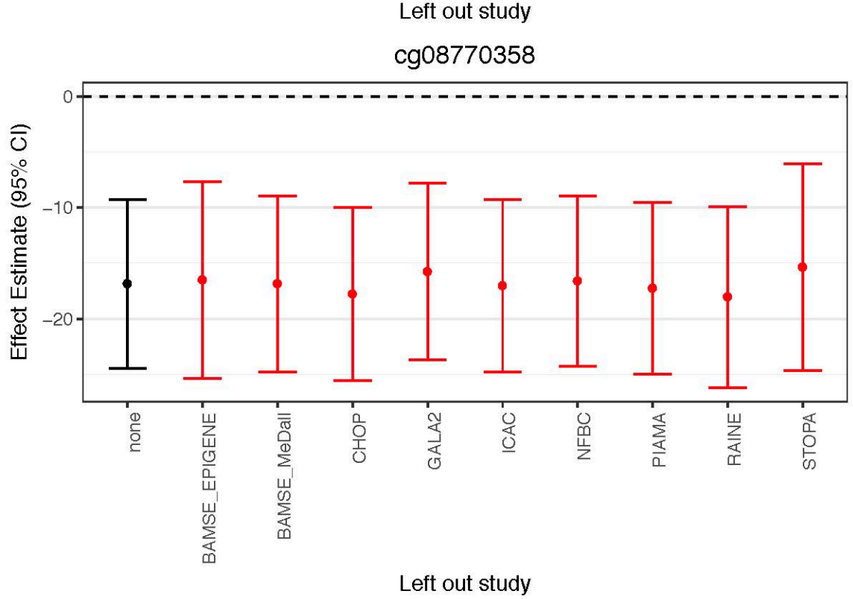
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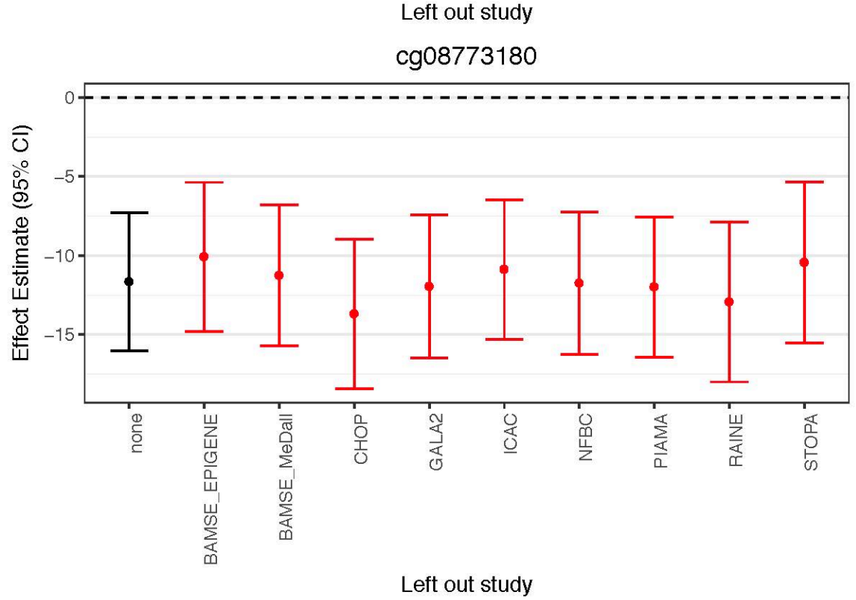
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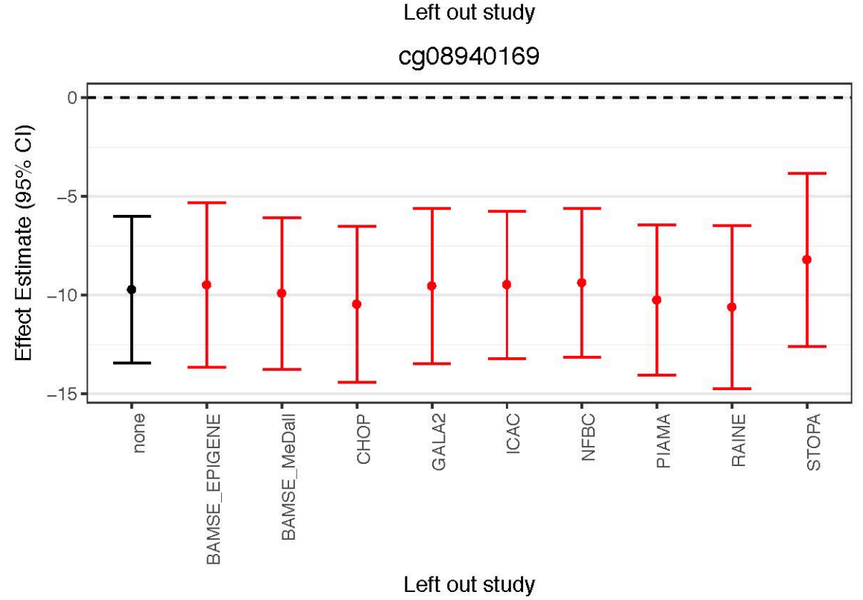
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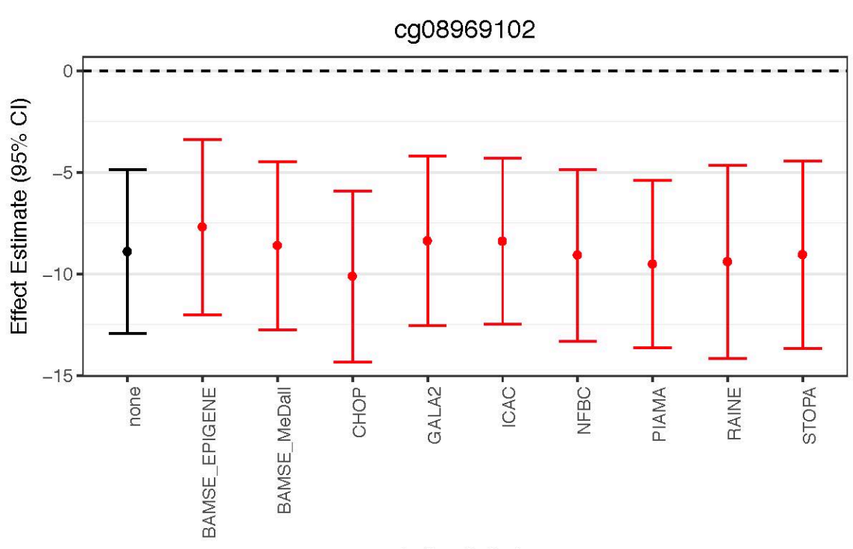
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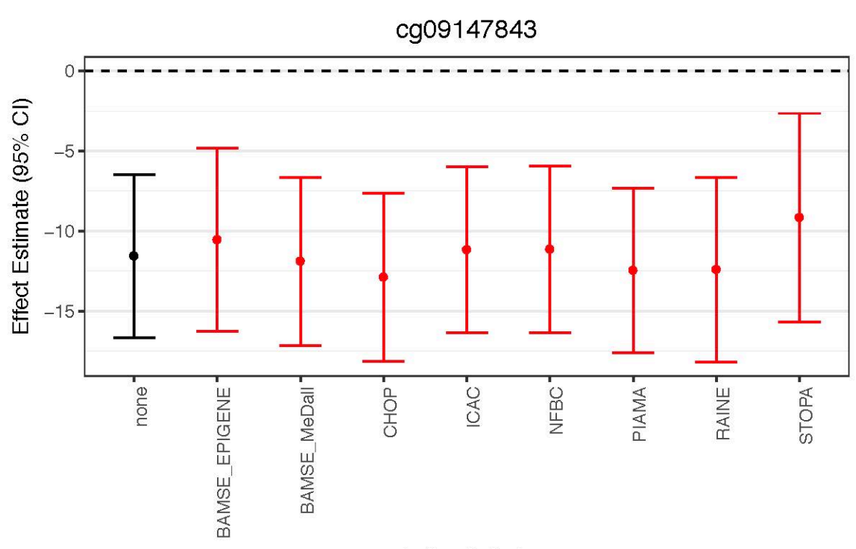
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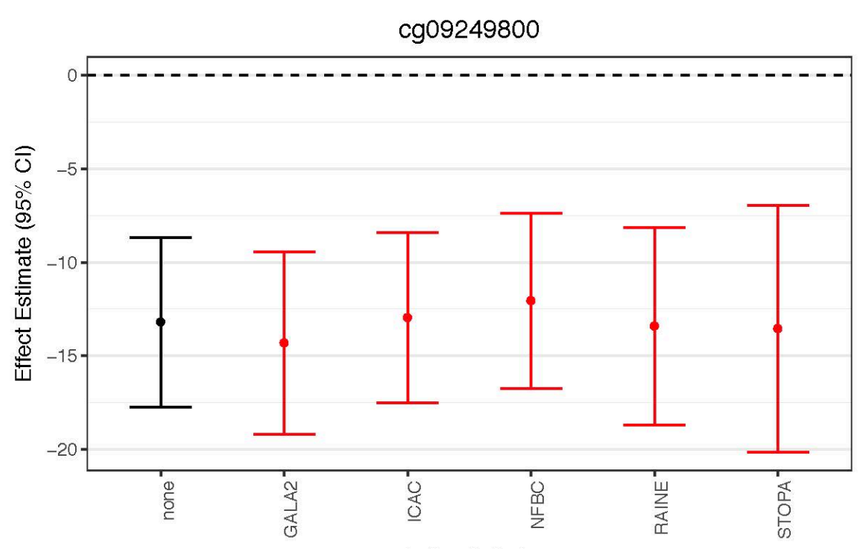
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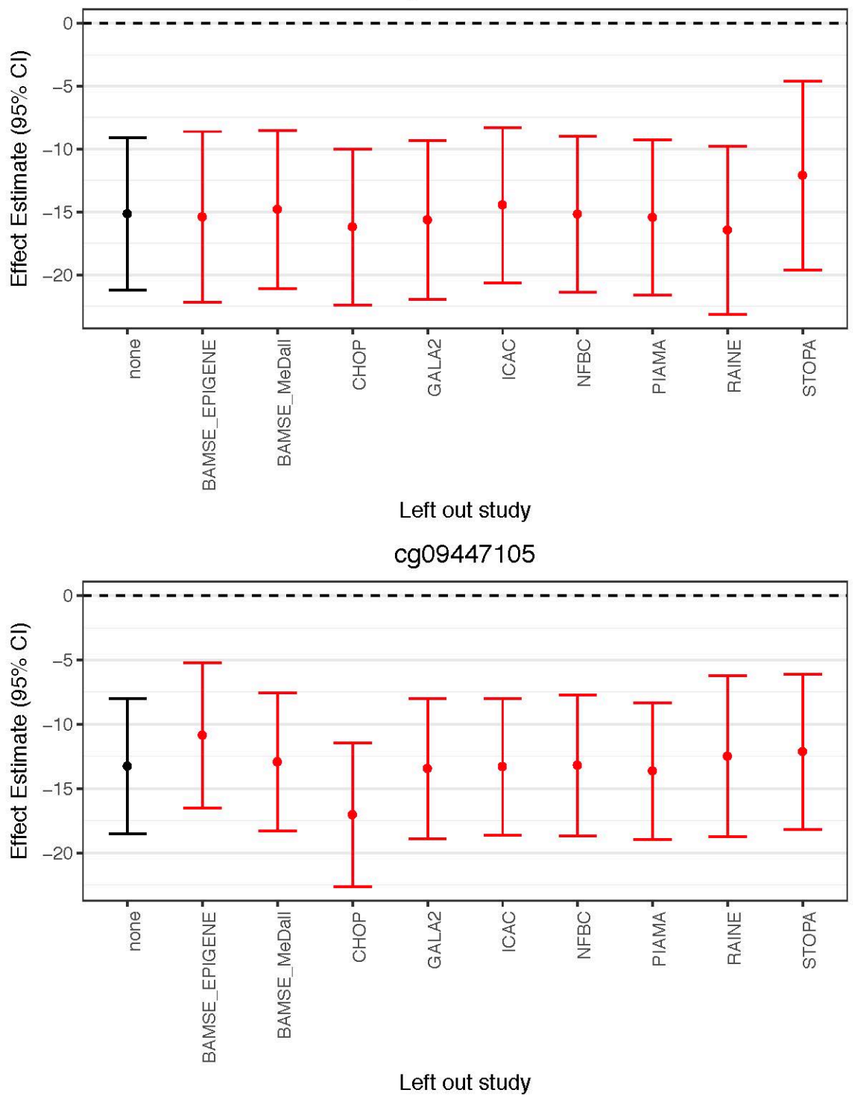

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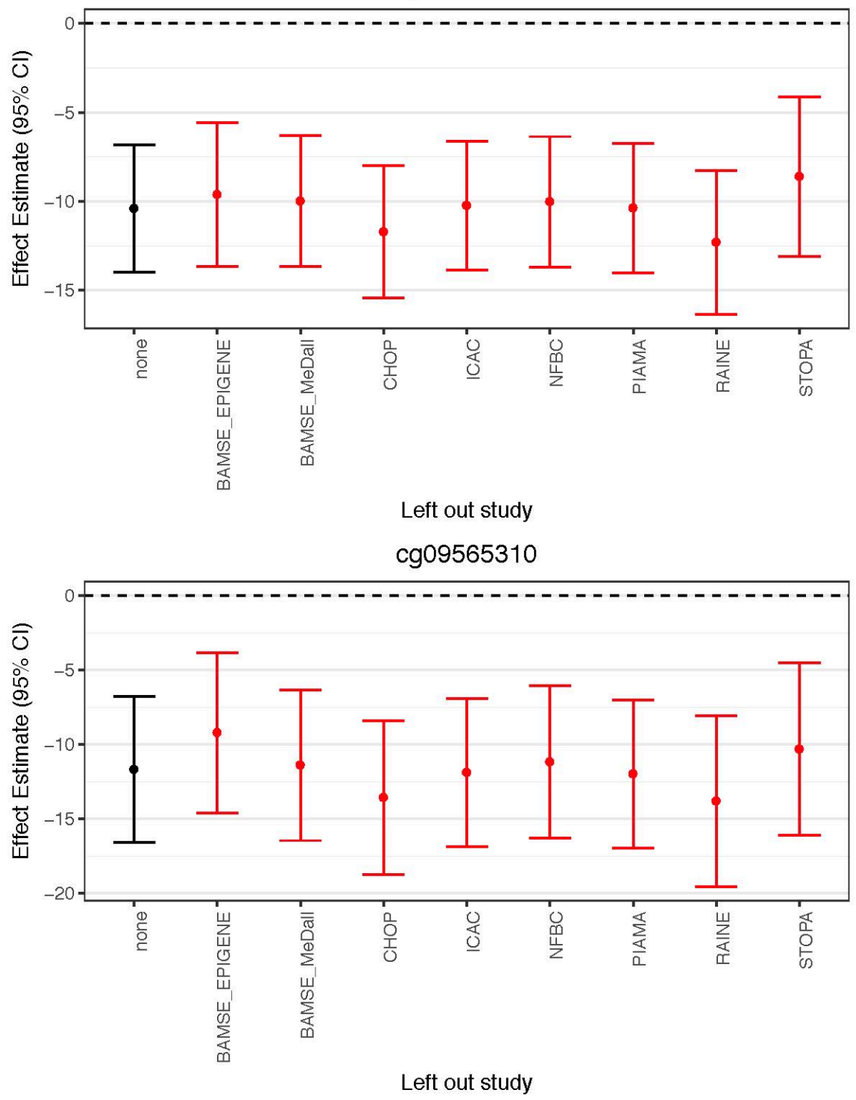

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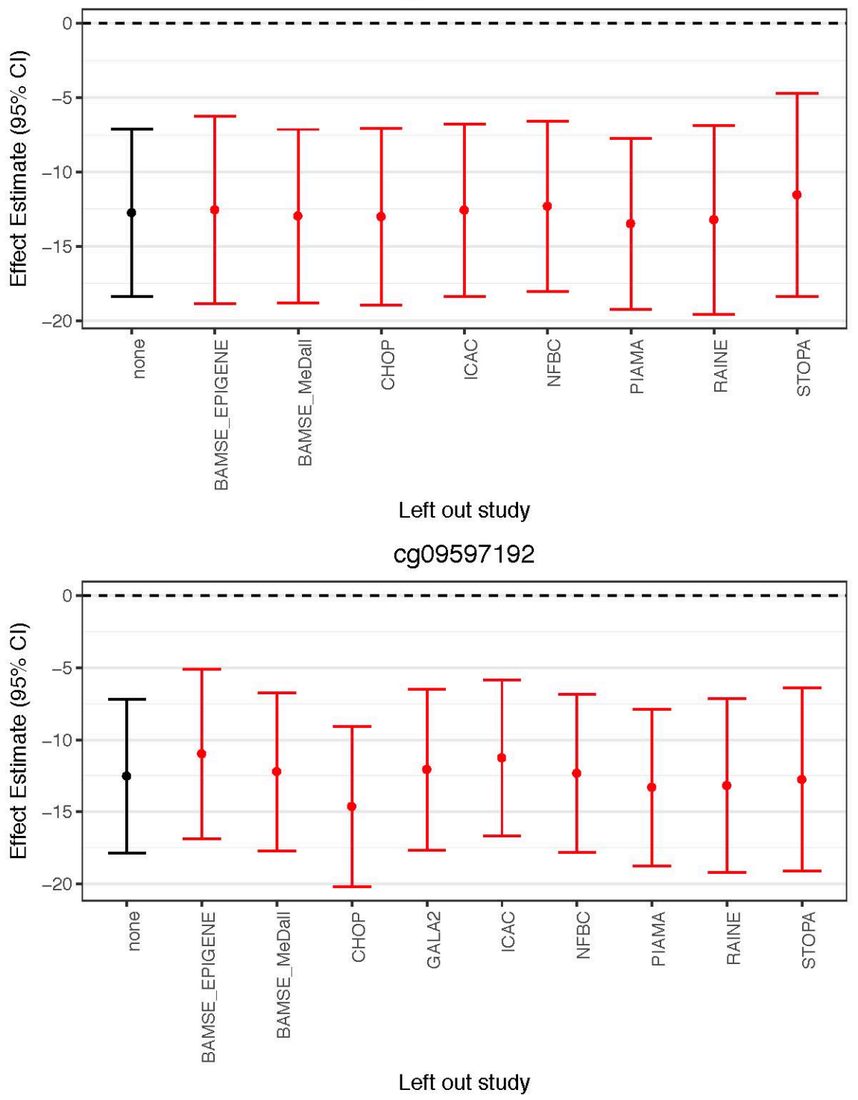

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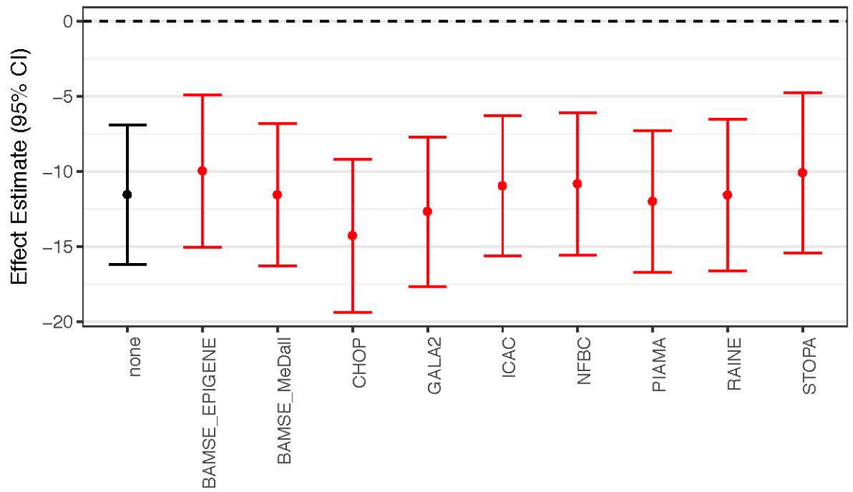

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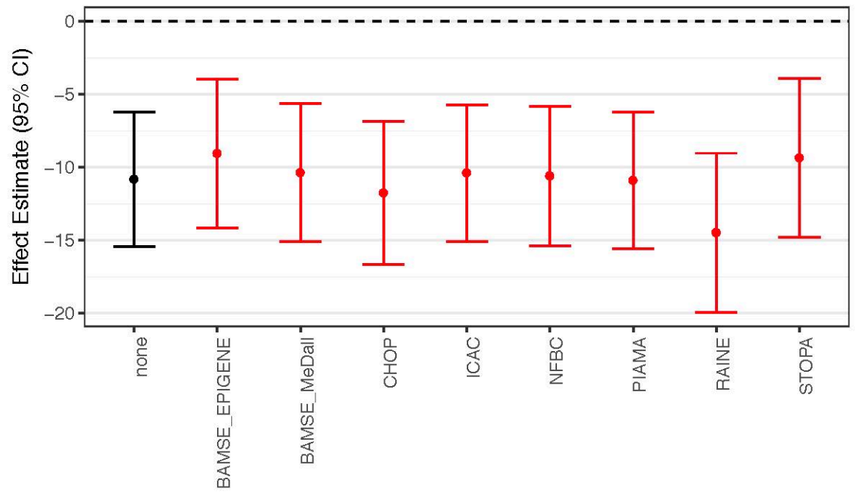

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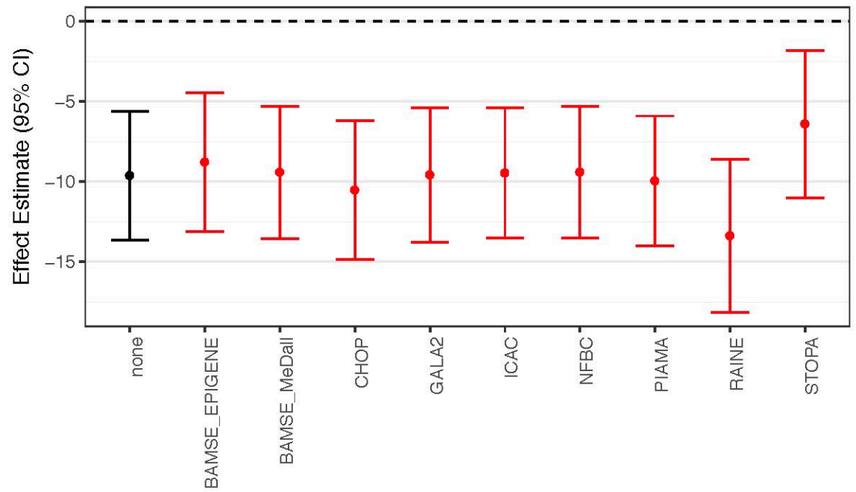

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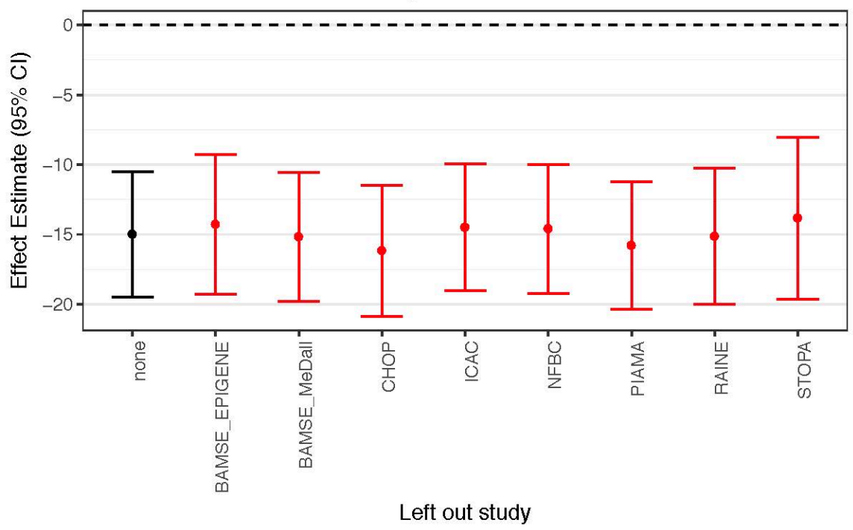

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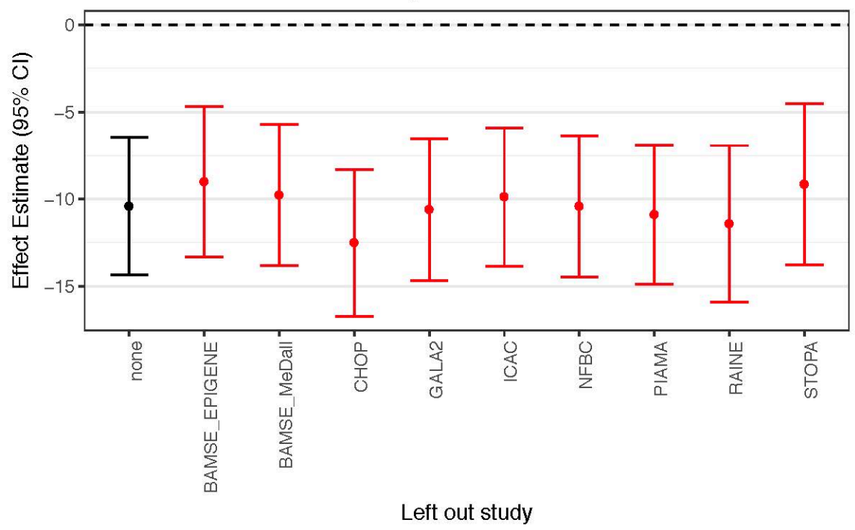

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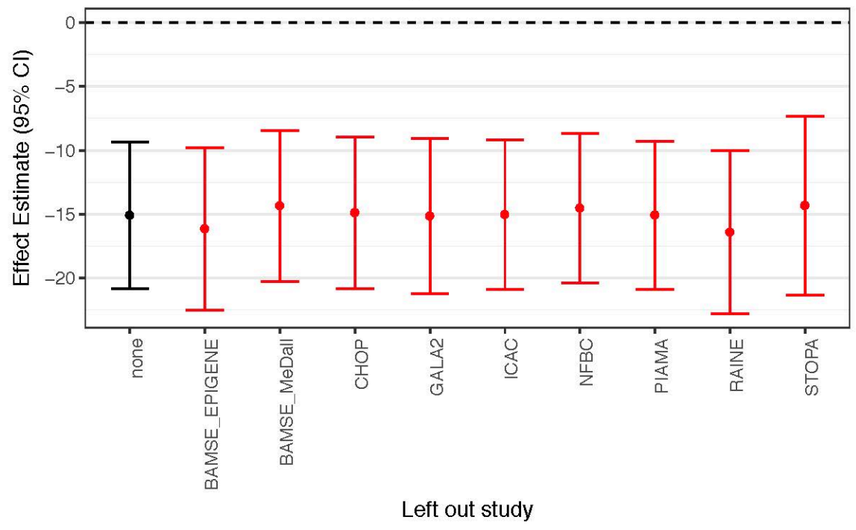

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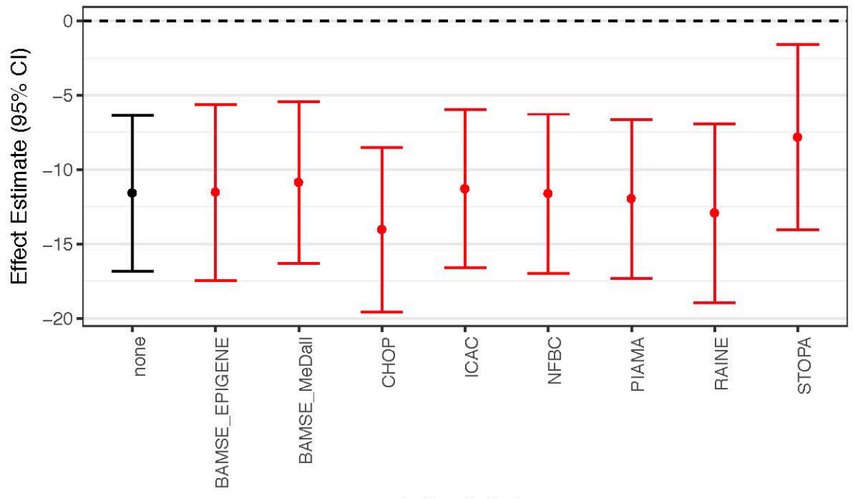

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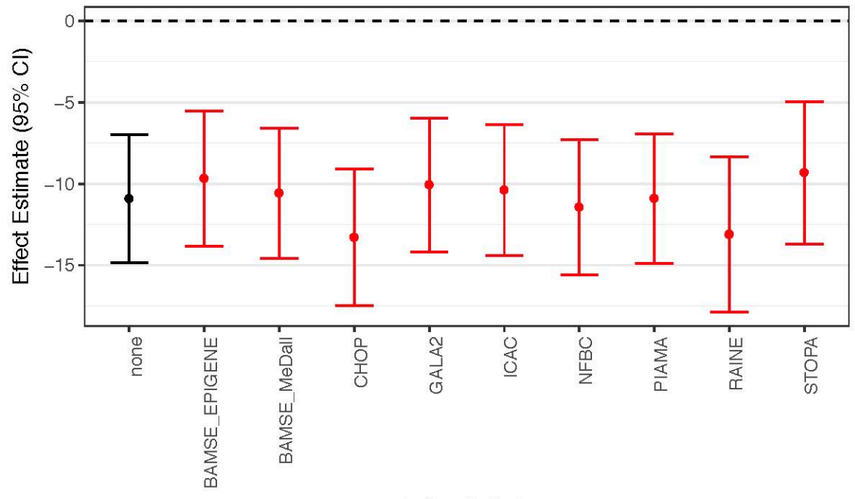

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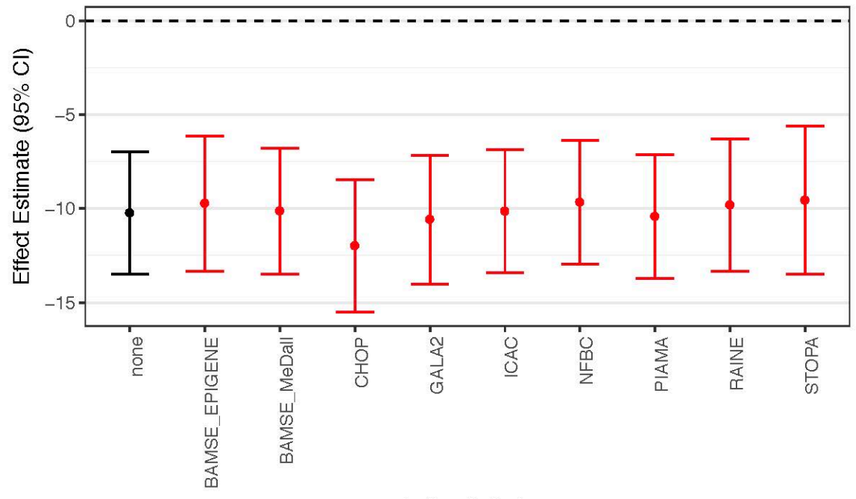

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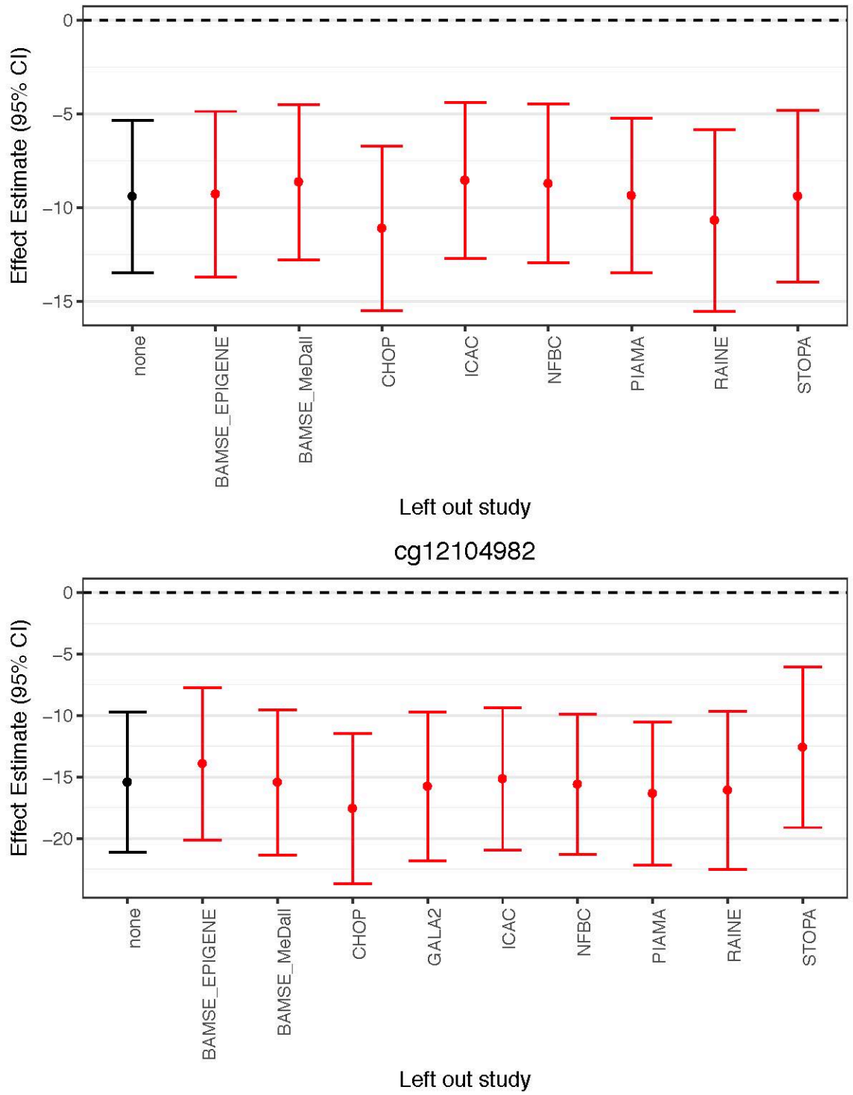

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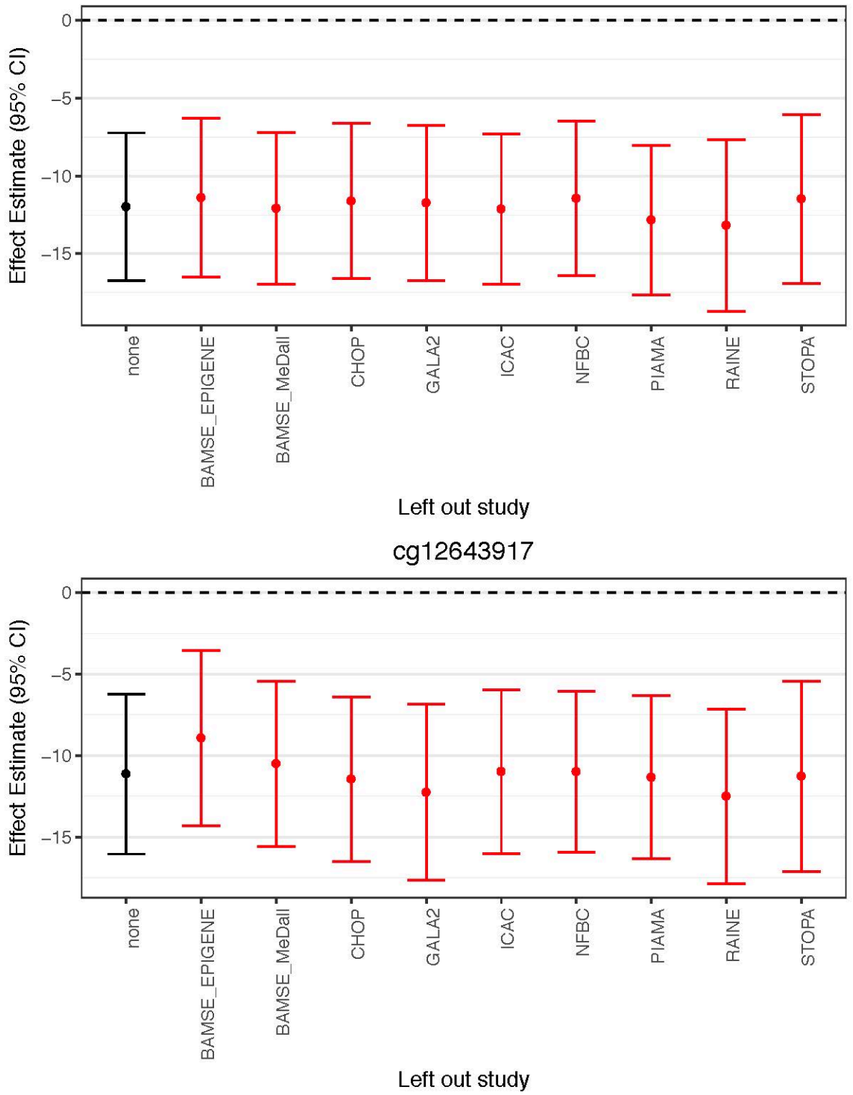

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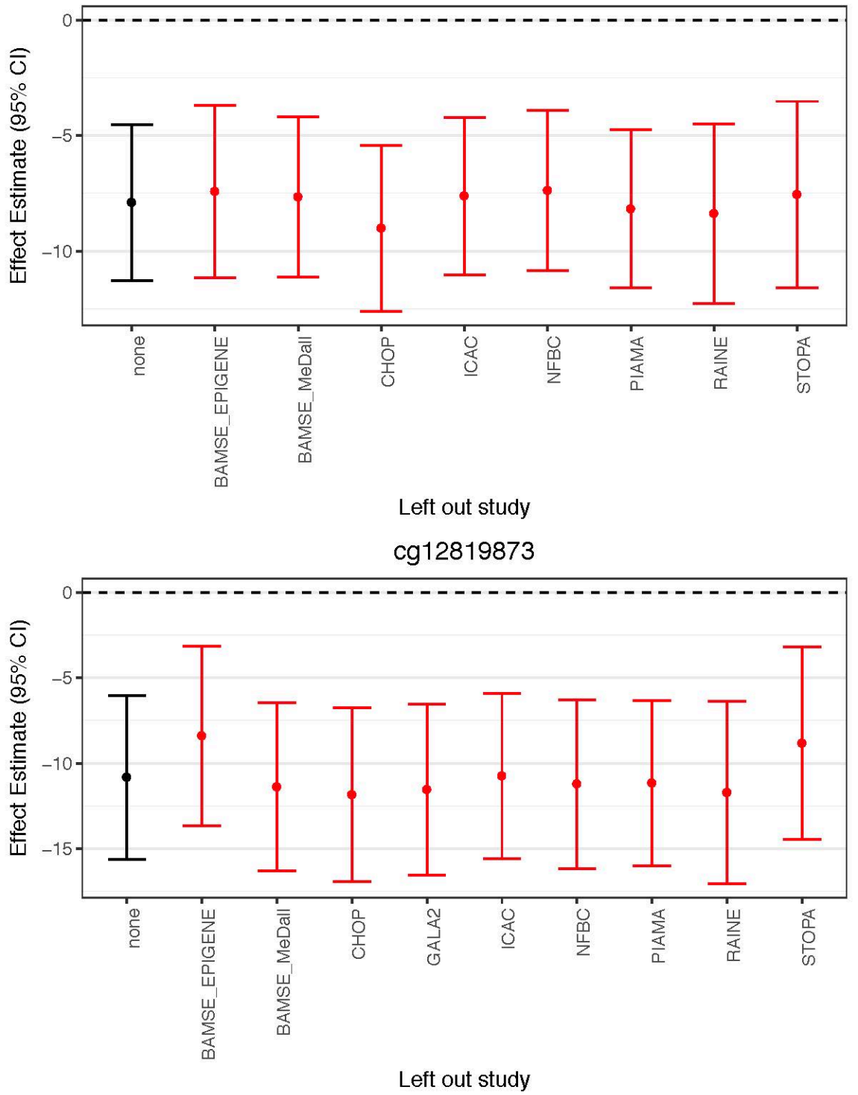

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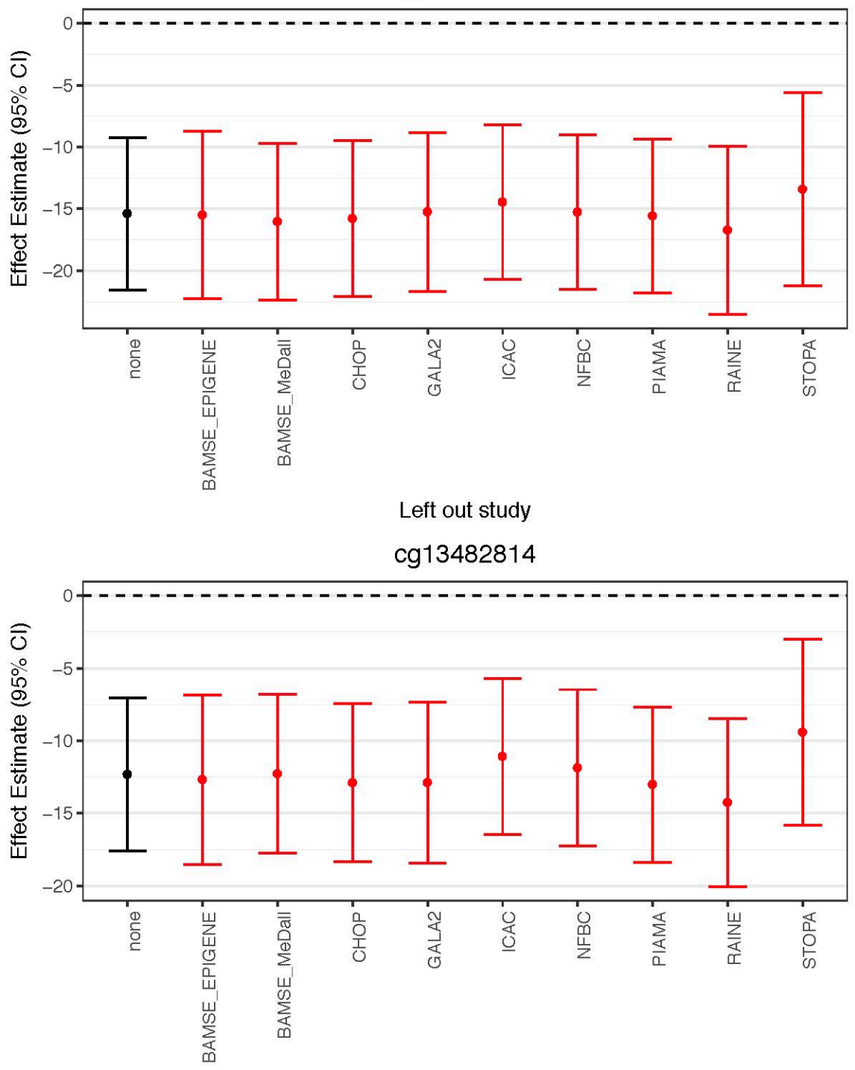

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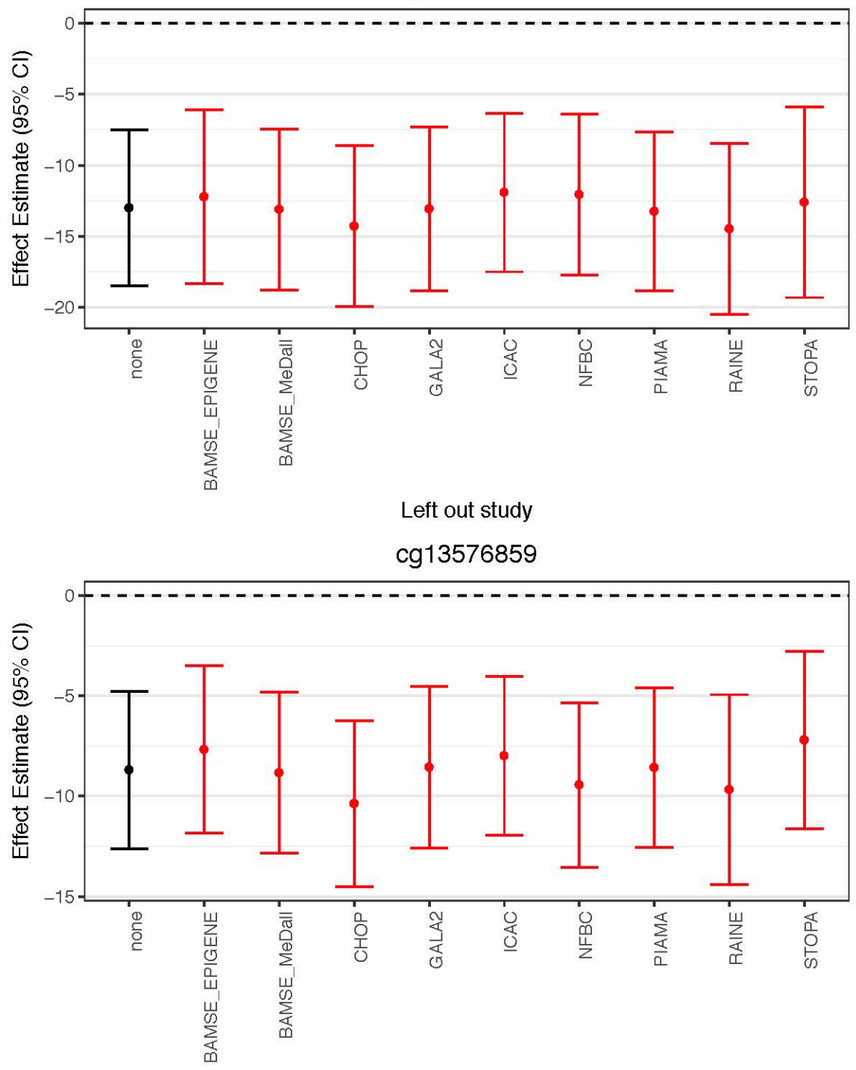

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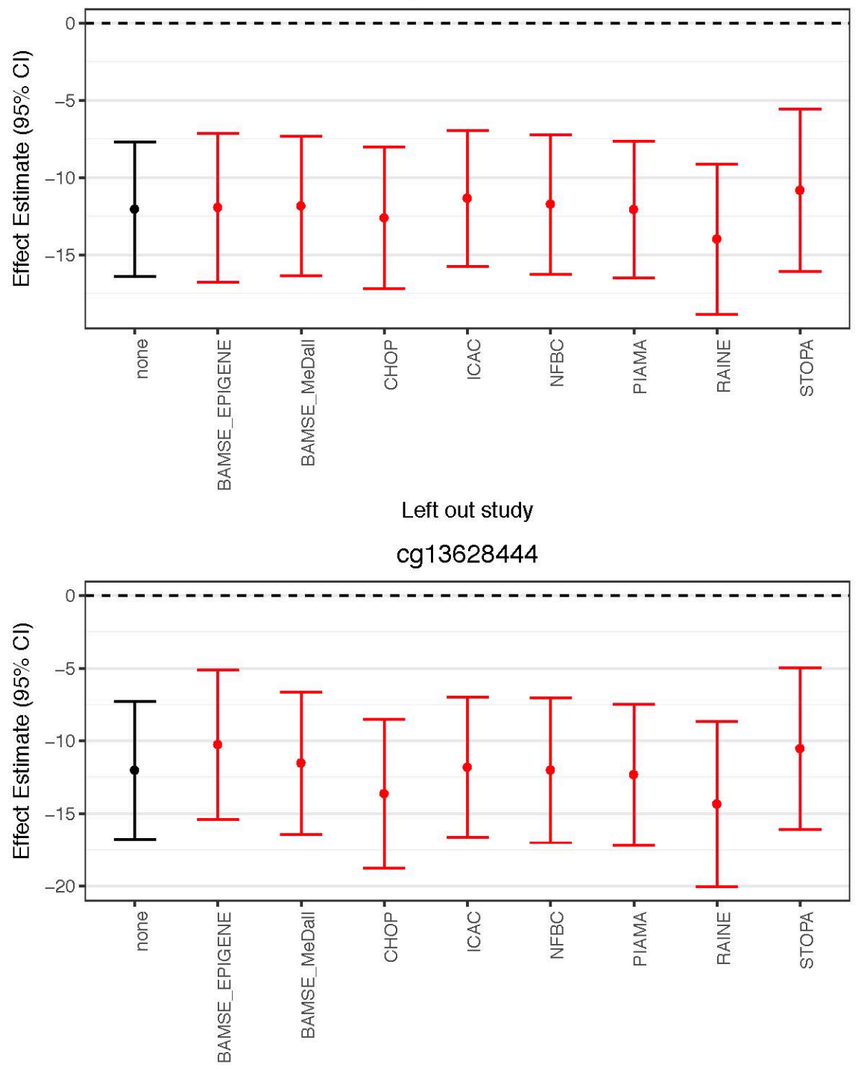

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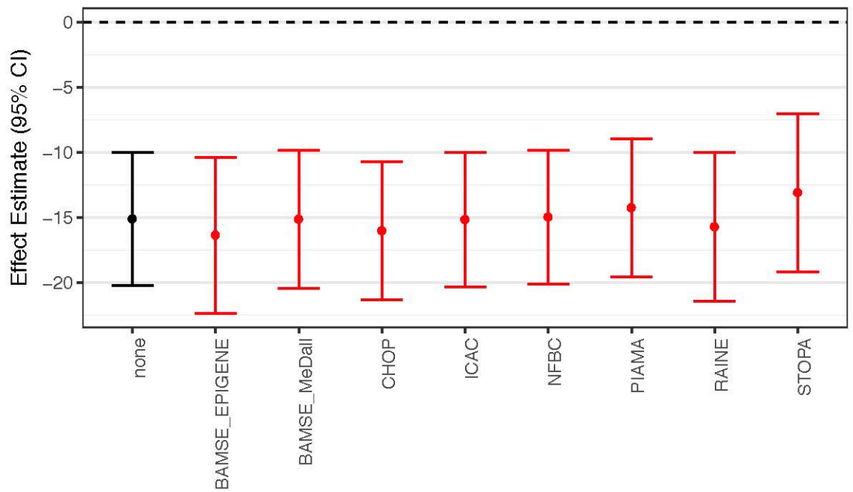

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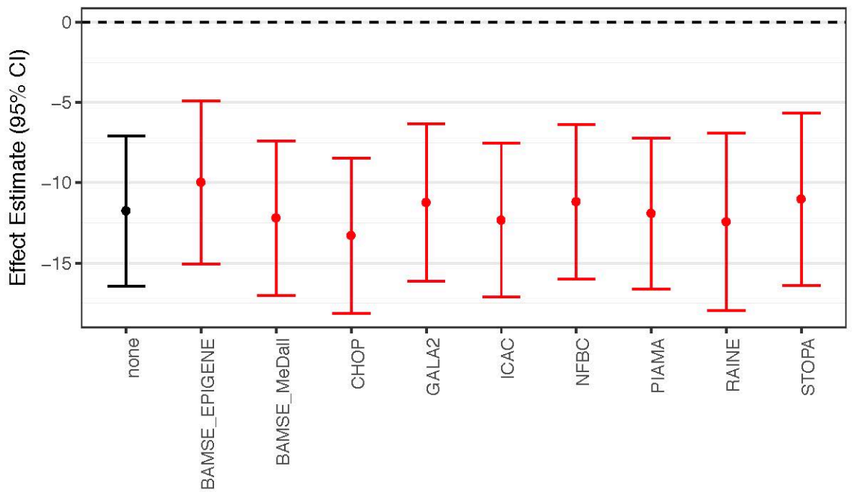

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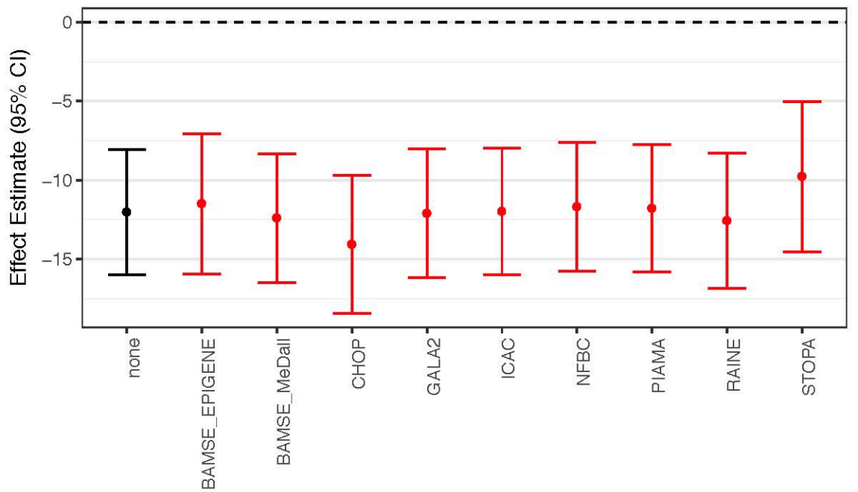

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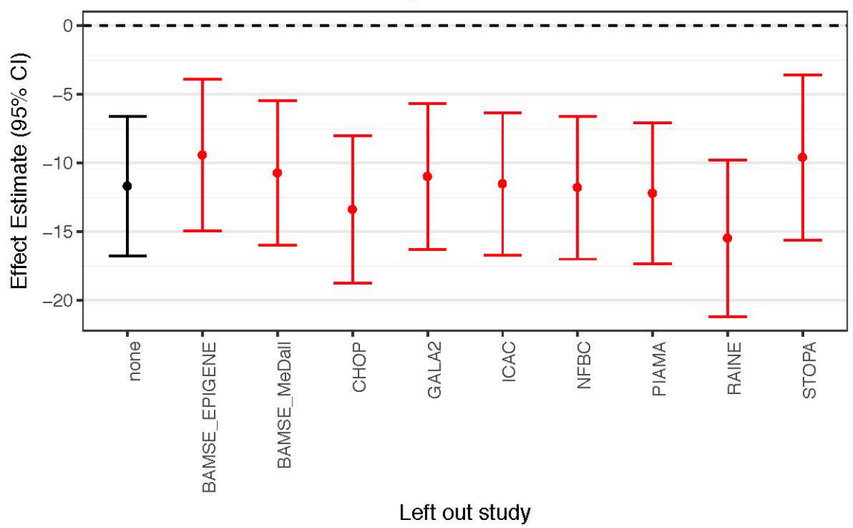

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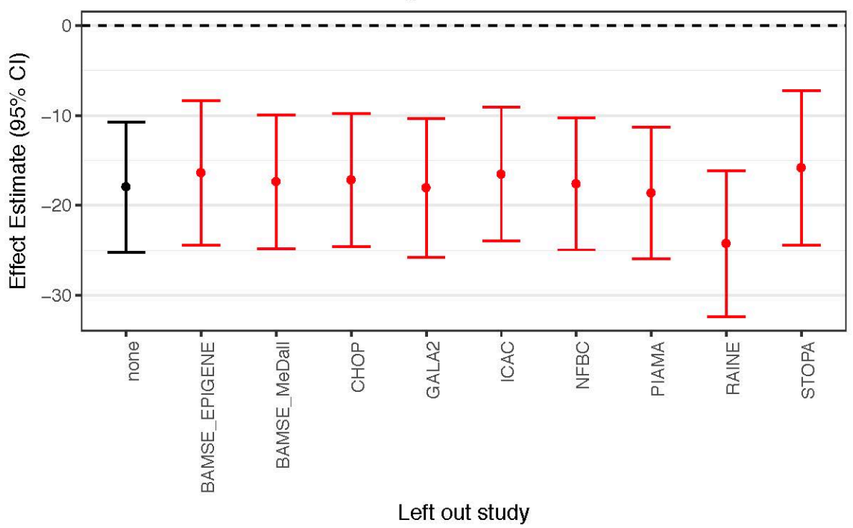

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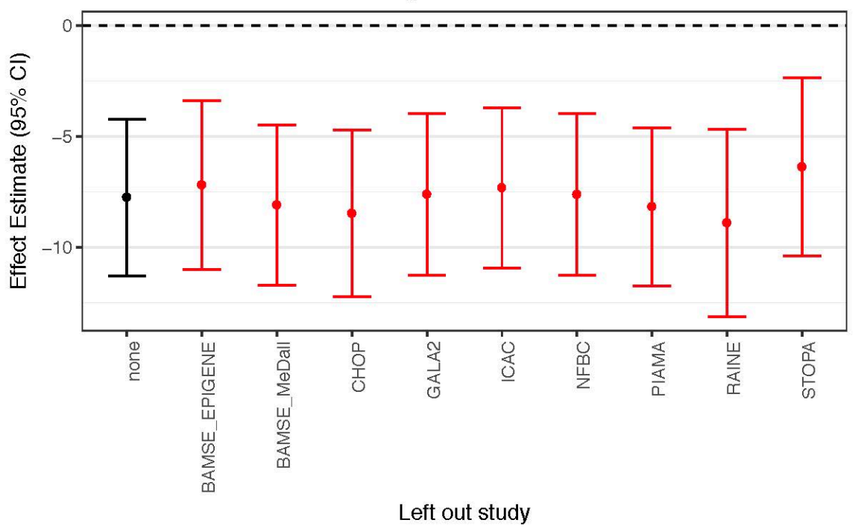

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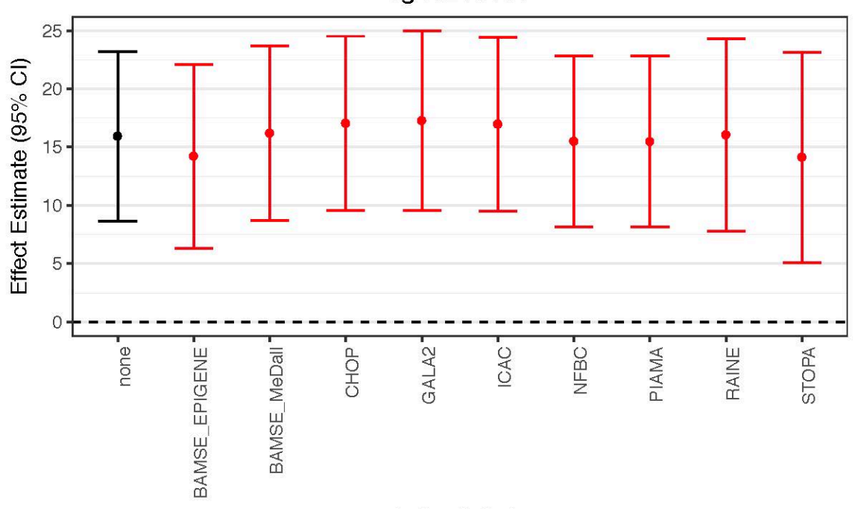

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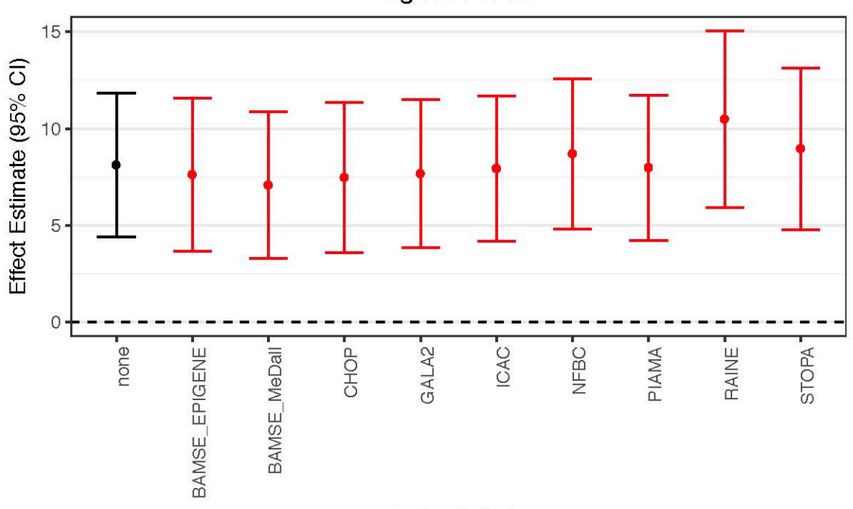

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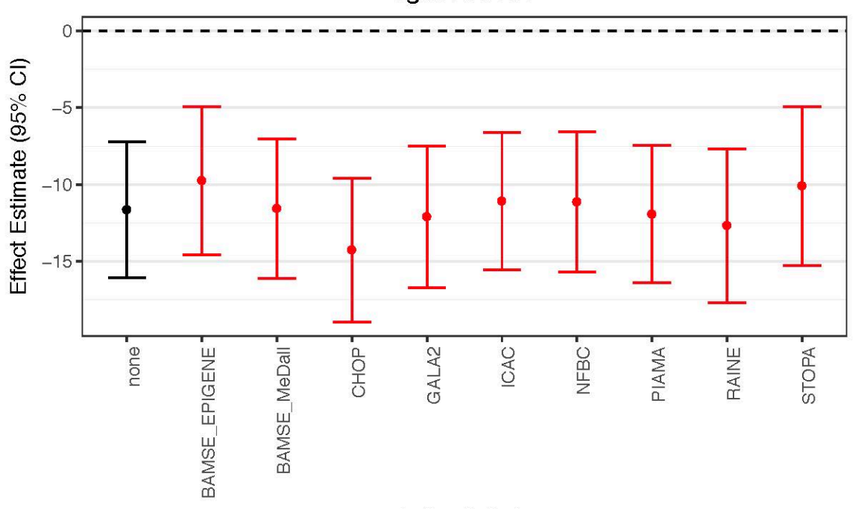

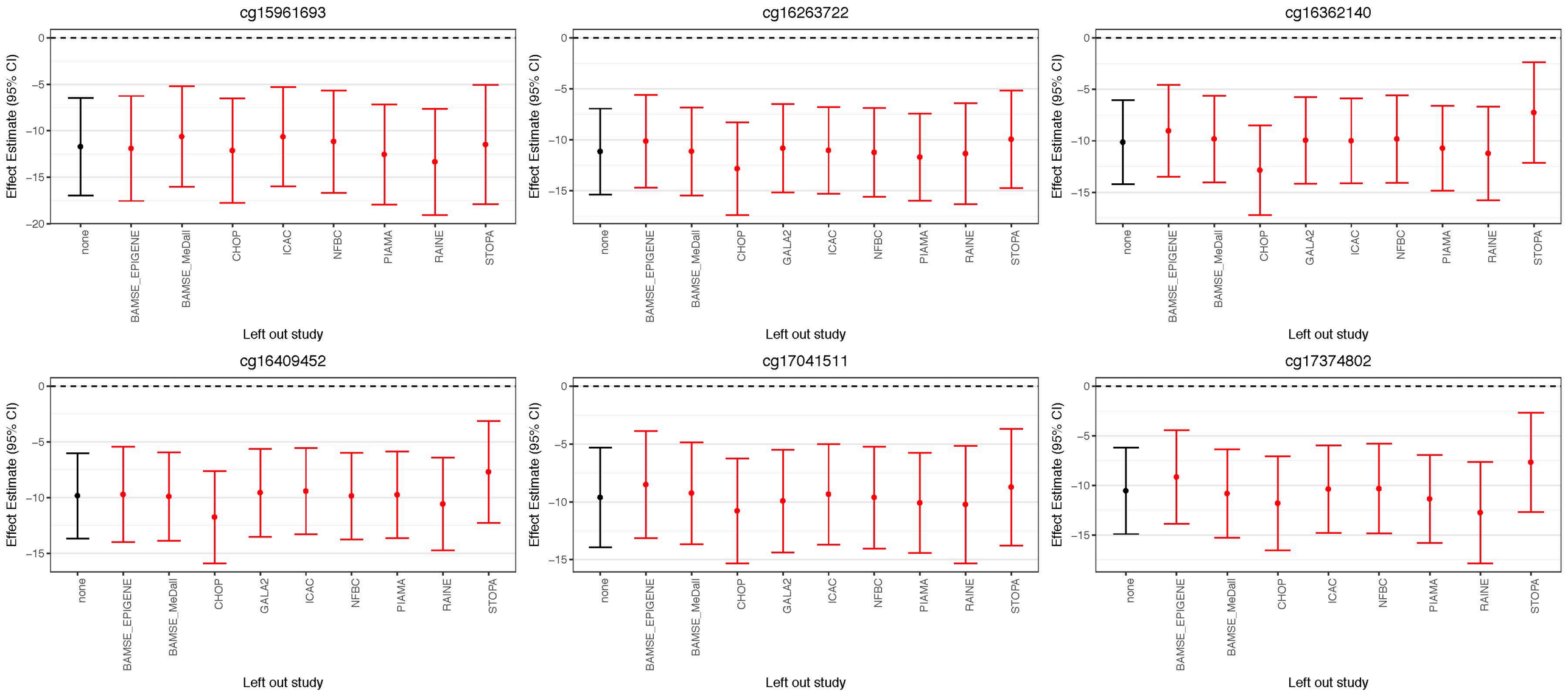
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Effect Estimate (95% CI)
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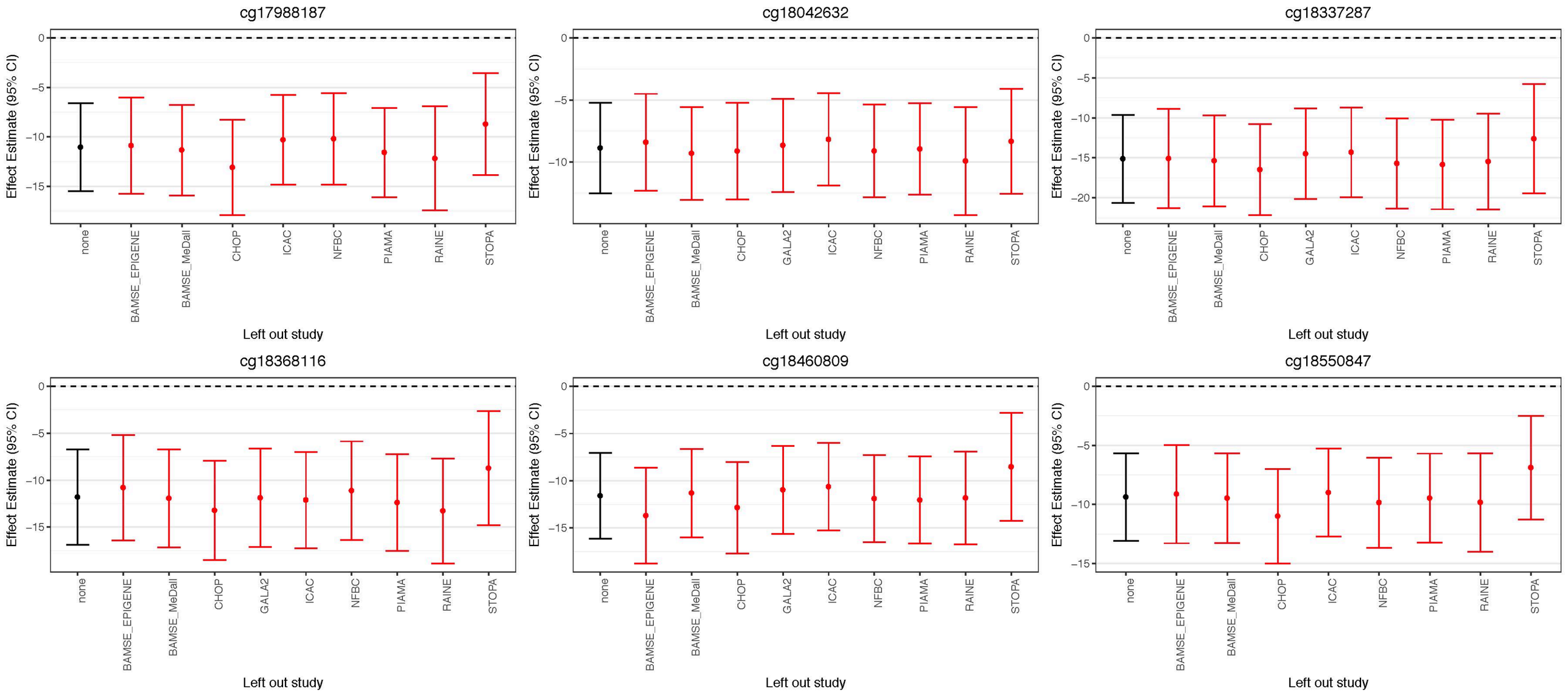
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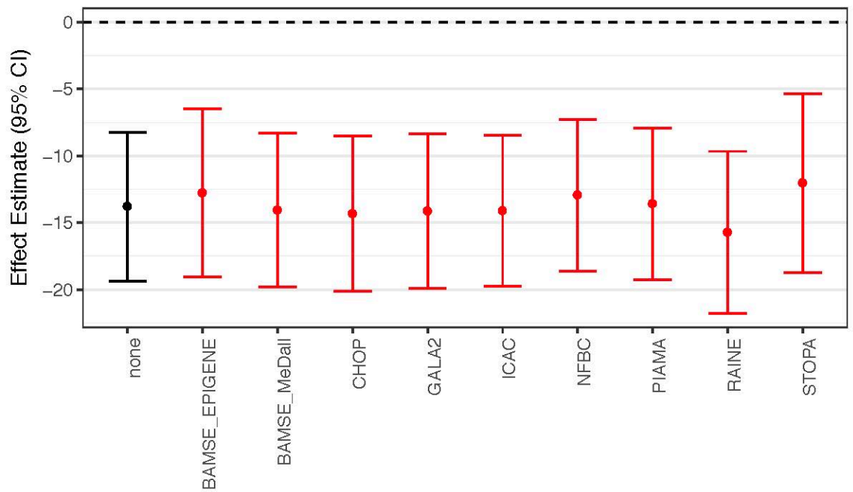

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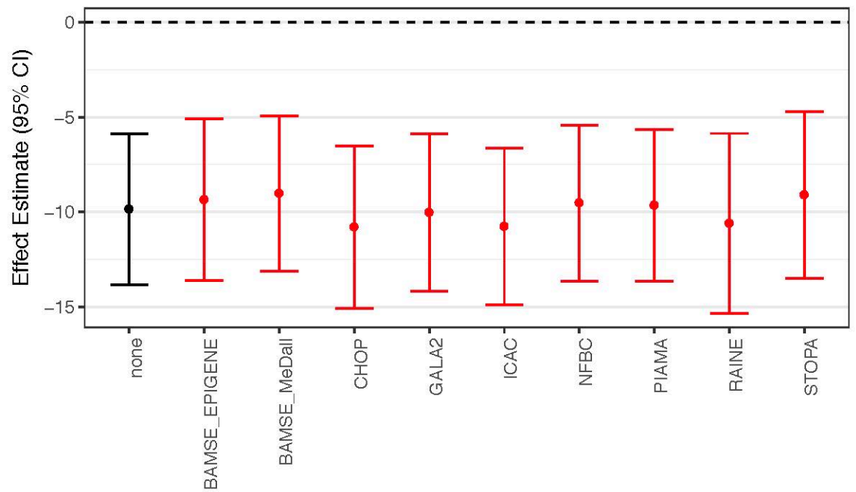

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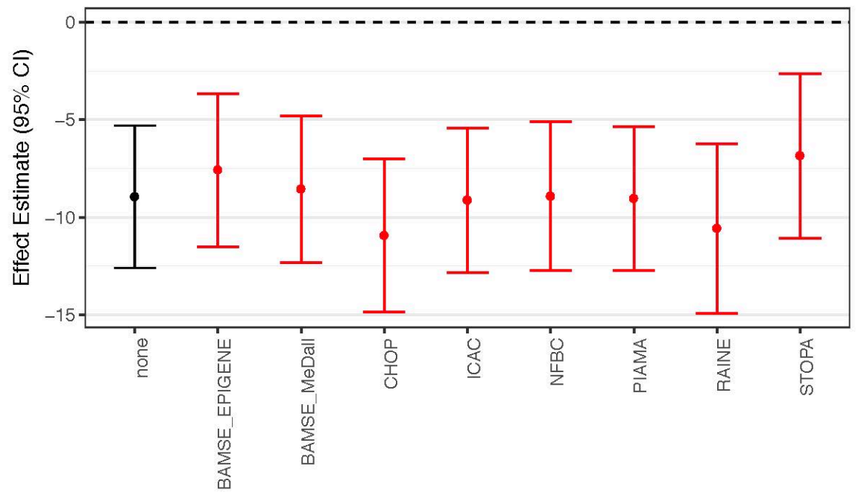

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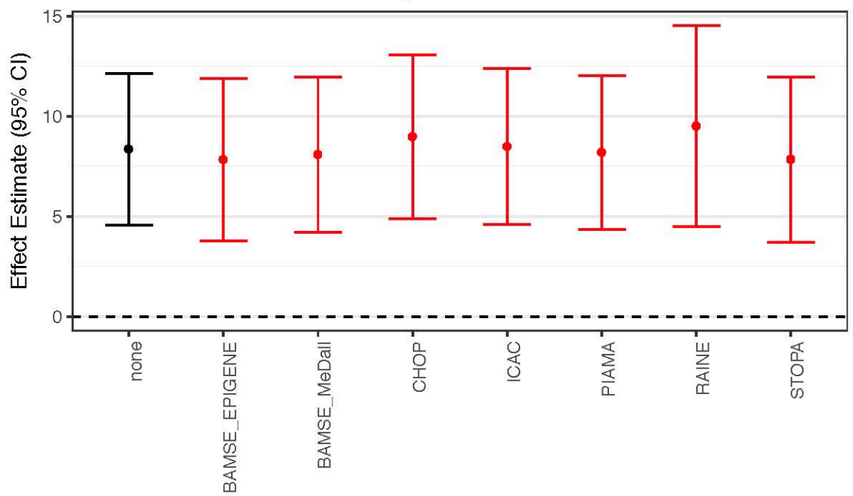

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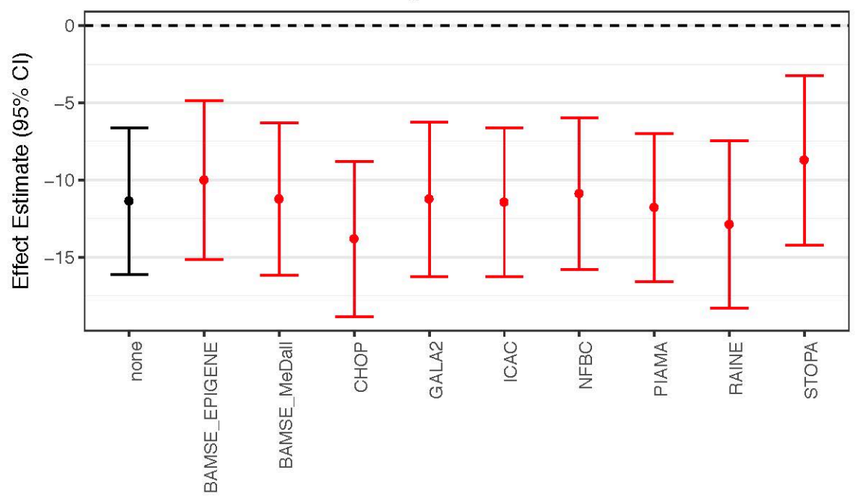

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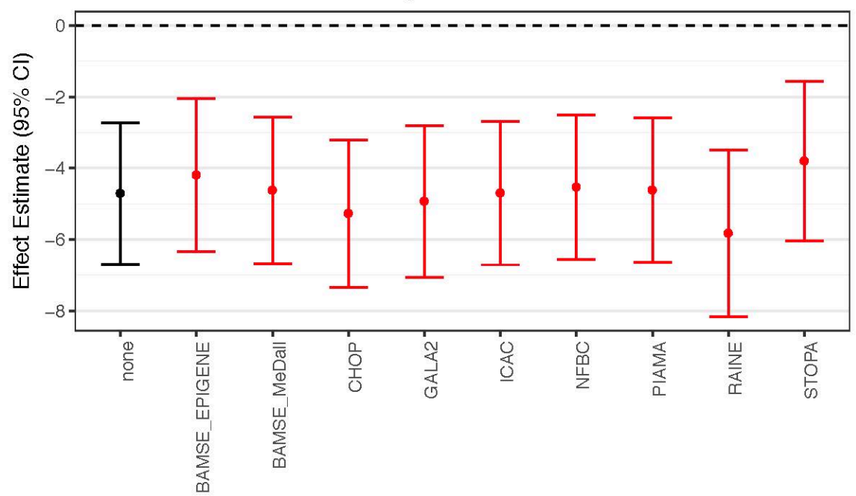

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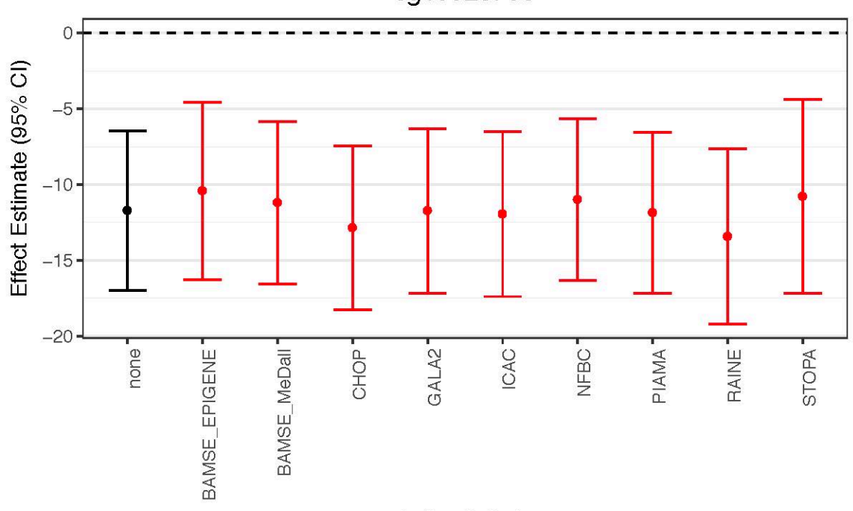

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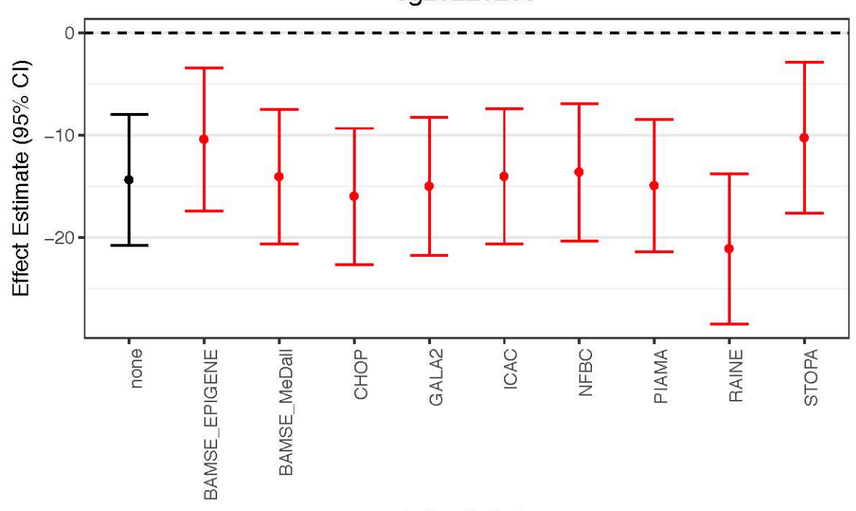

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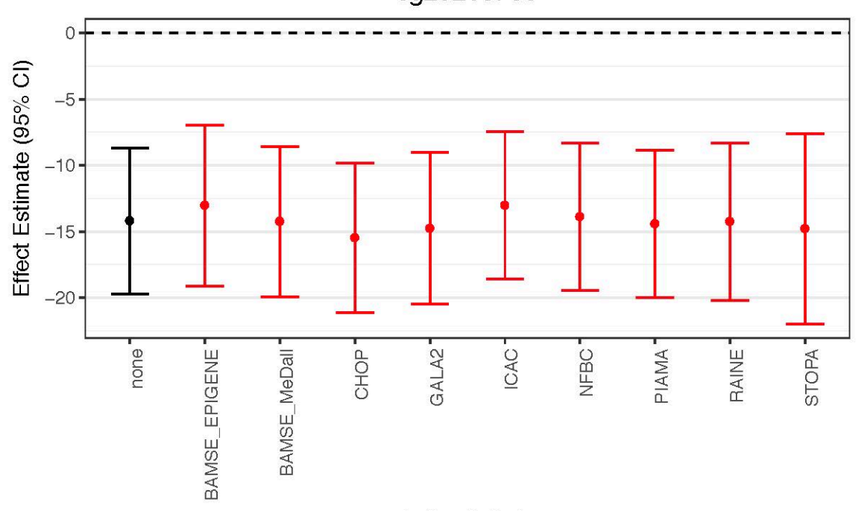

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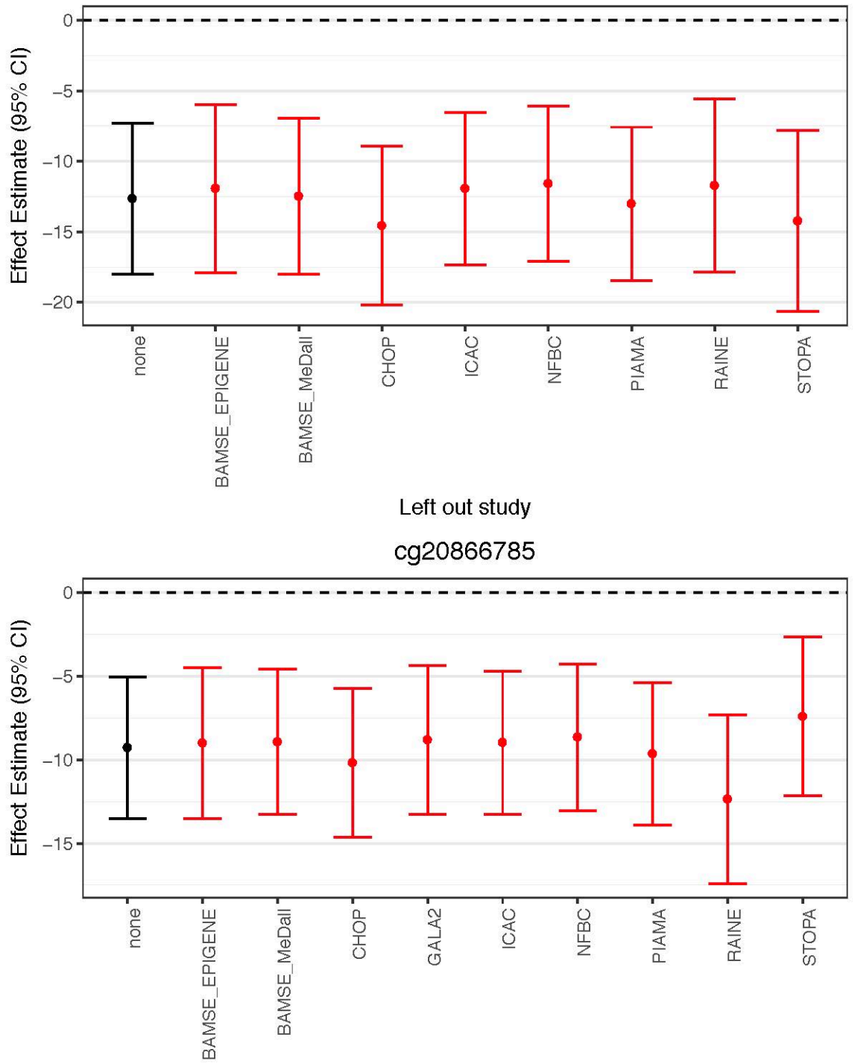

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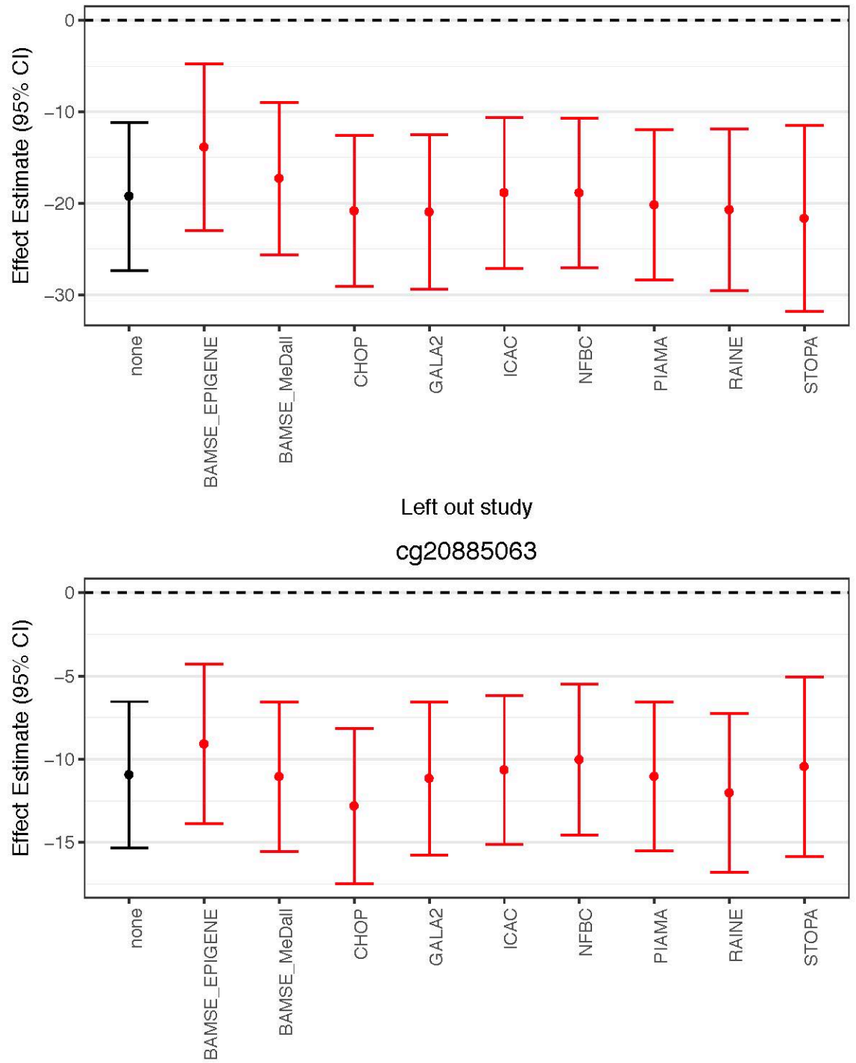

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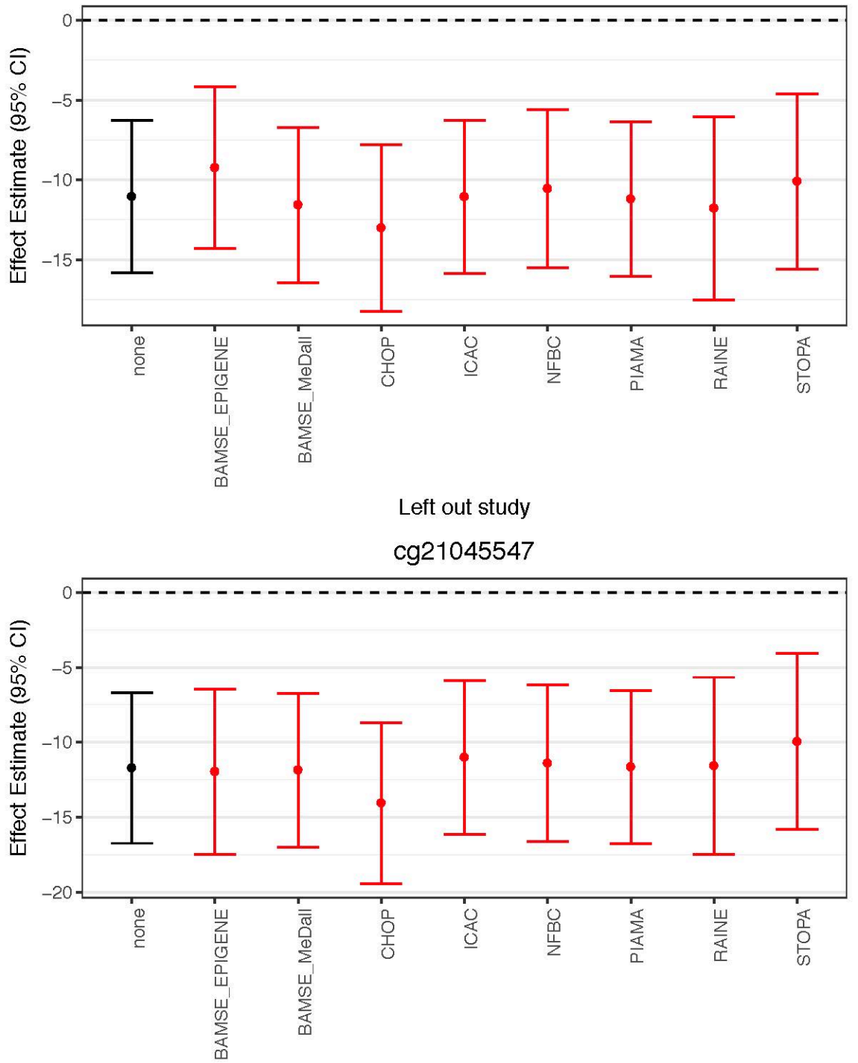

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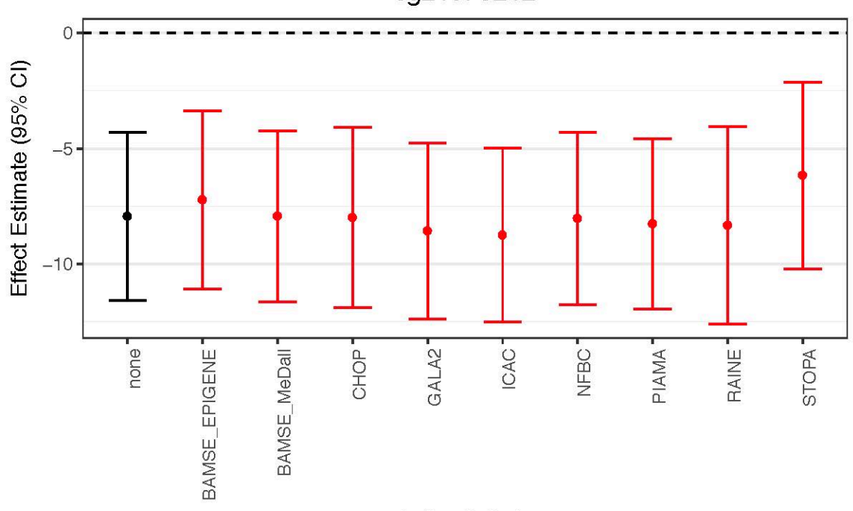

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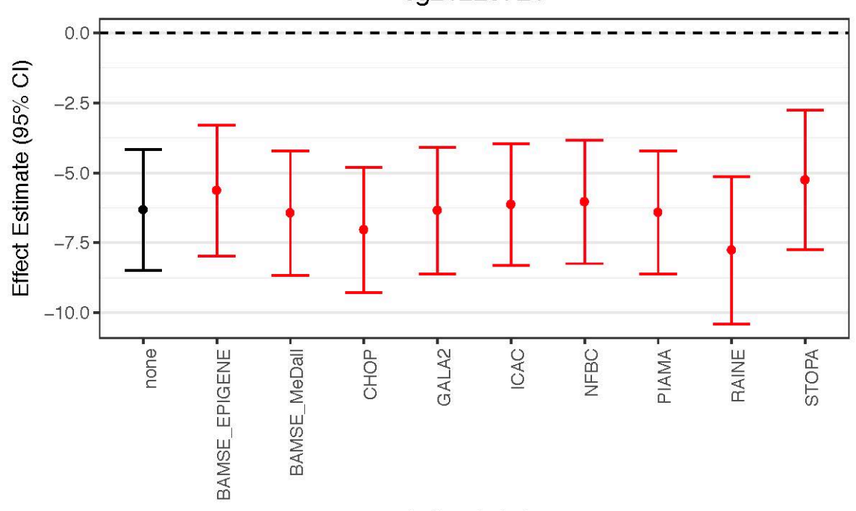

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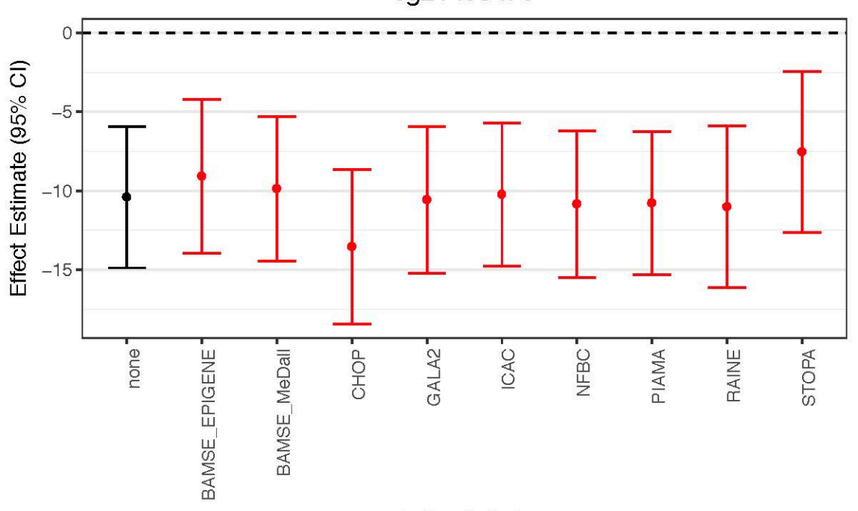

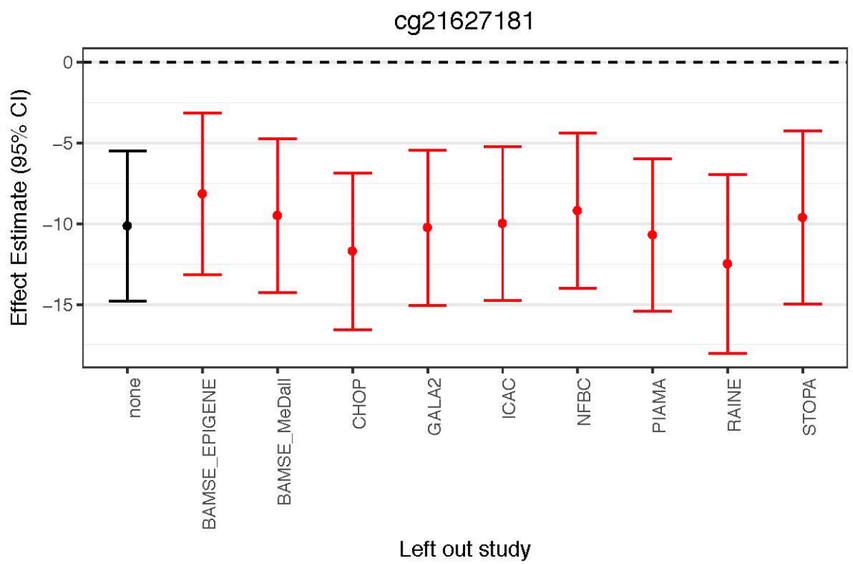
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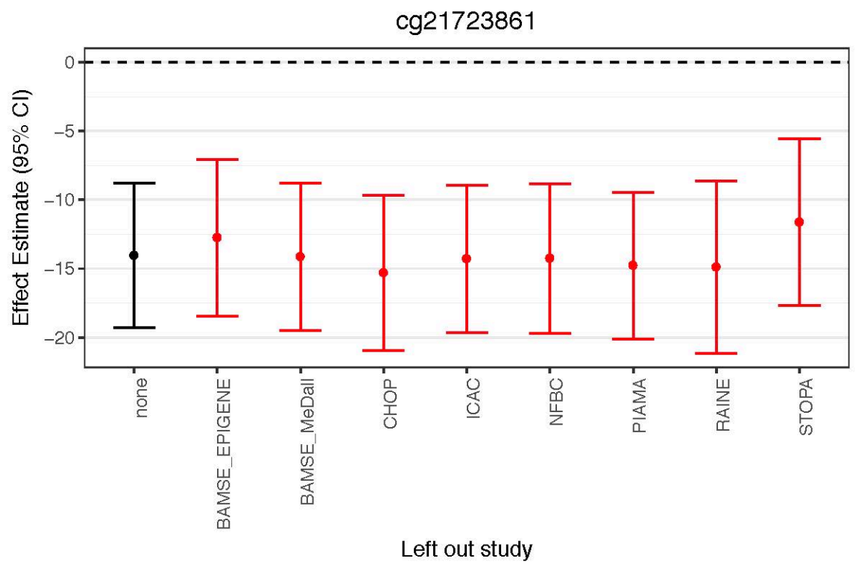
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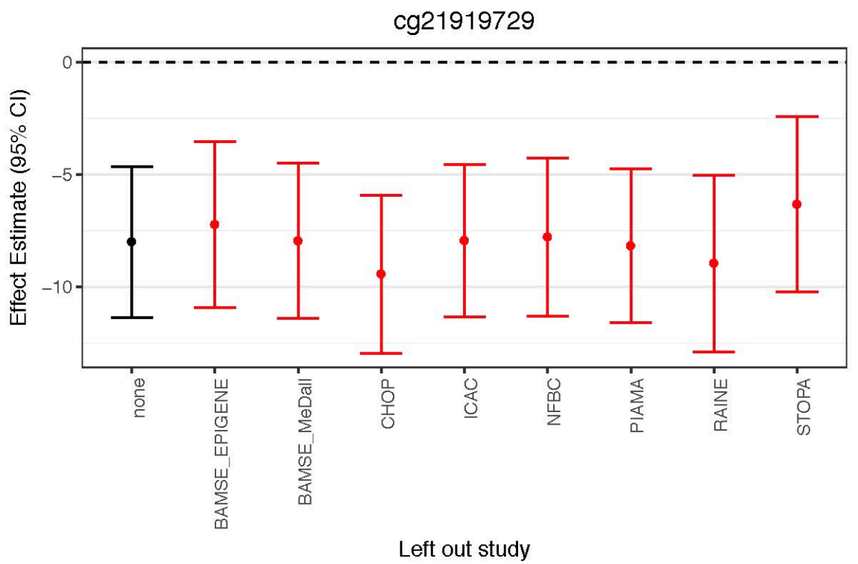
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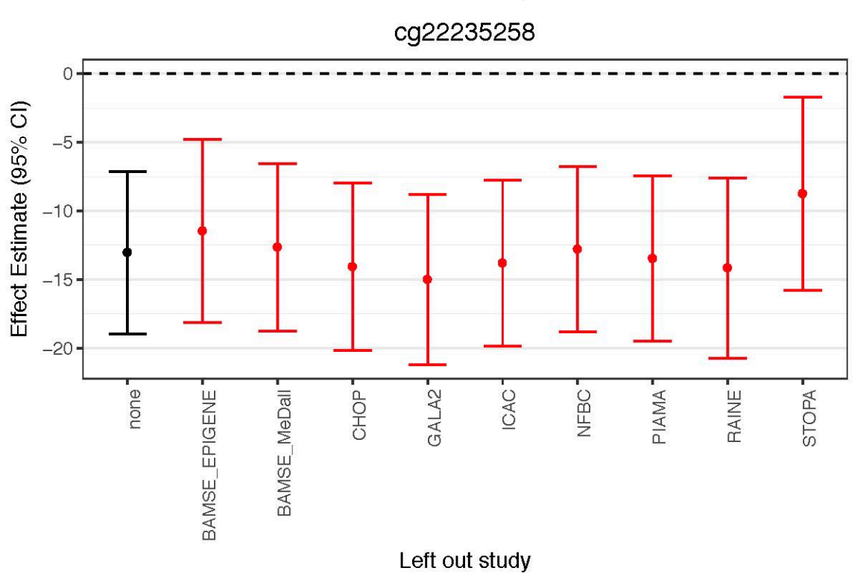
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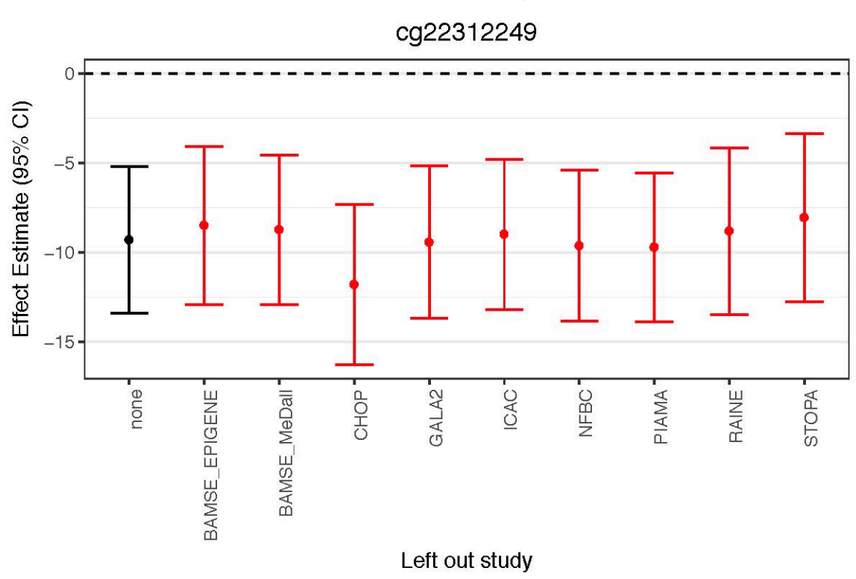
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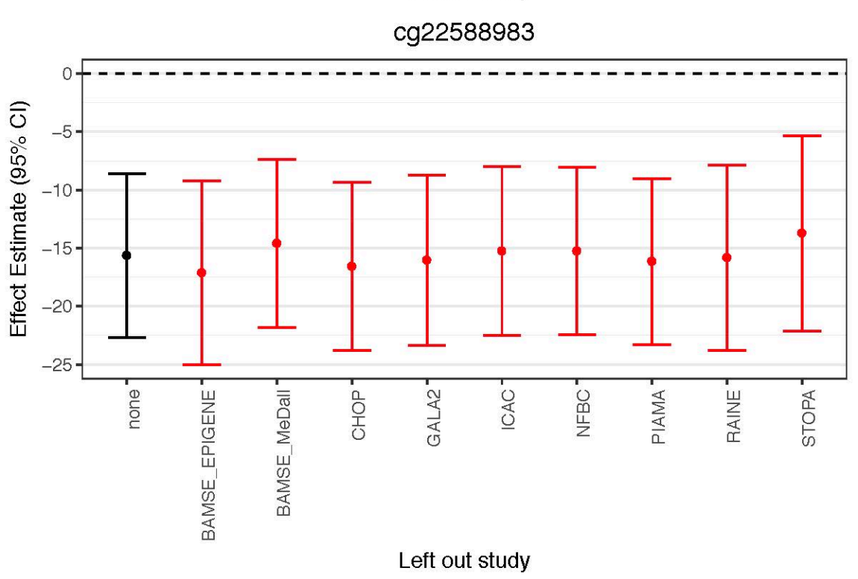
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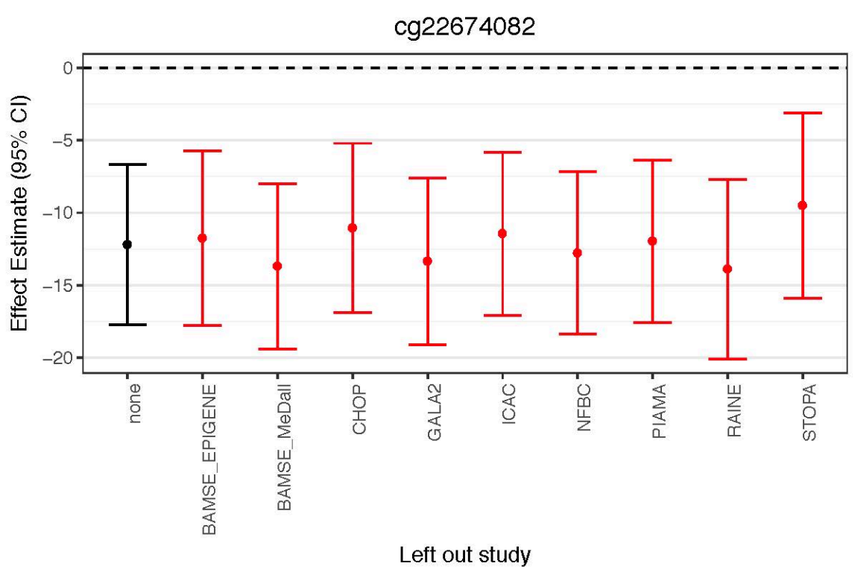
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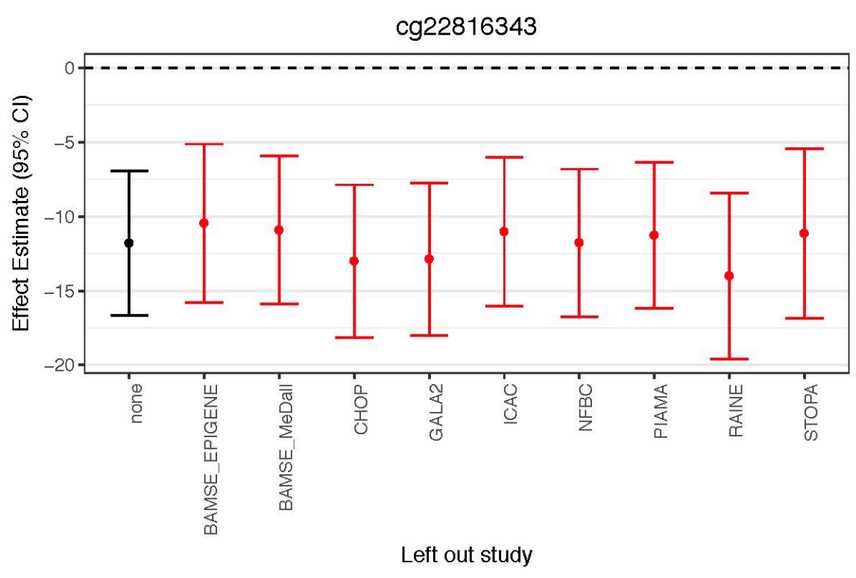
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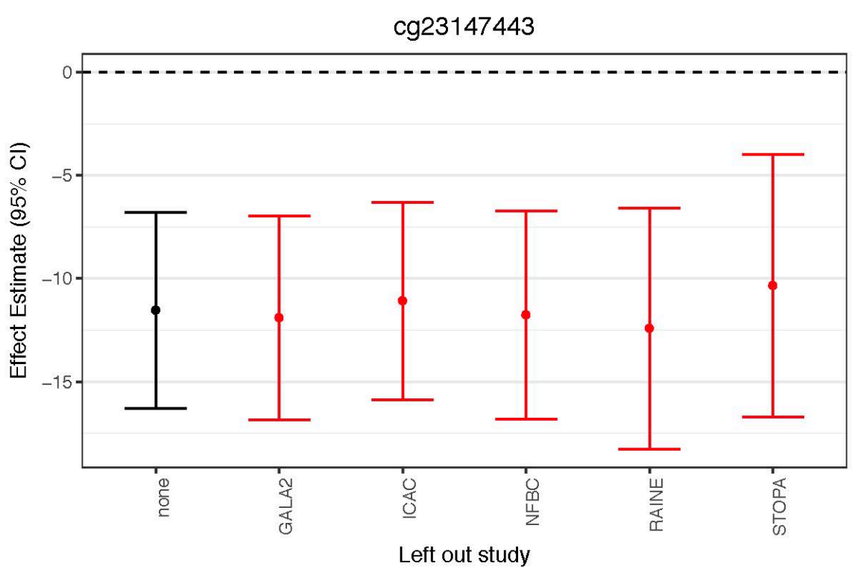
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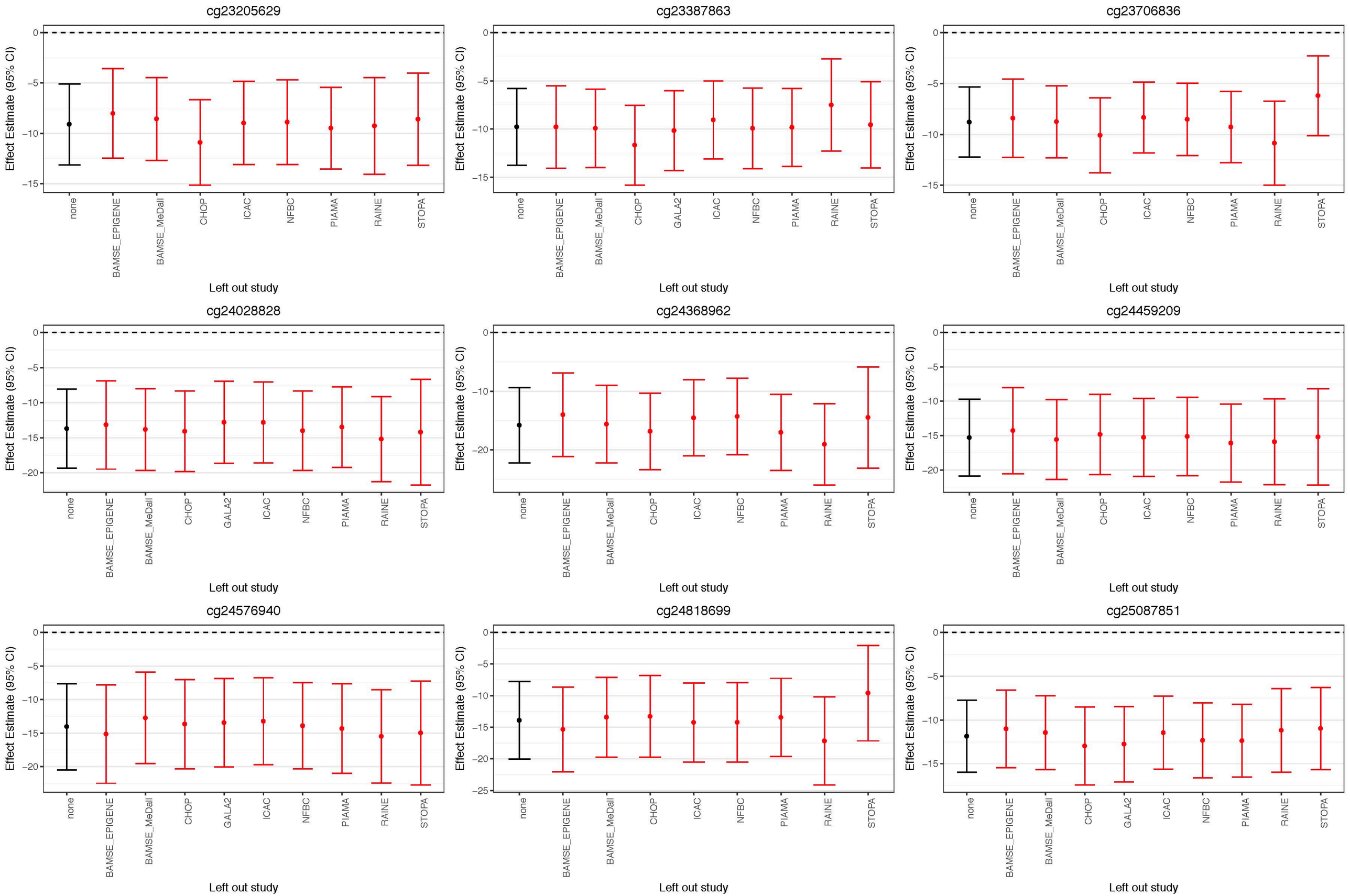
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Effect Estimate (95% CI)
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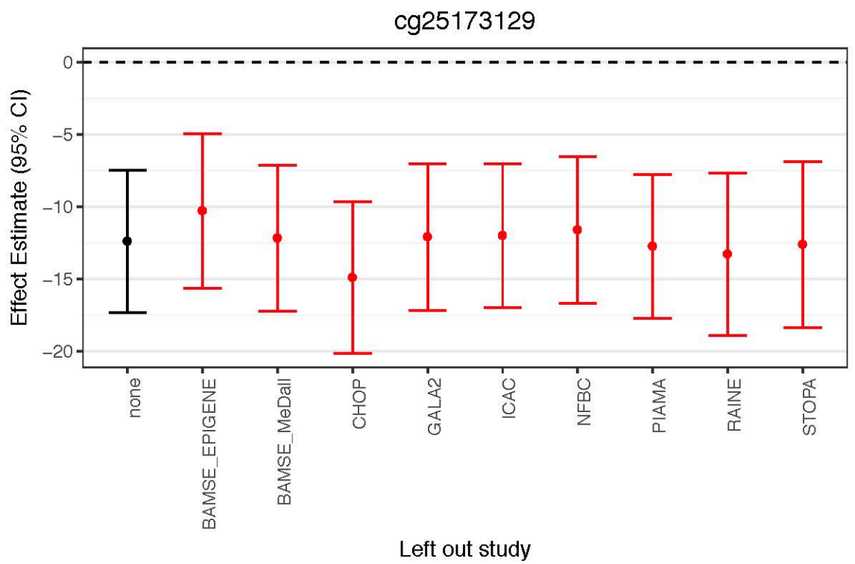
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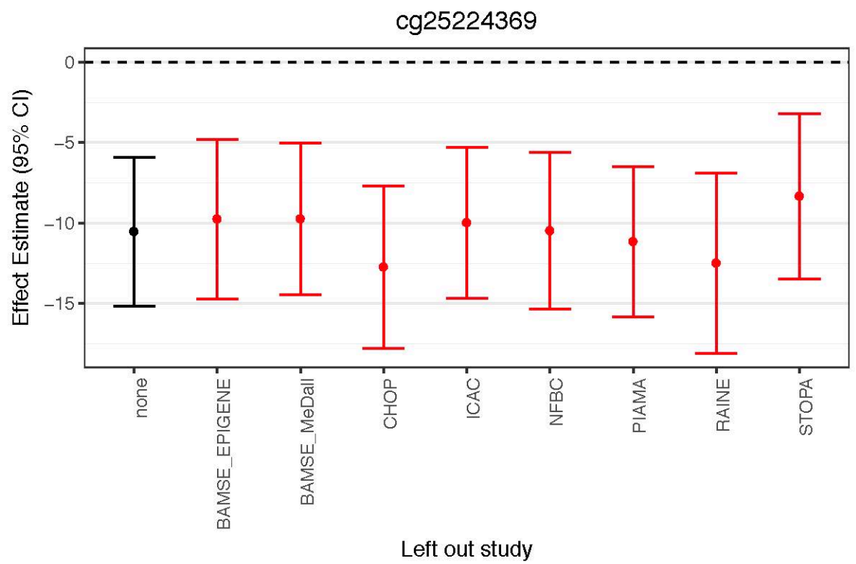
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RAINE
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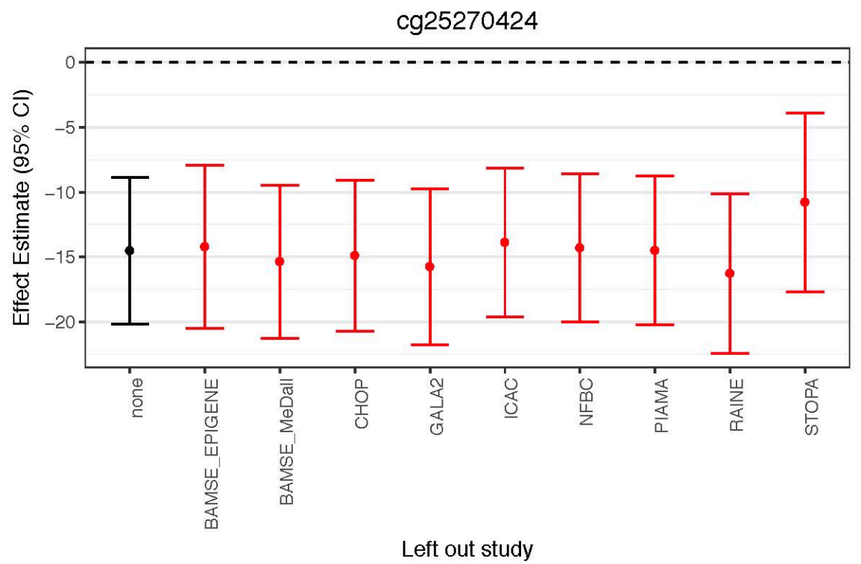
Left out study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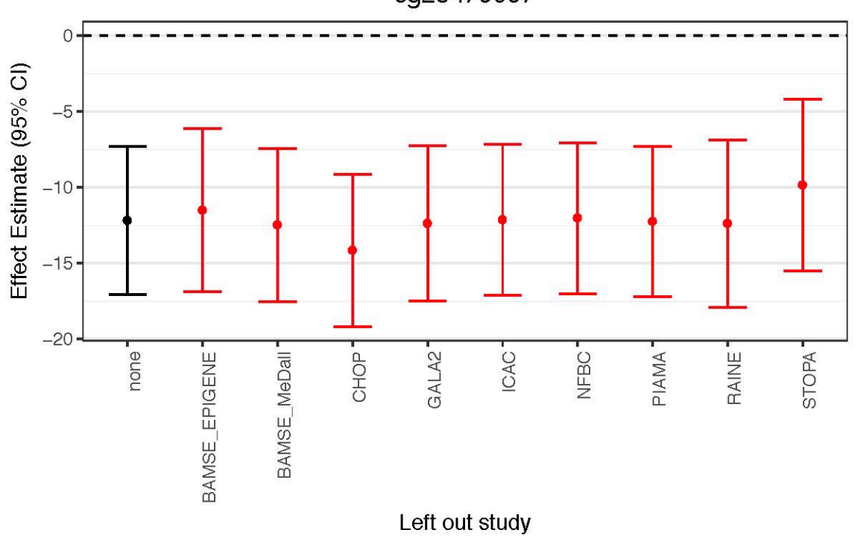
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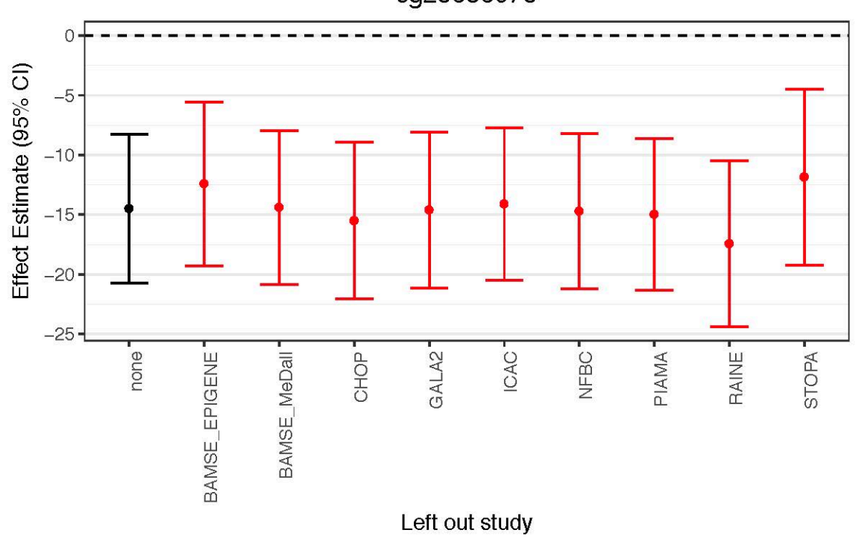
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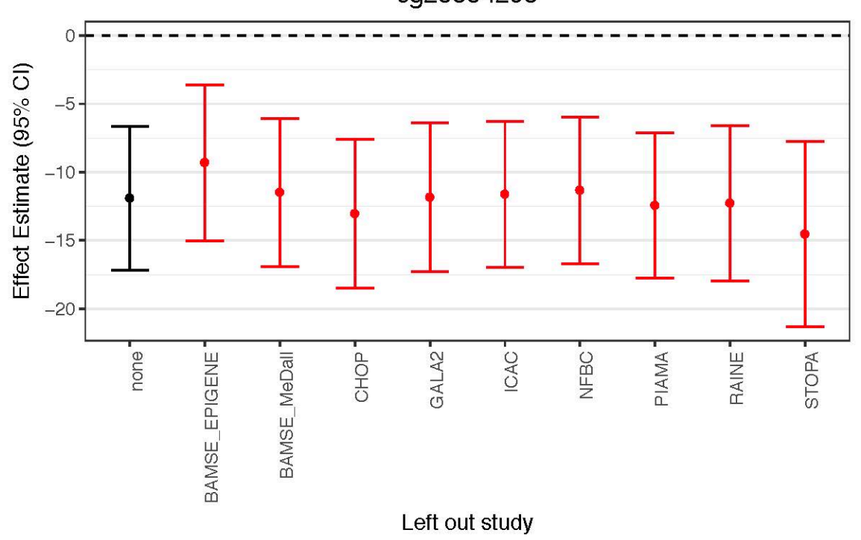
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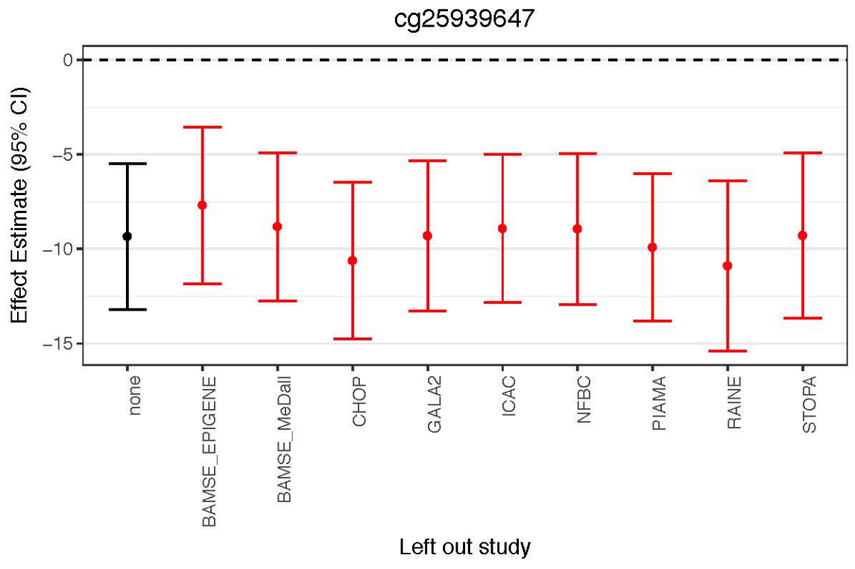
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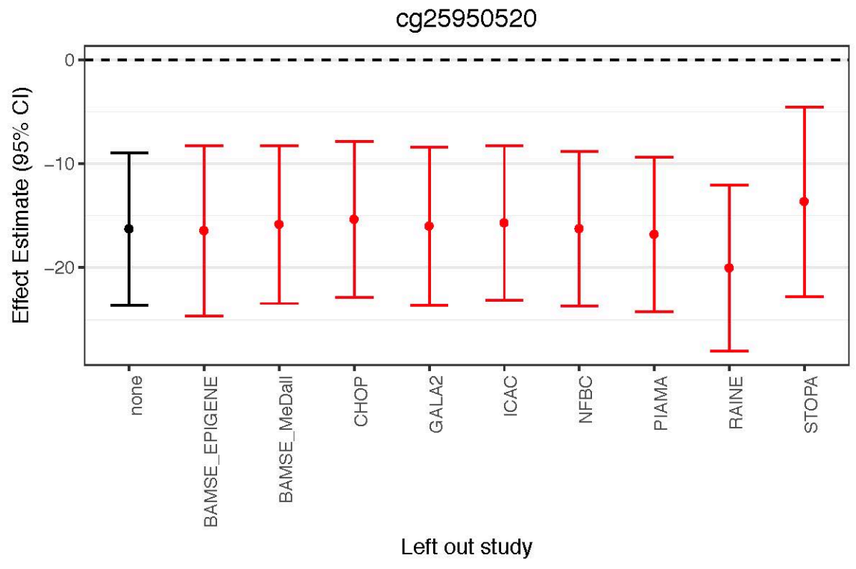
Left out study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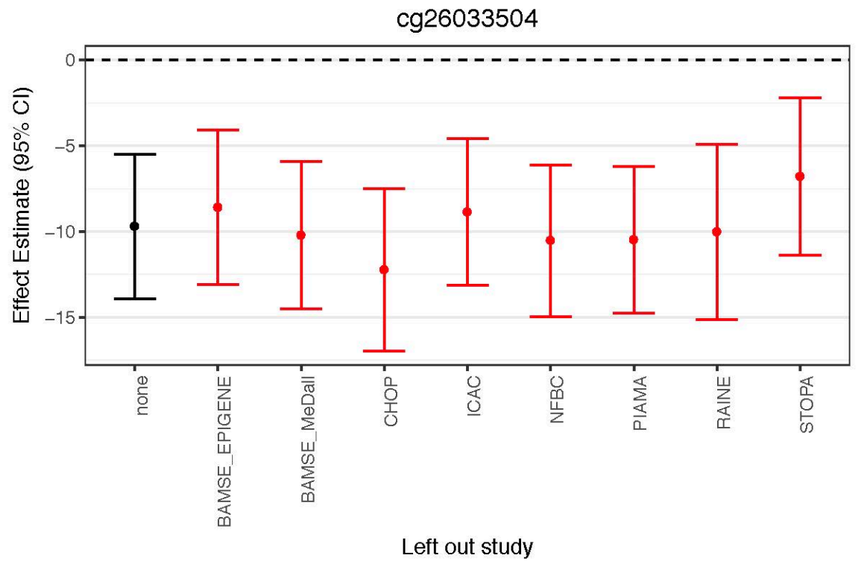
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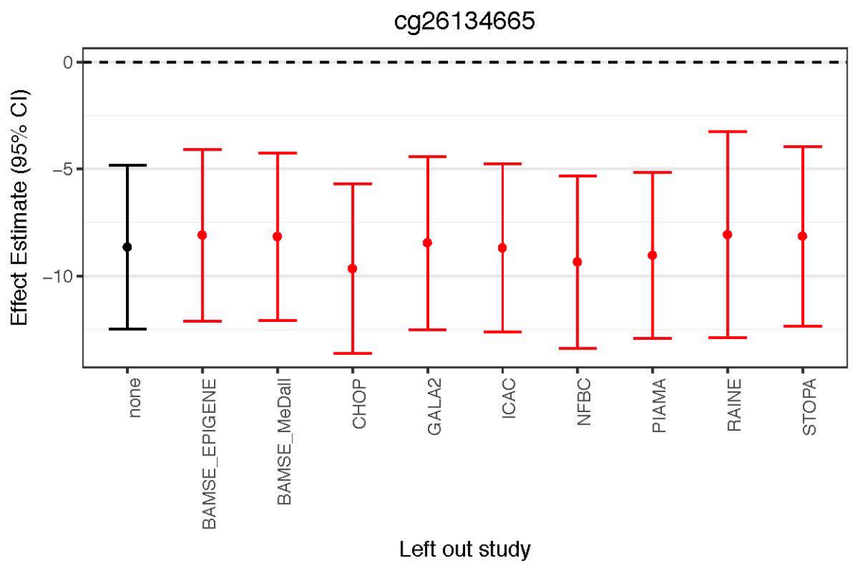
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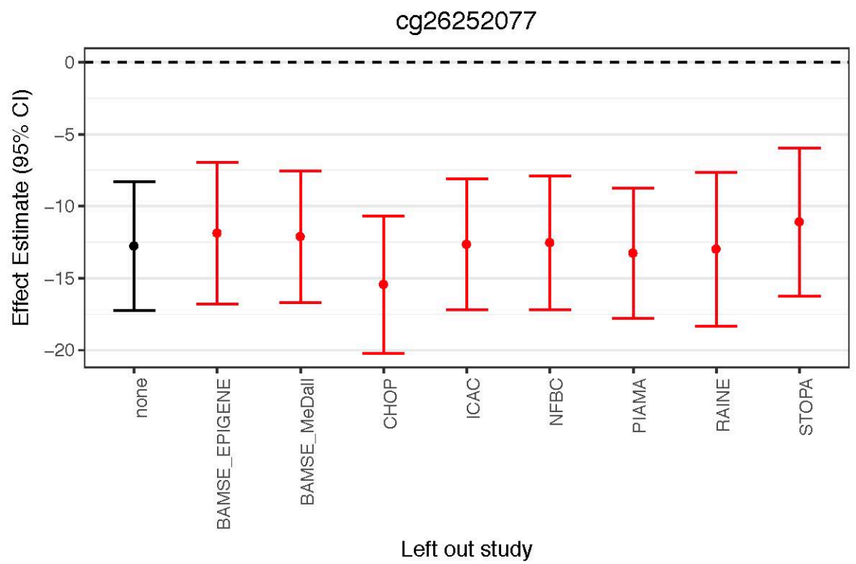
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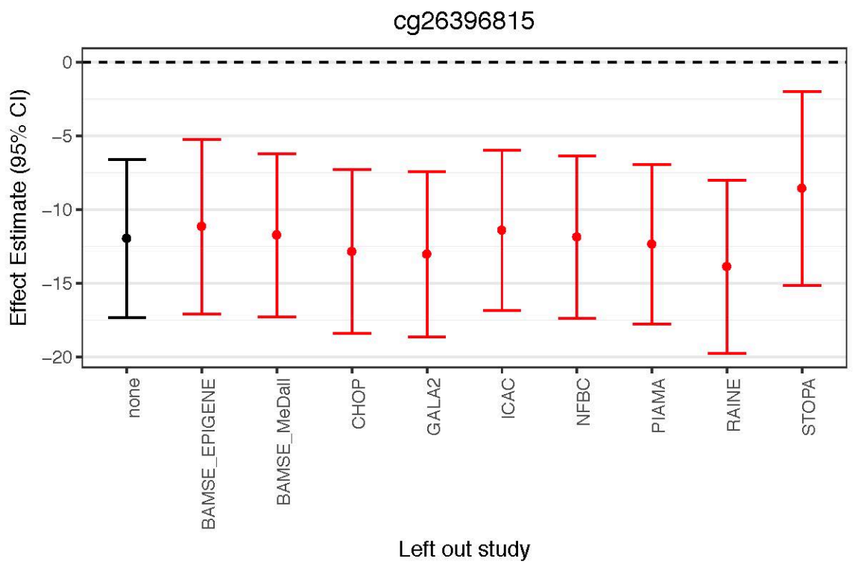
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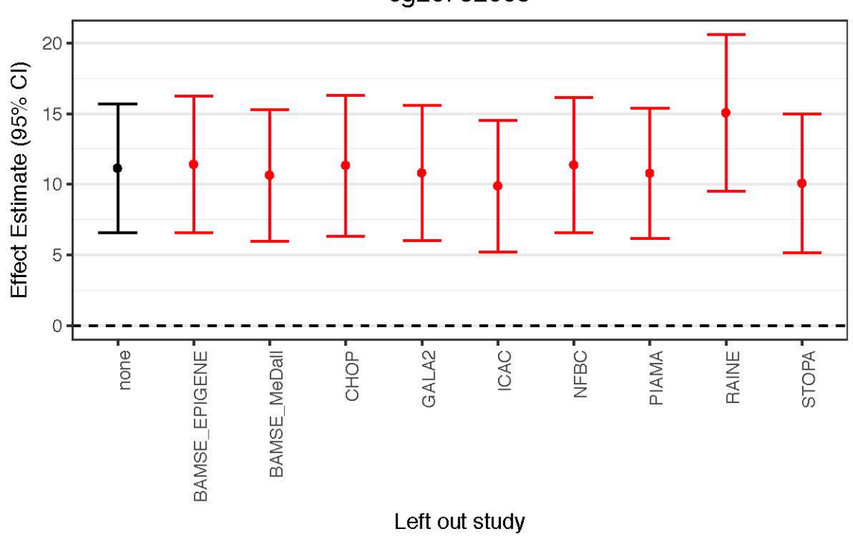
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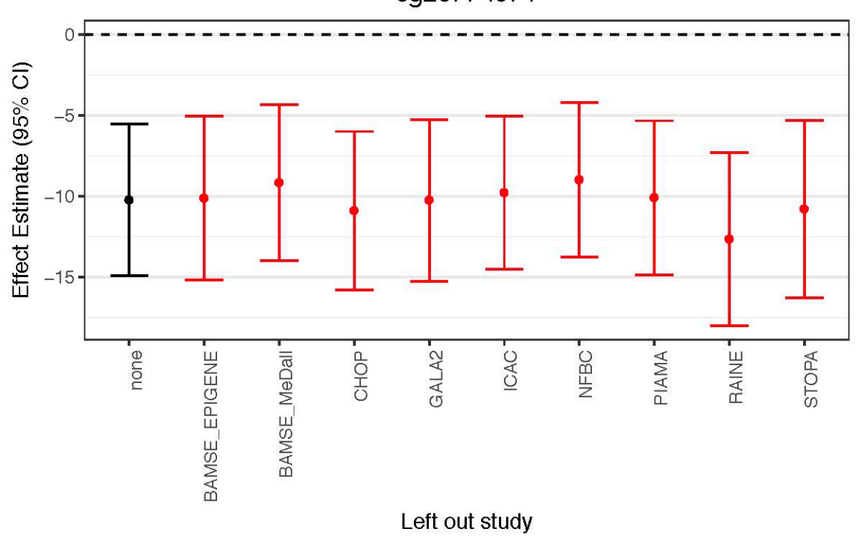
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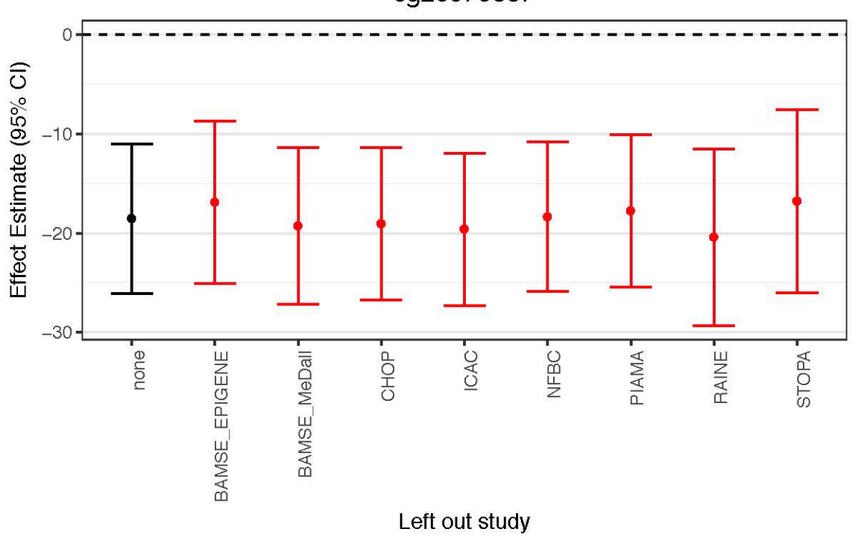
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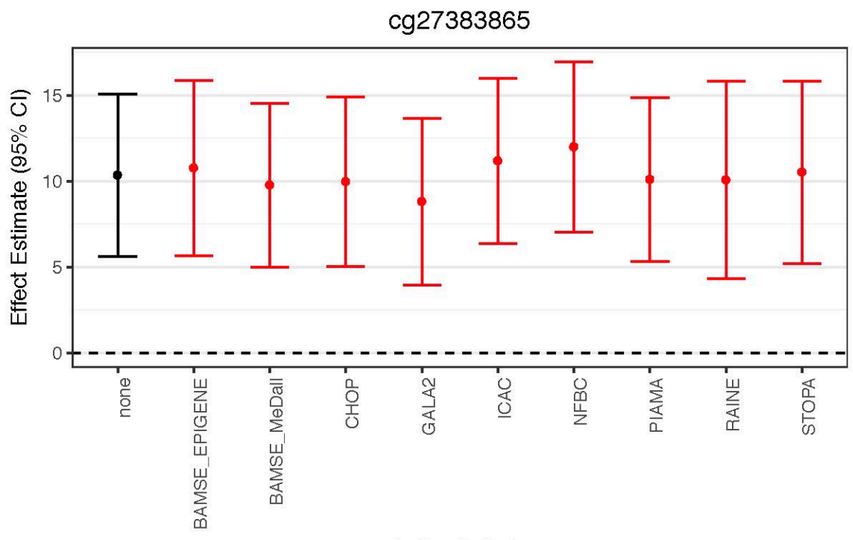
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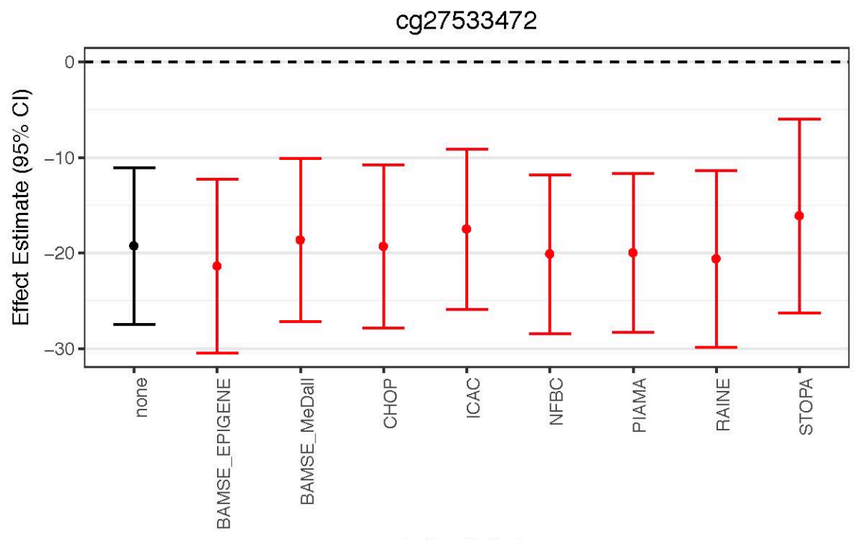
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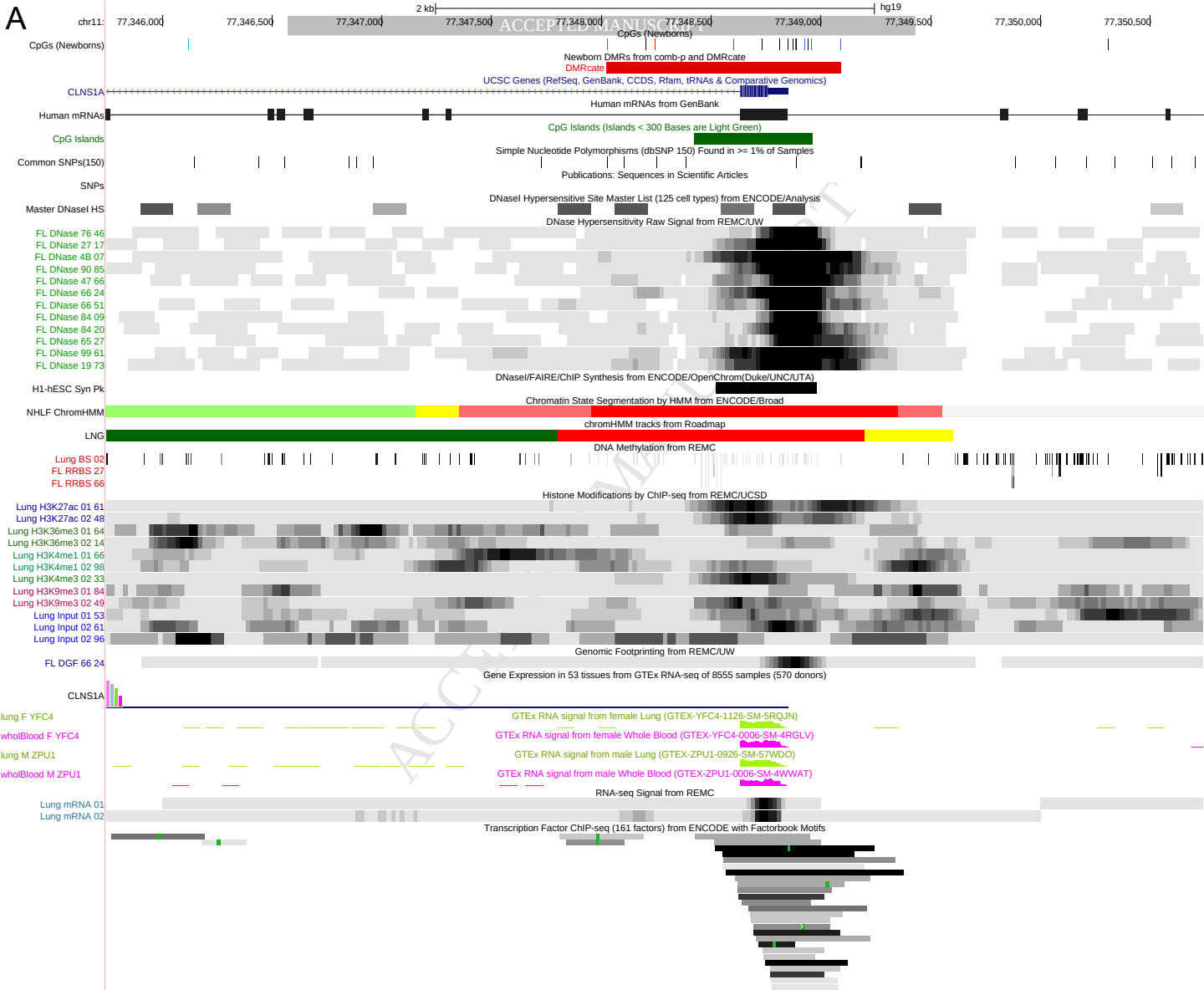
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ACCEPTED MANUSCRIPT
CpGs (Newborns)
CpGs (Newborns)
Newborn DMRs from comb-p and DMRcate
DMRcate
UCSC Genes (RefSeq, GenBank, CCDS, Rfam, tRNAs & Comparative Genomics)
CLNS1A
Human mRNAs from GenBank
Human mRNAs
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CpG Islands
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FL DNase 76 46
FL DNase 27 17
FL DNase 4B 07
FL DNase 90 85
FL DNase 47 66
FL DNase 66 24
FL DNase 66 51
FL DNase 84 09
FL DNase 84 20
FL DNase 65 27
FL DNase 99 61
FL DNase 19 73
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DNA Methylation from REMC
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FL RRBS 27
FL RRBS 66
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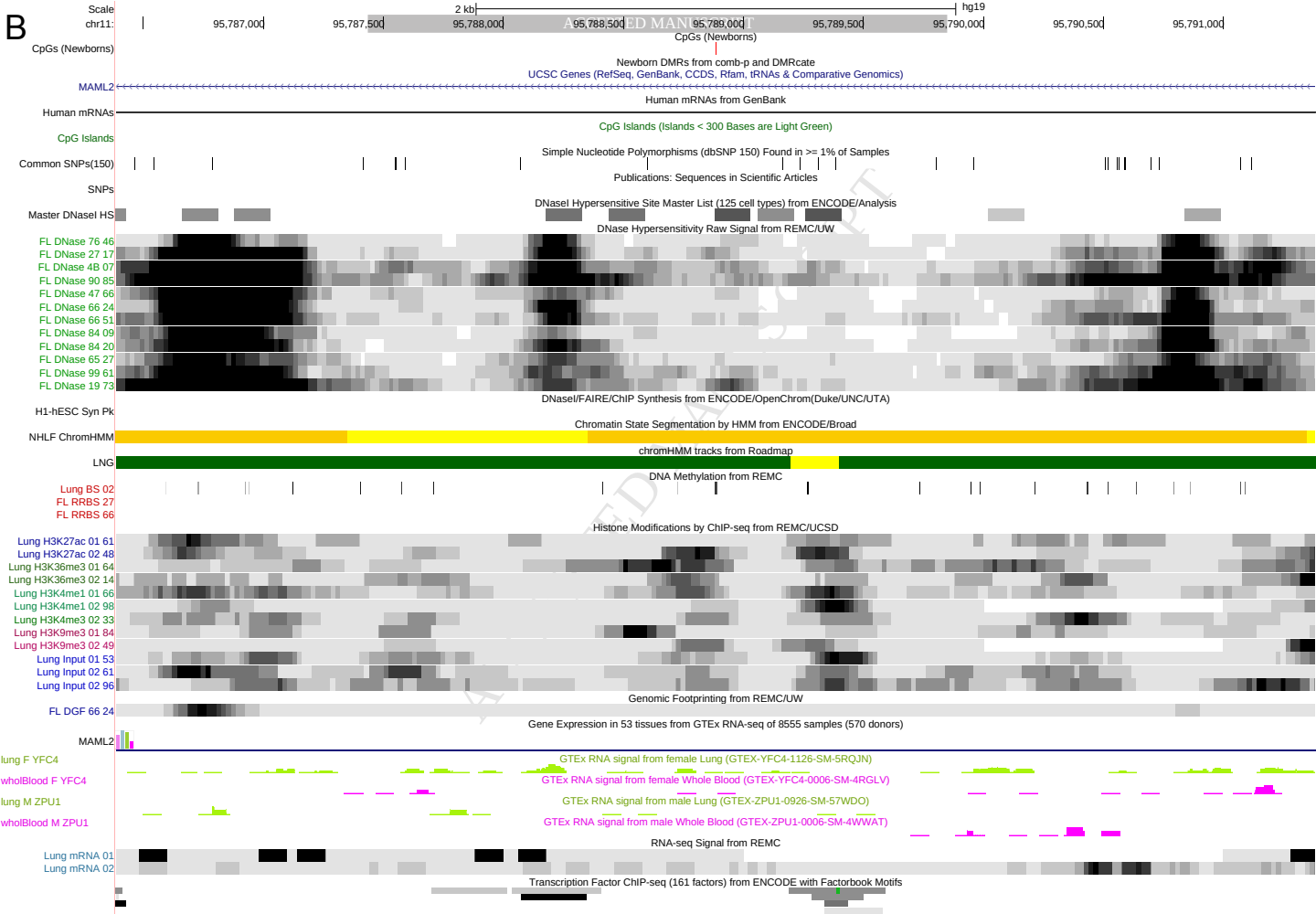
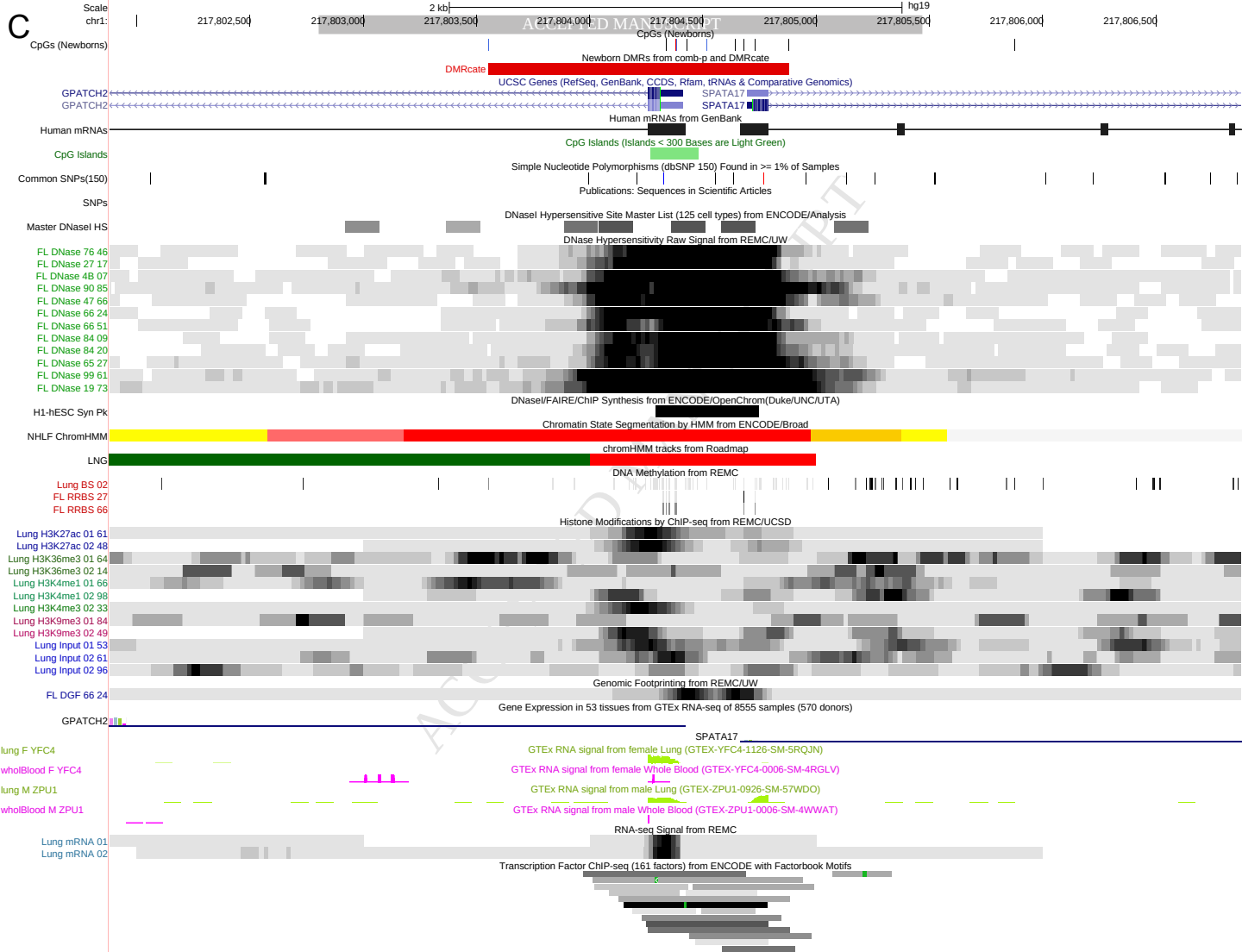
Lung H3K27ac 02 48
Lung H3K36me3 01 64
Lung H3K36me3 02 14
Lung H3K4me1 01 66
Lung H3K4me1 02 98
Lung H3K4me3 02 33
Lung H3K9me3 01 84
Lung H3K9me3 02 49
Lung Input 01 53
Lung Input 02 61
Lung Input 02 96
Genomic Footprinting from REMC/UW
FL DGF 66 24
Gene Expression in 53 tissues from GTEx RNA-seq of 8555 samples (570 donors)
CLNS1A
lung F YFC4
GTEx RNA signal from female Lung (GTEX-YFC4-1126-SM-5RQJN)
wholBlood F YFC4
GTEx RNA signal from female Whole Blood (GTEX-YFC4-0006-SM-4RGLV)
lung M ZPU1
GTEx RNA signal from male Lung (GTEX-ZPU1-0926-SM-57WDO)
wholBlood M ZPU1
GTEx RNA signal from male Whole Blood (GTEX-ZPU1-0006-SM-4WWAT)
RNA-seq Signal from REMC
Lung mRNA 01
Lung mRNA 02
Transcription Factor ChIP-seq (161 factors) from ENCODE with Factorbook Motifs

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ACCEPTED MANUSCRIPT
CpGs (Newborns)
CpGs (Newborns)
Newborn DMRs from comb-p and DMRcate
DMRcate
UCSC Genes (RefSeq, GenBank, CCDS, Rfam, tRNAs & Comparative Genomics)
GPATCH2
SPATA17
GPATCH2
SPATA17
Human mRNAs from GenBank
Human mRNAs
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CpG Islands
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FL DNase 76 46
FL DNase 27 17
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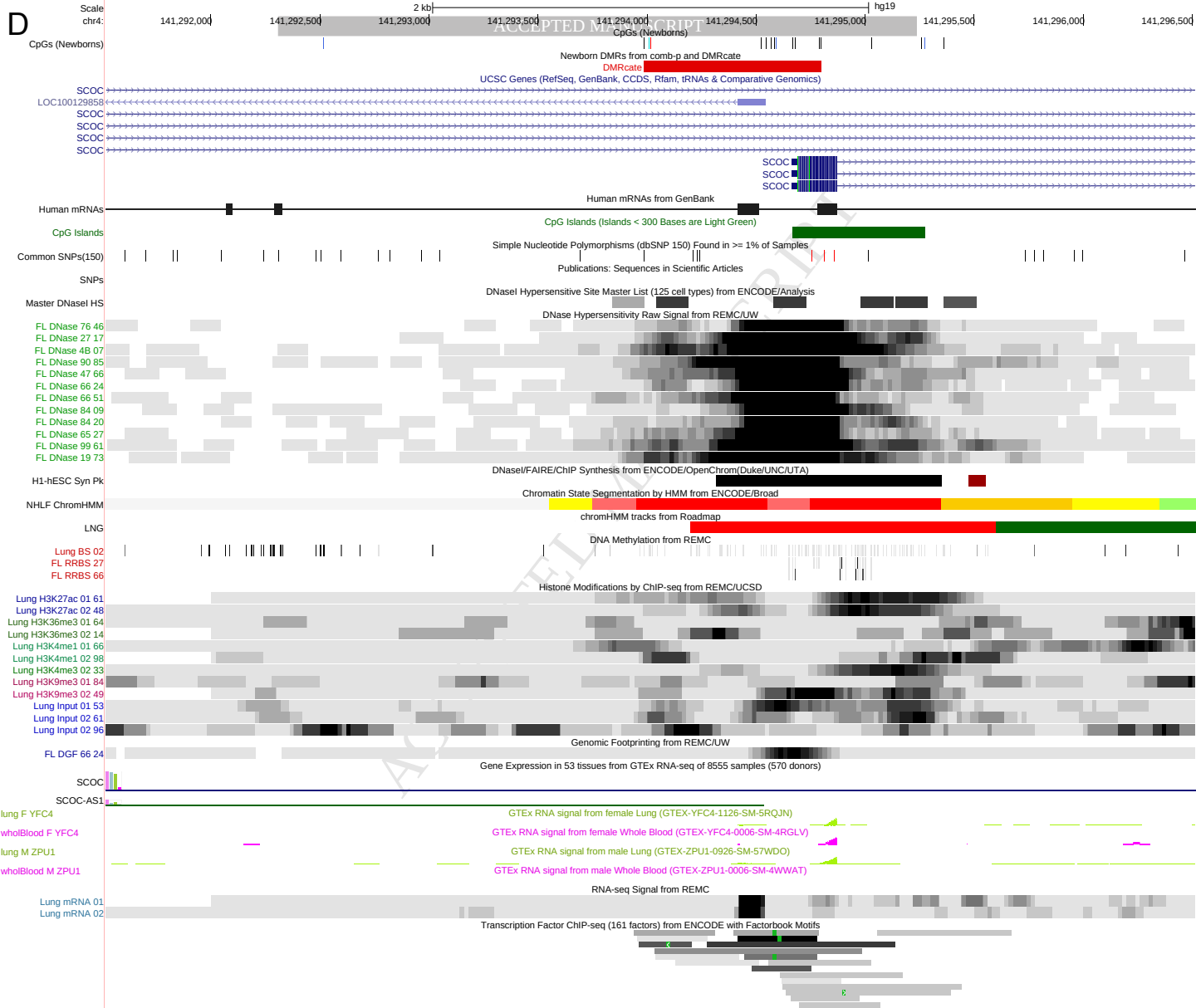
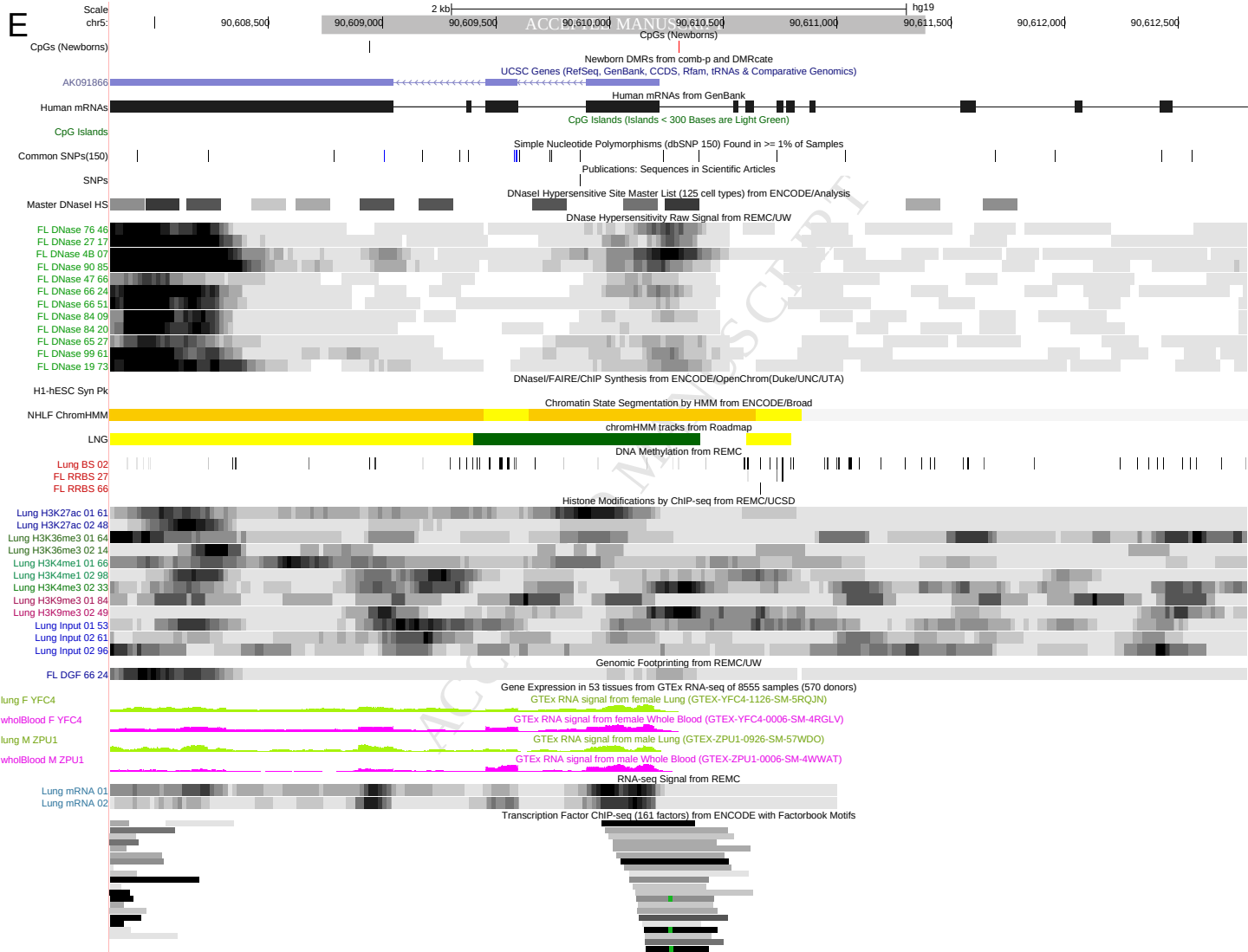
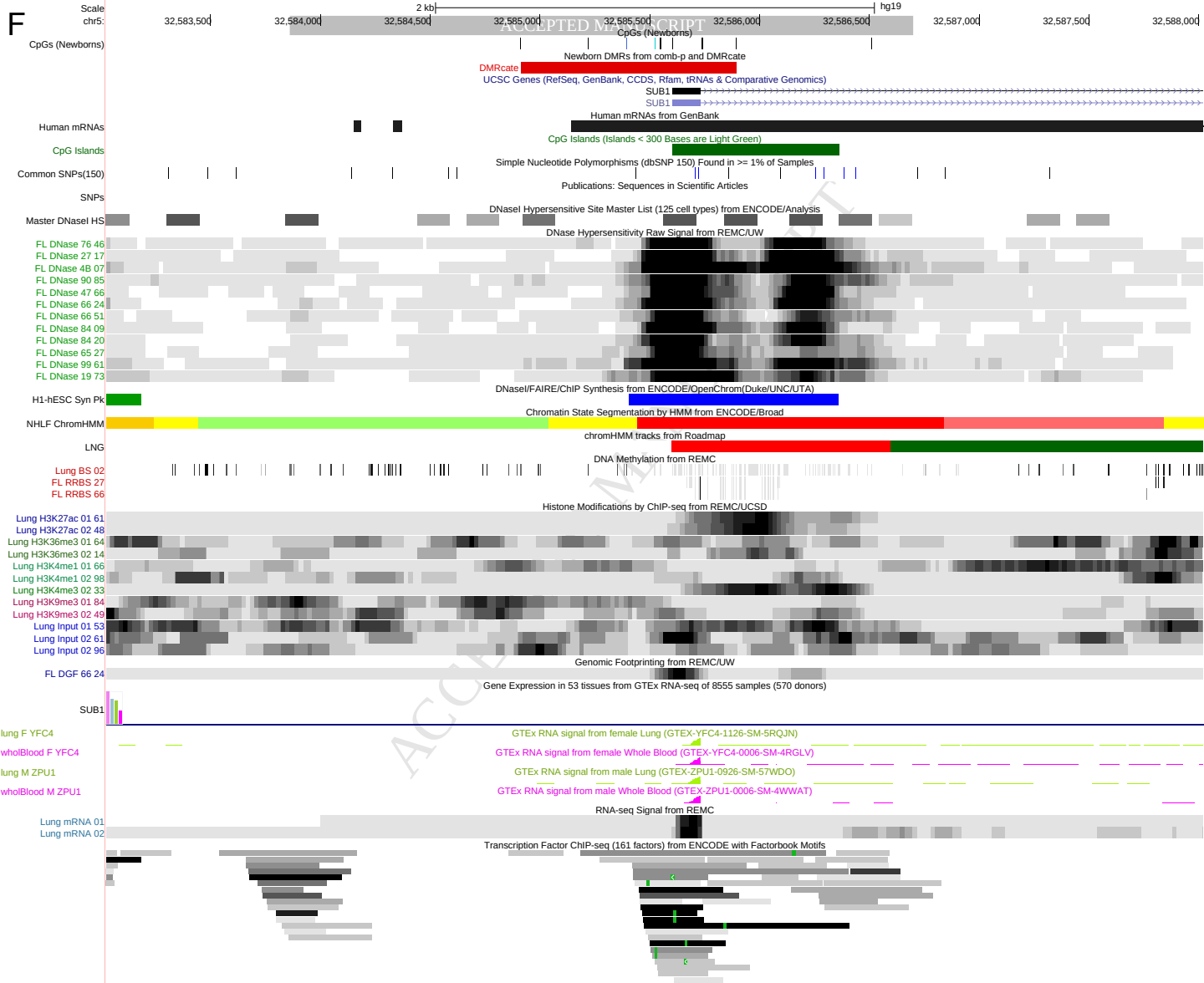
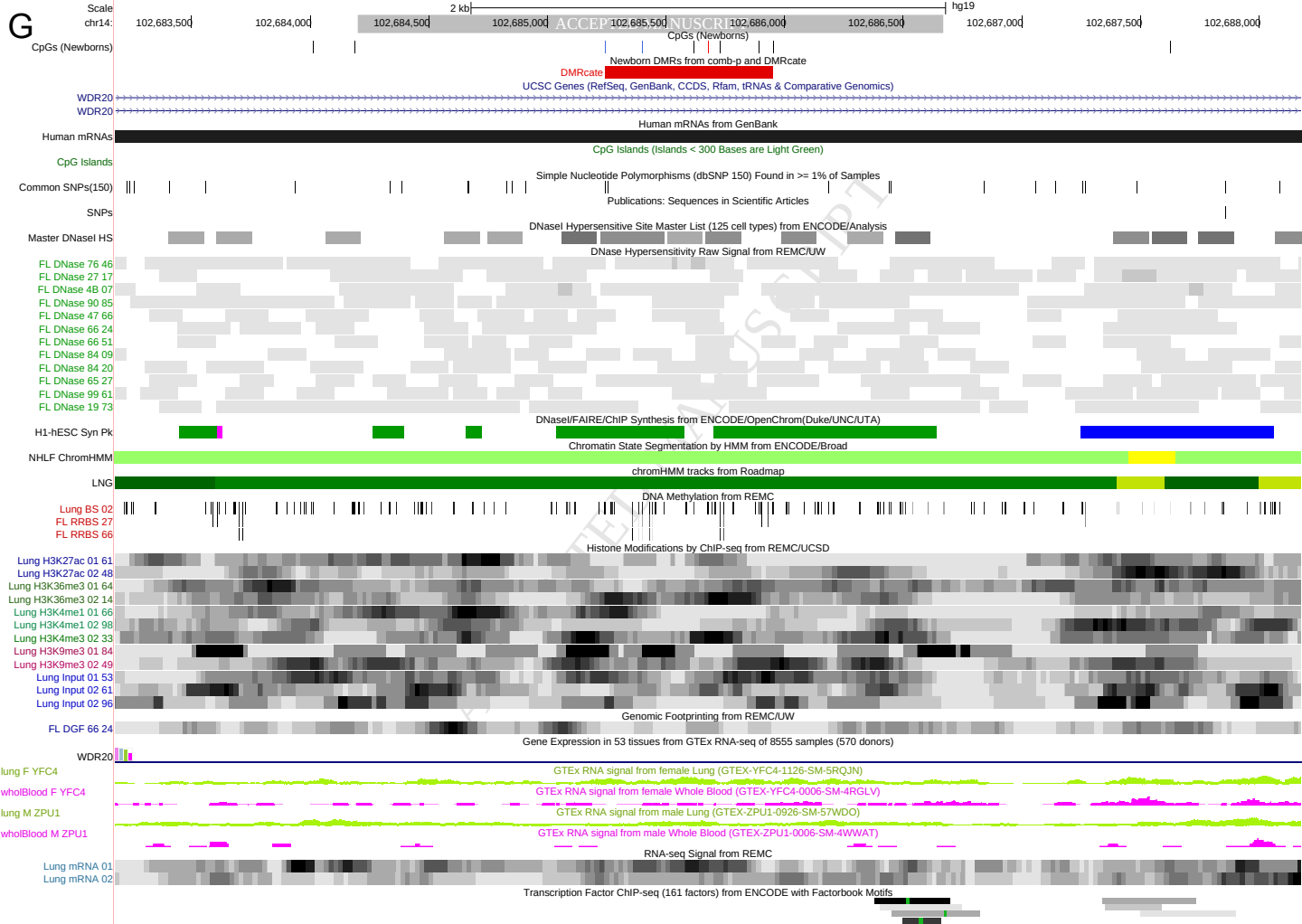
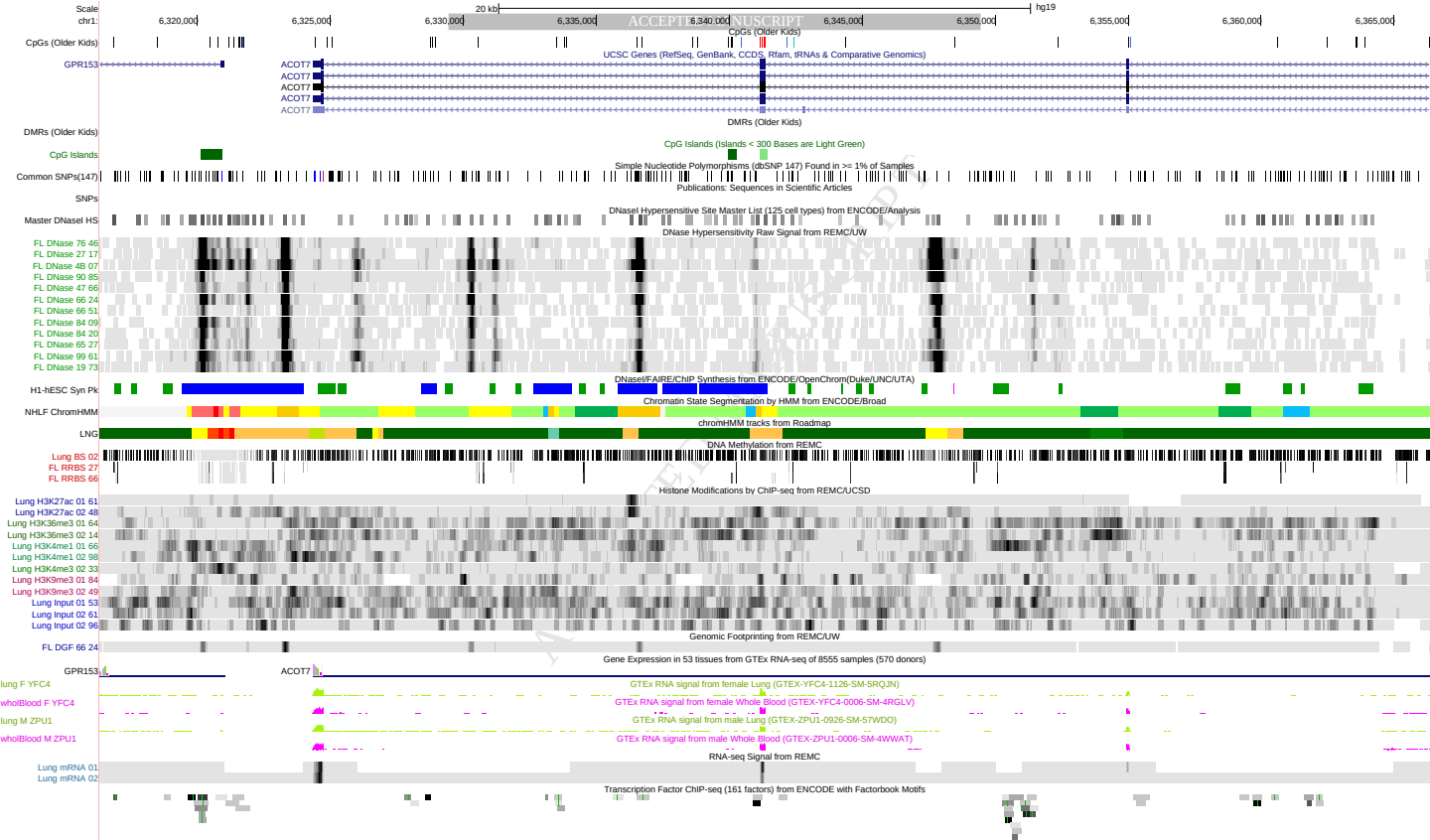
FL DNase 90 85
FL DNase 47 66
FL DNase 66 24
FL DNase 66 51
FL DNase 84 09
FL DNase 84 20
FL DNase 65 27
FL DNase 99 61
FL DNase 19 73
DNaseI/FAIRE/ChIP Synthesis from ENCODE/OpenChrom(Duke/UNC/UTA)
H1-hESC Syn Pk
Chromatin State Segmentation by HMM from ENCODE/Broad
NHLF ChromHMM
chromHMM tracks from Roadmap
LNG
DNA Methylation from REMC
Lung BS 02
FL RRBS 27
FL RRBS 66
Histone Modifications by ChIP-seq from REMC/UCSD
Lung H3K27ac 01 61
Lung H3K27ac 02 48
Lung H3K36me3 01 64
Lung H3K36me3 02 14
Lung H3K4me1 01 66
Lung H3K4me1 02 98
Lung H3K4me3 02 33
Lung H3K9me3 01 84
Lung H3K9me3 02 49
Lung Input 01 53
Lung Input 02 61
Lung Input 02 96
Genomic Footprinting from REMC/UW
FL DGF 66 24
Gene Expression in 53 tissues from GTEx RNA-seq of 8555 samples (570 donors)
GPATCH2
SPATA17
lung F YFC4
GTEx RNA signal from female Lung (GTEX-YFC4-1126-SM-5RQJN)
wholBlood F YFC4
GTEx RNA signal from female Whole Blood (GTEX-YFC4-0006-SM-4RGLV)
lung M ZPU1
GTEx RNA signal from male Lung (GTEX-ZPU1-0926-SM-57WDO)
wholBlood M ZPU1
GTEx RNA signal from male Whole Blood (GTEX-ZPU1-0006-SM-4WWAT)
RNA-seq Signal from REMC
Lung mRNA 01
Lung mRNA 02
Transcription Factor ChIP-seq (161 factors) from ENCODE with Factorbook Motifs

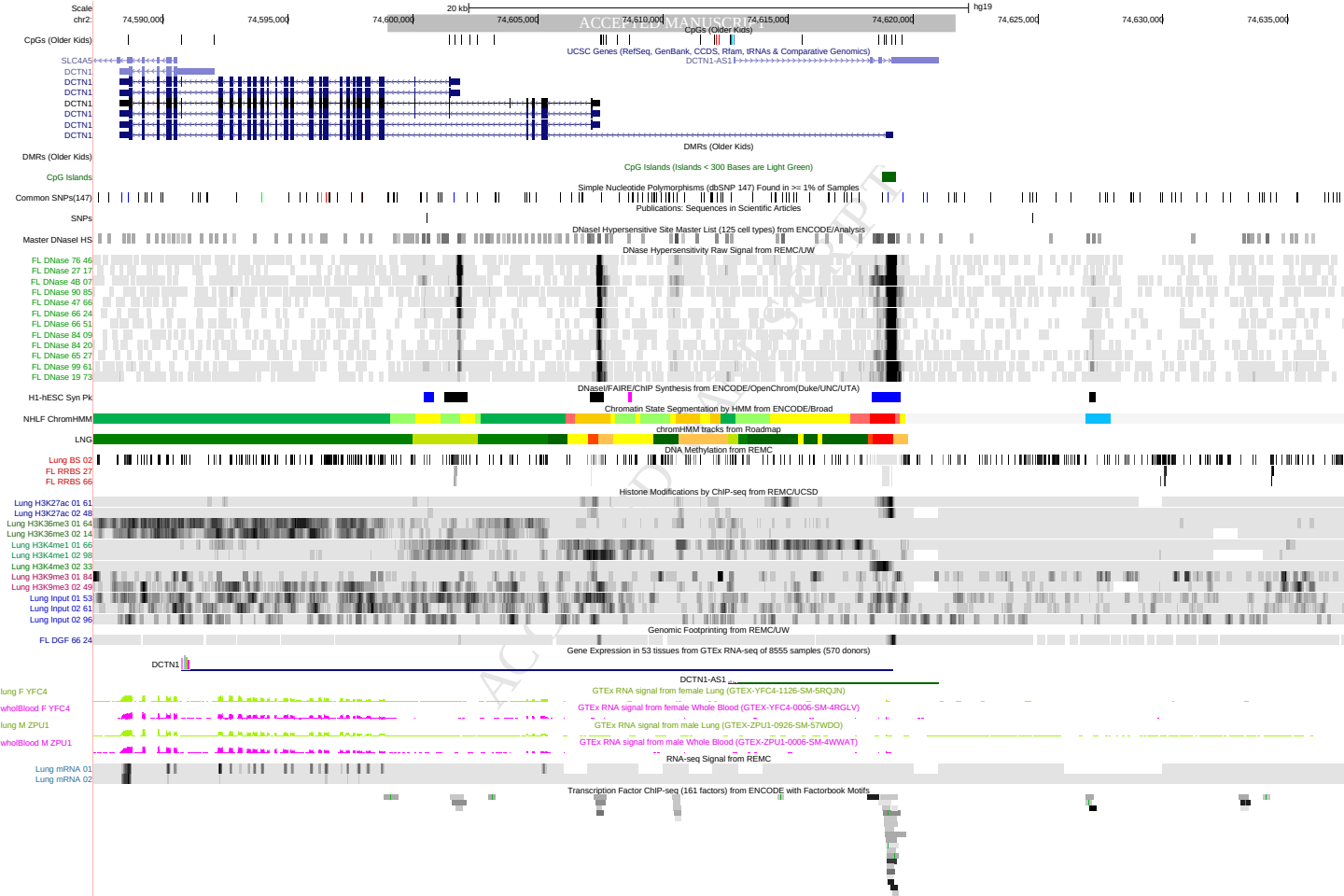


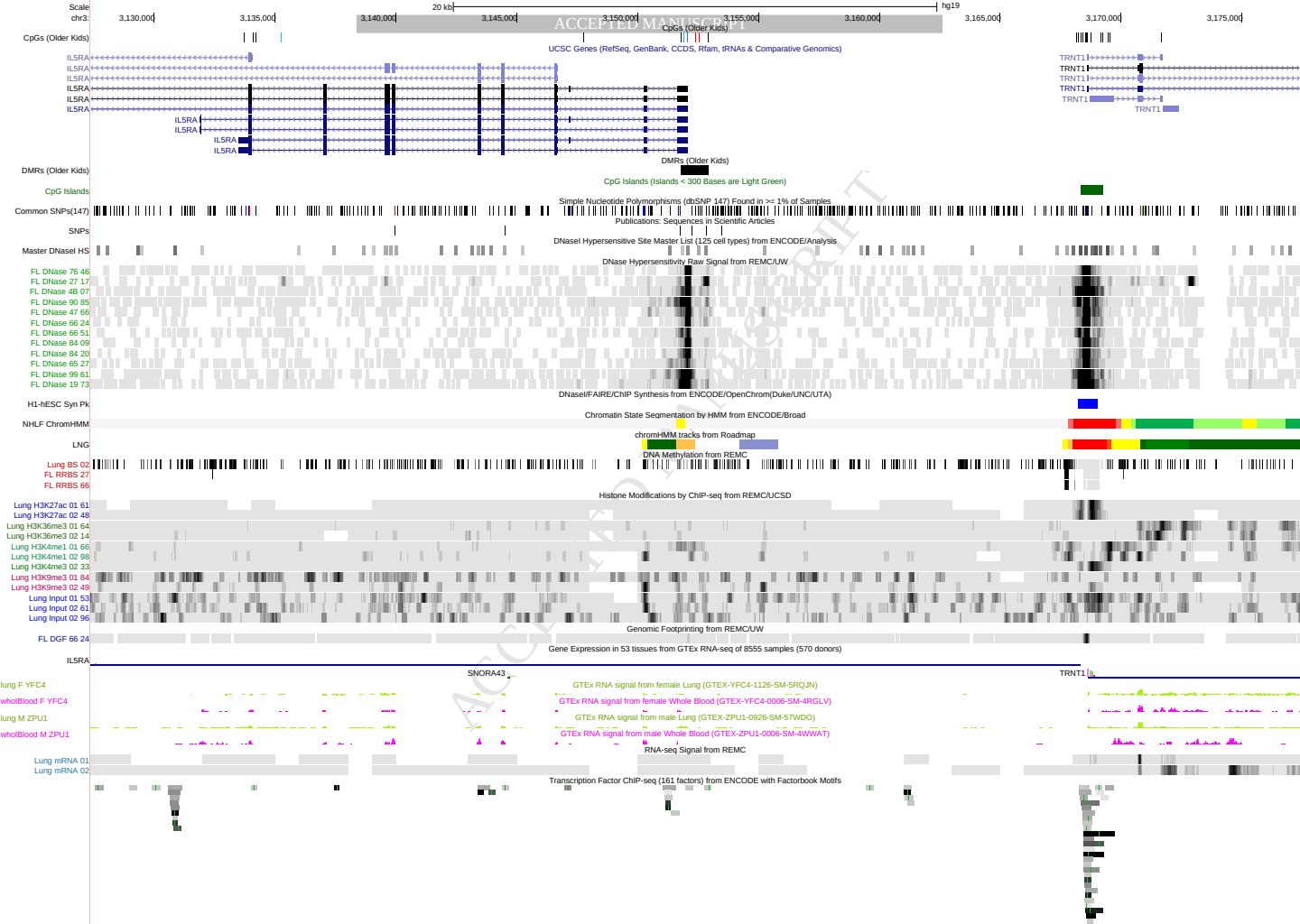


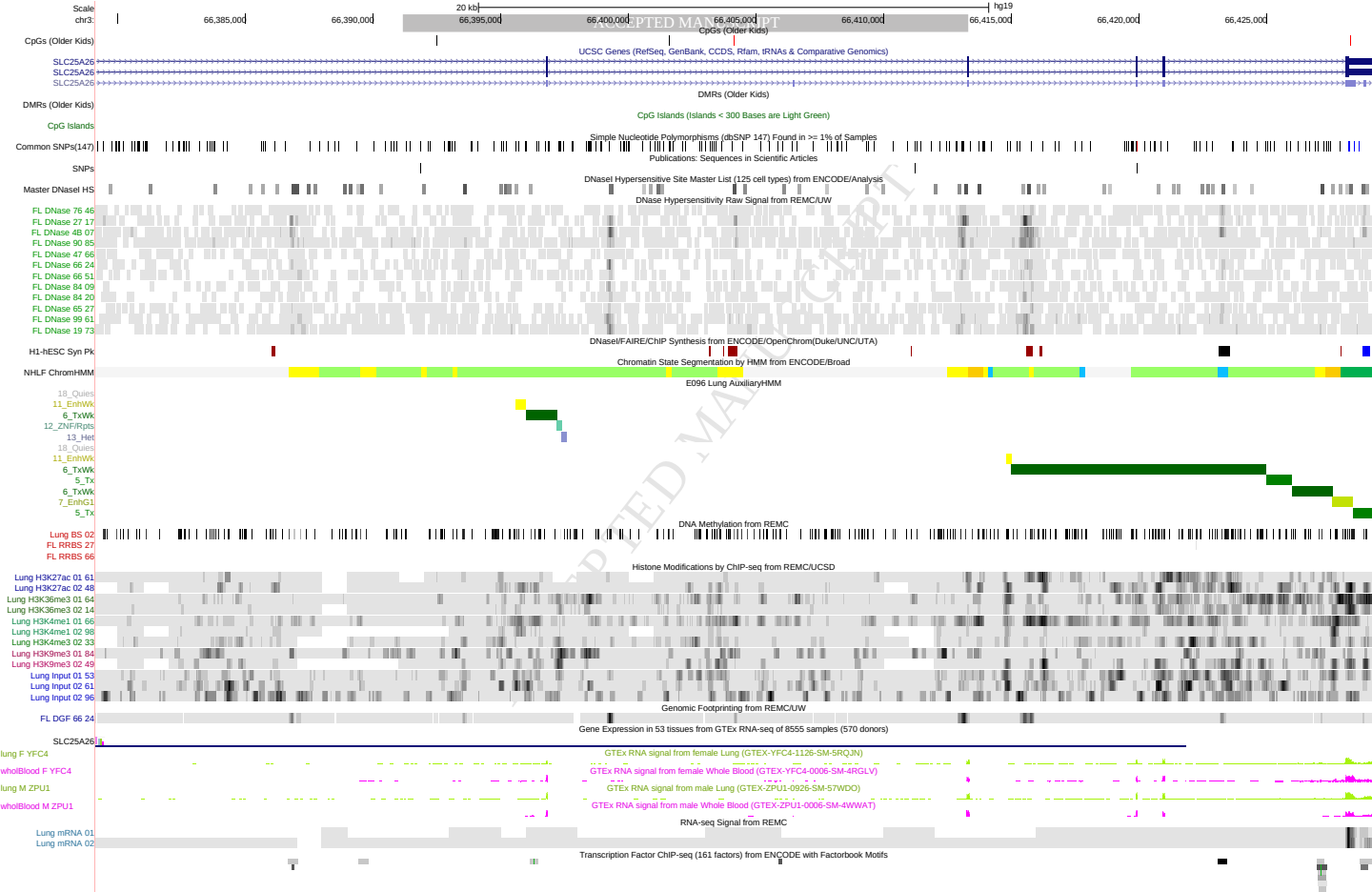


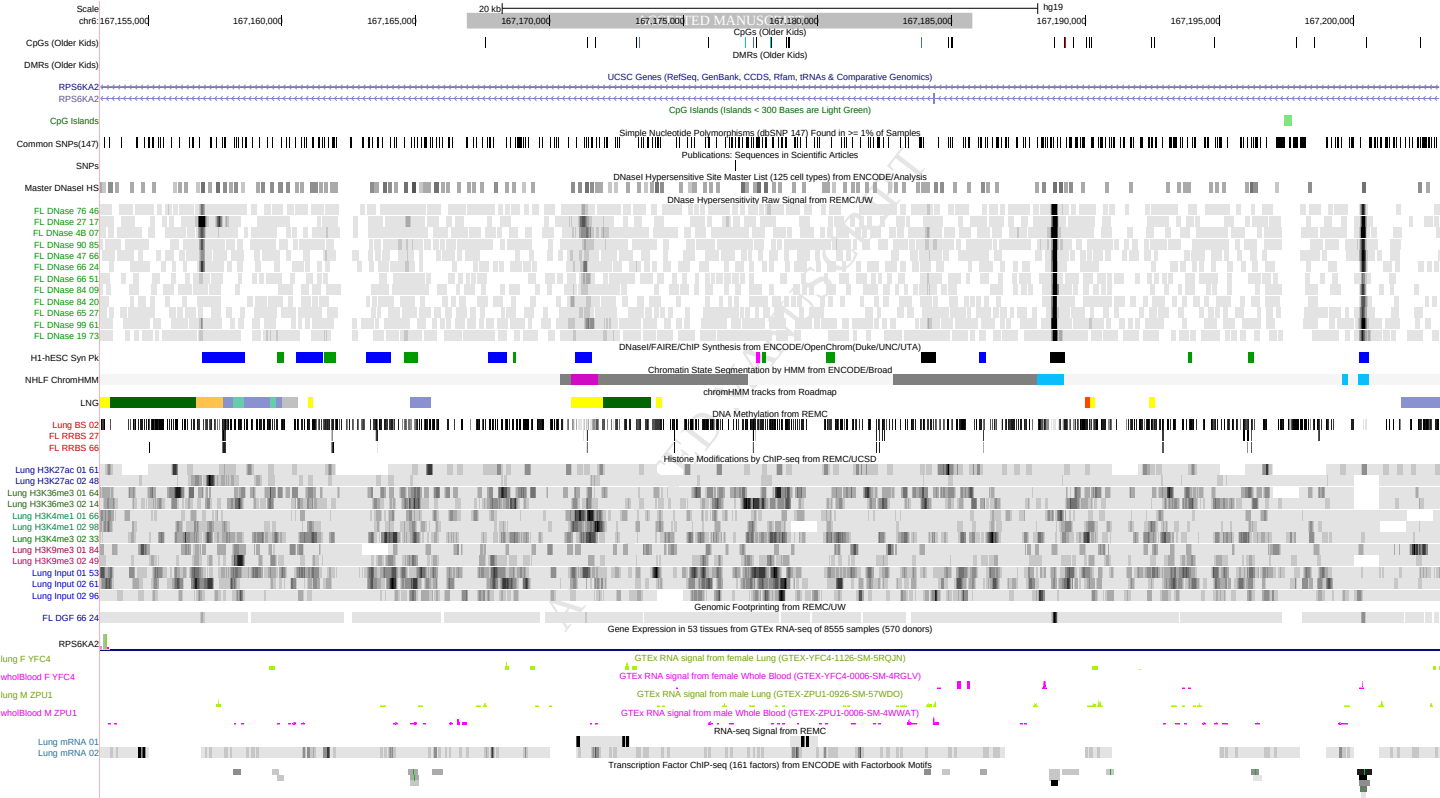








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CpGs (Older Kids)
DMRs (Older Kids)
UCSC Genes (RefSeq, GenBank, CCDS, Rfam, tRNAs & Comparative Genomics)
RPS6KA2
CpG Islands (Islands < 300 Bases are Light Green)
Simple Nucleotide Polymorphisms (dbSNP 147) Found in >= 1% of Samples
Common SNPs(147)
Publications: Sequences in Scientific Articles
SNPs
DNaseI Hypersensitive Site Master List (125 cell types) from ENCODE/Analysis
Master DNaseI HS
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FL DNase 76 46
FL DNase 27 17
FL DNase 48 07
FL DNase 90 85
FL DNase 47 66
FL DNase 66 24
FL DNase 66 51
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FL DNase 84 20
FL DNase 65 27
FL DNase 99 61
FL DNase 19 73
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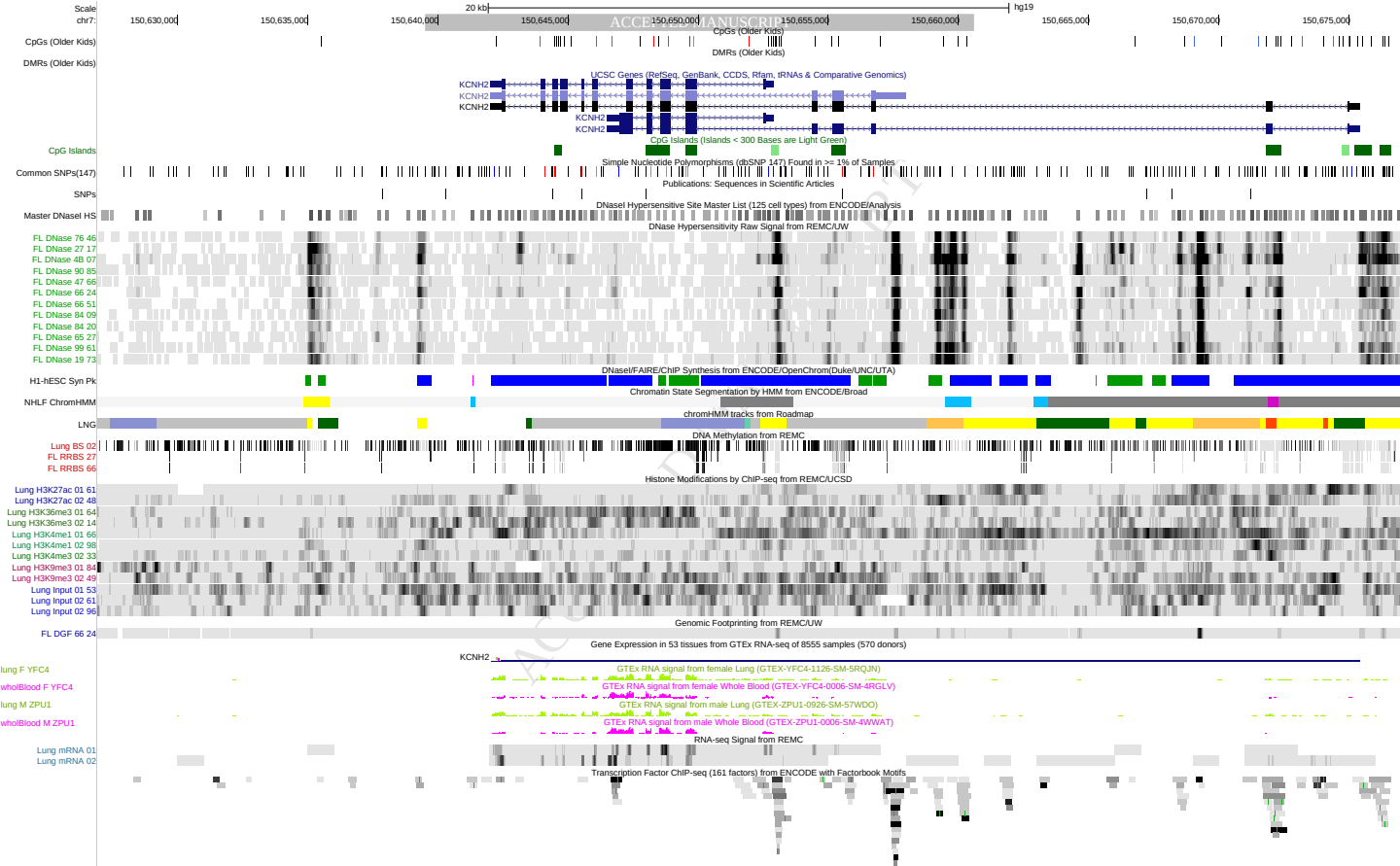
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CpGs (Older Kids)
DMRs (Older Kids)
UCSC Genes (RefSeq, GenBank, CCDS, Rfam, tRNAs & Comparative Genomics)
KCNH2
KCNH2
KCNH2
KCNH2
KCNH2
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CpG Islands (Islands < 300 Bases are Light Green)
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Lung H3K4me1 02 98
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Lung H3K9me3 01 84
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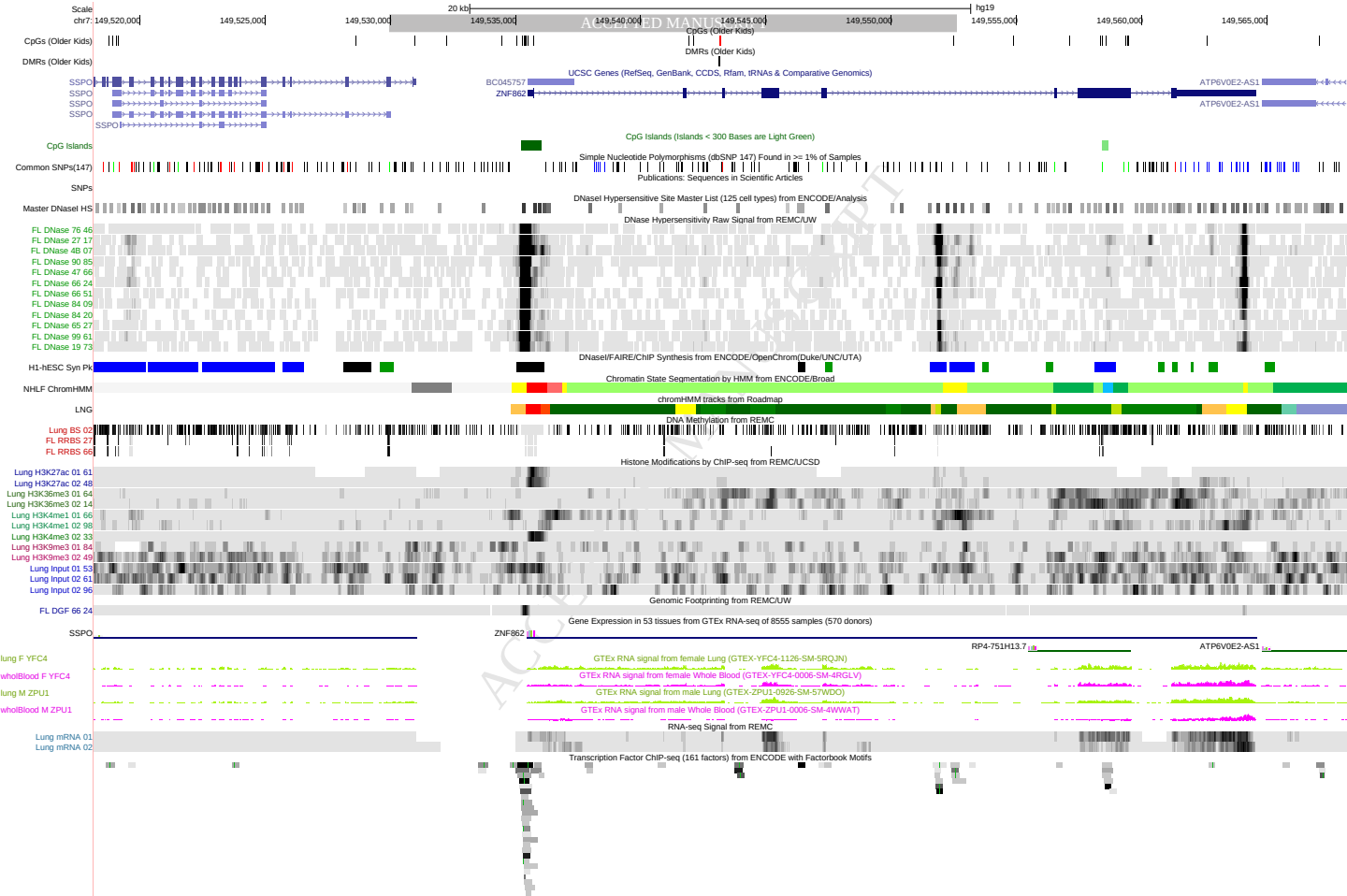
GTEx RNA signal from female Lung (GTEX-YFC4-1126-SM-5RQJN)
wholBlood F YFC4
GTEx RNA signal from female Whole Blood (GTEX-YFC4-0006-SM-4RGLV)
lung M ZPU1
GTEx RNA signal from male Lung (GTEX-ZPU1-0926-SM-57WDO)
wholBlood M ZPU1
GTEx RNA signal from male Whole Blood (GTEX-ZPU1-0006-SM-4WWAT)
RNA-seq Signal from REMC
Lung mRNA 01
Lung mRNA 02
Transcription Factor ChIP-seq (161 factors) from ENCODE with Factorbook Motifs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CpGs (Older Kids)
DMRs (Older Kids)
UCSC Genes (RefSeq, GenBank, CCDS, Rfam, tRNAs & Comparative Genomics)
SSPO
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ATP6V0E2-AS1
CpG Islands
CpG Islands (Islands < 300 Bases are Light Green)
Common SNPs(147)
Simple Nucleotide Polymorphisms (dbSNP 147) Found in >= 1% of Samples
Publications: Sequences in Scientific Articles
SNPs
Master DNaseI HS
DNaseI Hypersensitive Site Master List (125 cell types) from ENCODE/Analysis
DNase Hypersensitivity Raw Signal from REMC/UW
FL DNase 76 46
FL DNase 27 17
FL DNase 4B 07
FL DNase 90 85
FL DNase 47 66
FL DNase 66 24
FL DNase 66 51
FL DNase 84 09
FL DNase 84 20
FL DNase 65 27
FL DNase 99 61
FL DNase 19 73
H1-hESC Syn Pk
DNaseI/FAIRE/ChIP Synthesis from ENCODE/OpenChrom(Duke/UNC/UTA)
NHLF ChromHMM
Chromatin State Segmentation by HMM from ENCODE/Broad
LNG
chromHMM tracks from Roadmap
Lung BS 02
FL RRBS 27
FL RRBS 66
DNA Methylation from REMC
Histone Modifications by ChIP-seq from REMC/UCSD
Lung H3K27ac 01 61
Lung H3K27ac 02 48
Lung H3K36me3 01 64
Lung H3K36me3 02 14
Lung H3K4me1 01 66
Lung H3K4me1 02 98
Lung H3K4me3 02 33
Lung H3K9me3 01 84
Lung H3K9me3 02 49
Lung Input 01 53
Lung Input 02 61
Lung Input 02 96
Genomic Footprinting from REMC/UW
FL DGF 66 24
Gene Expression in 53 tissues from GTEx RNA-seq of 8555 samples (570 donors)
RP4-751H13.7
lung F YFC4
GTEx RNA signal from female Lung (GTEX-YFC4-1126-SM-5RQJN)
wholBlood F YFC4
GTEx RNA signal from female Whole Blood (GTEX-YFC4-0006-SM-4RGLV)
lung M ZPU1
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wholBlood M ZPU1
GTEx RNA signal from male Whole Blood (GTEX-ZPU1-0006-SM-4WWAT)
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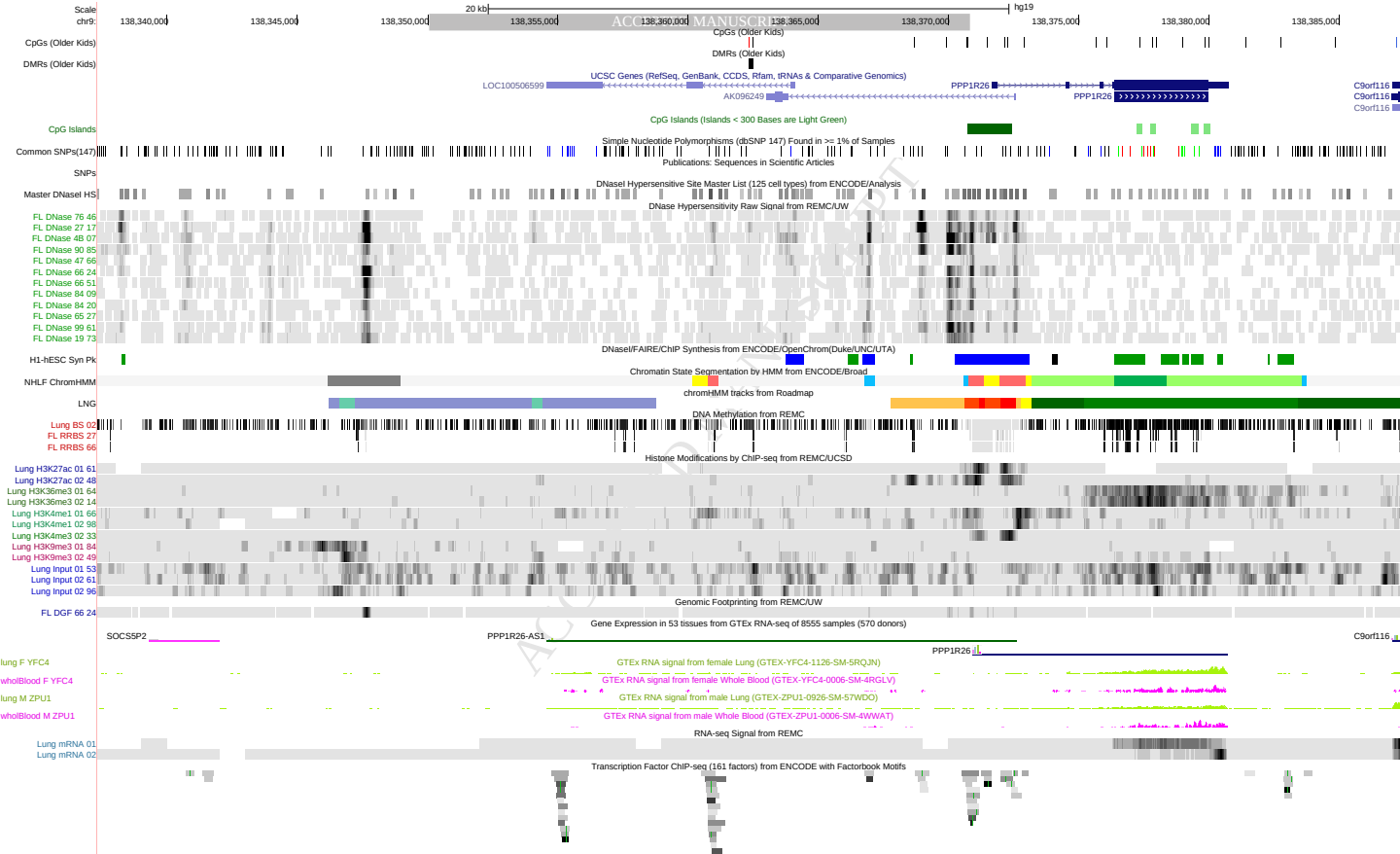
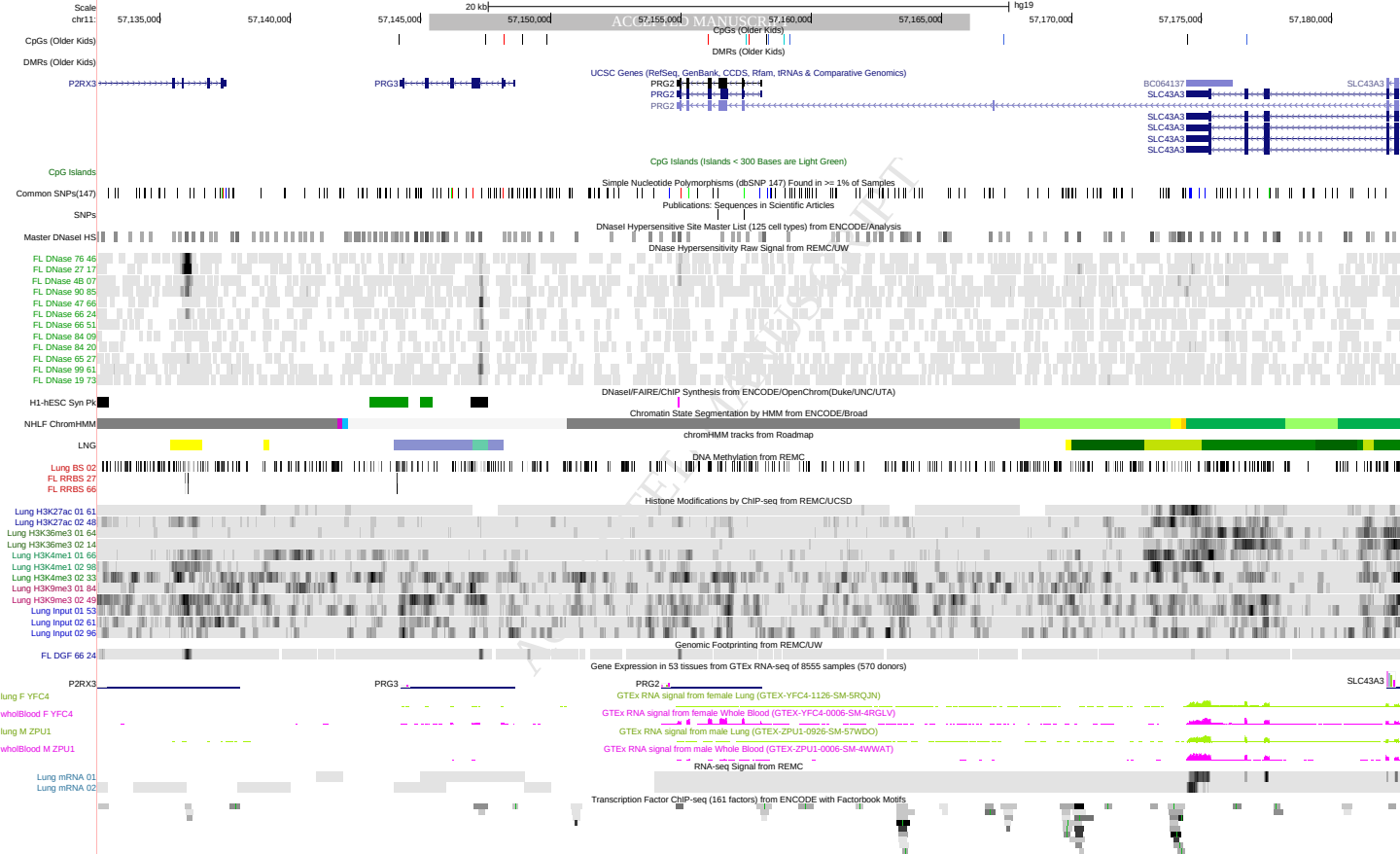
Lung mRNA 01
Lung mRNA 02
Transcription Factor ChIP-seq (161 factors) from ENCODE with Factorbook Motifs

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CpGs (Older Kids)
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UCSC Genes (RefSeq, GenBank, CCDS, Rfam, tRNAs & Comparative Genomics)
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CpG Islands
CpG Islands (Islands < 300 Bases are Light Green)
Common SNPs(147)
Simple Nucleotide Polymorphisms (dbSNP 147) Found in >= 1% of Samples
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FL DNase 27 17
FL DNase 4B 07
FL DNase 90 85
FL DNase 47 66
FL DNase 66 24
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FL DNase 84 09
FL DNase 84 20
FL DNase 65 27
FL DNase 99 61
FL DNase 19 73
H1-hESC Syn Pk
DNaseI/FAIRE/ChIP Synthesis from ENCODE/OpenChrom(Duke/UNC/UTA)
NHLF ChromHMM
Chromatin State Segmentation by HMM from ENCODE/Broad
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chromHMM tracks from Roadmap
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RNA-seq Signal from REMC
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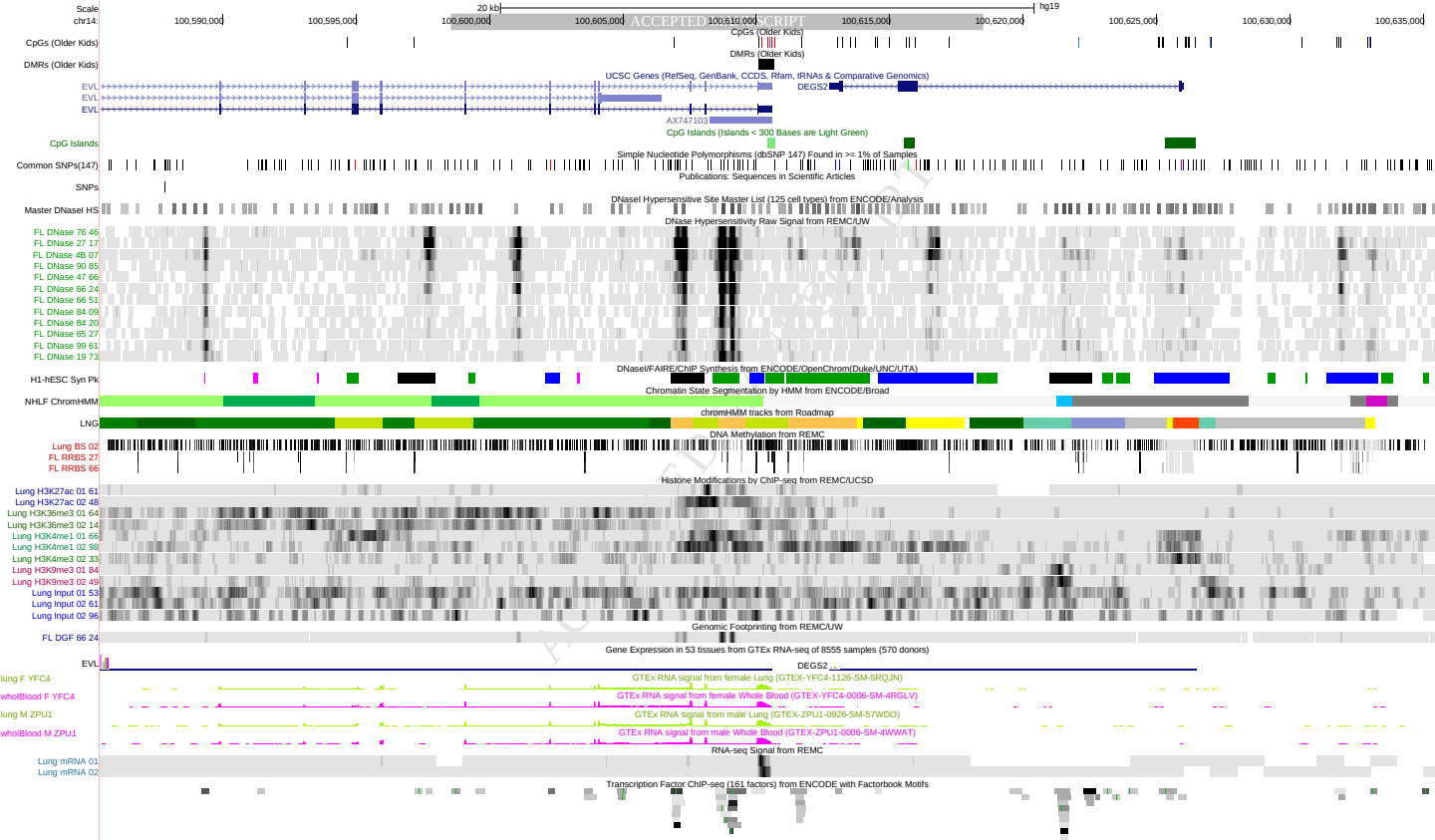
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ACCEPTED MANUSCRIPT
CpGs (Older Kids)
DMRs (Older Kids)
UCSC Genes (RefSeq, GenBank, CCDS, Rfam, tRNAs & Comparative Genomics)
EVL
DEGS2
AX747103
CpG Islands (Islands < 300 Bases are Light Green)
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FL DNase 84 09
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FL DNase 19 73
DNaseI/FAIRE/ChIP Synthesis from ENCODE/OpenChrom(Duke/UNC/UTA)
H1-hESC Syn Pk
Chromatin State Segmentation by HMM from ENCODE/Broad
NHLF ChromHMM
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Lung Input 02 96
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DEGS2
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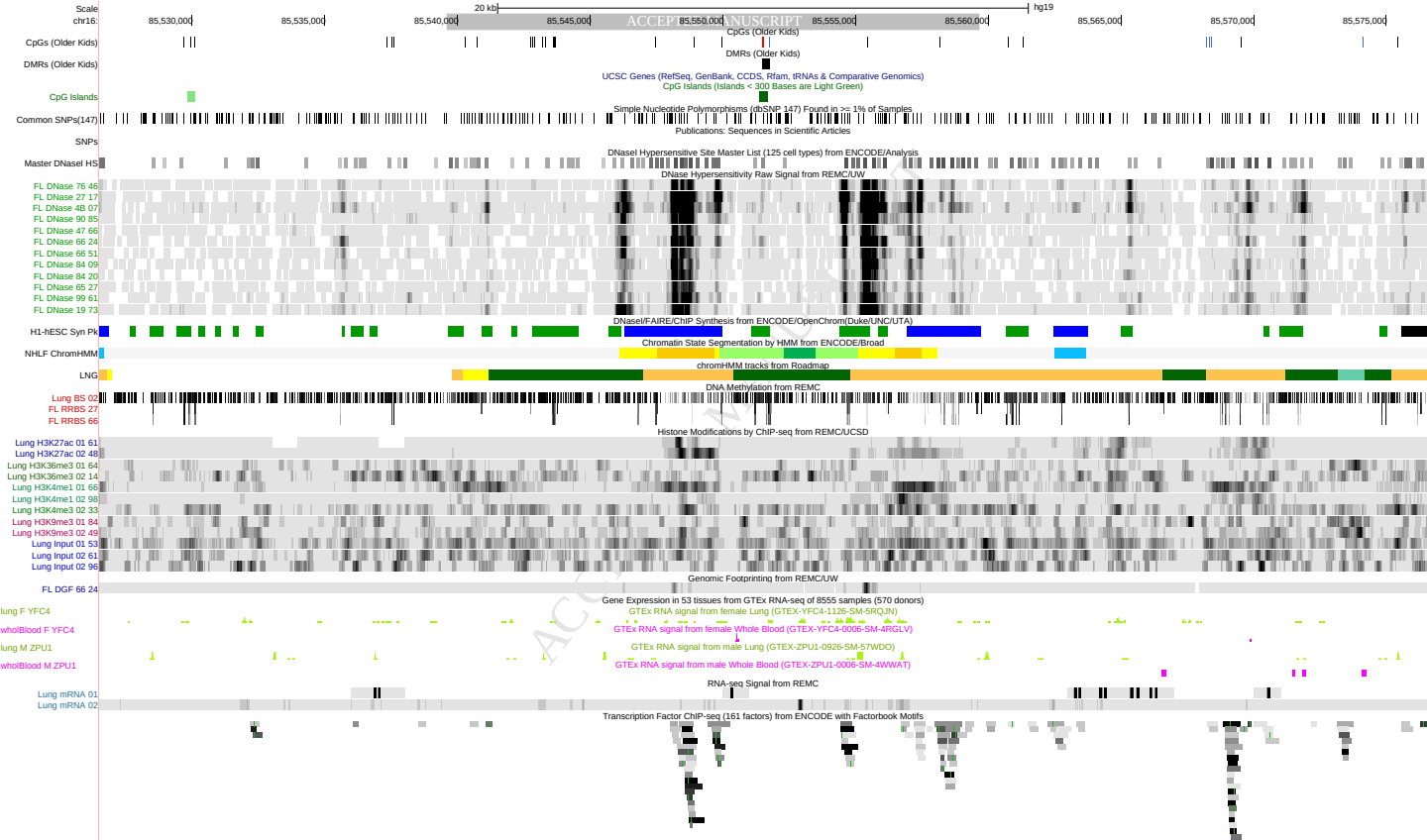

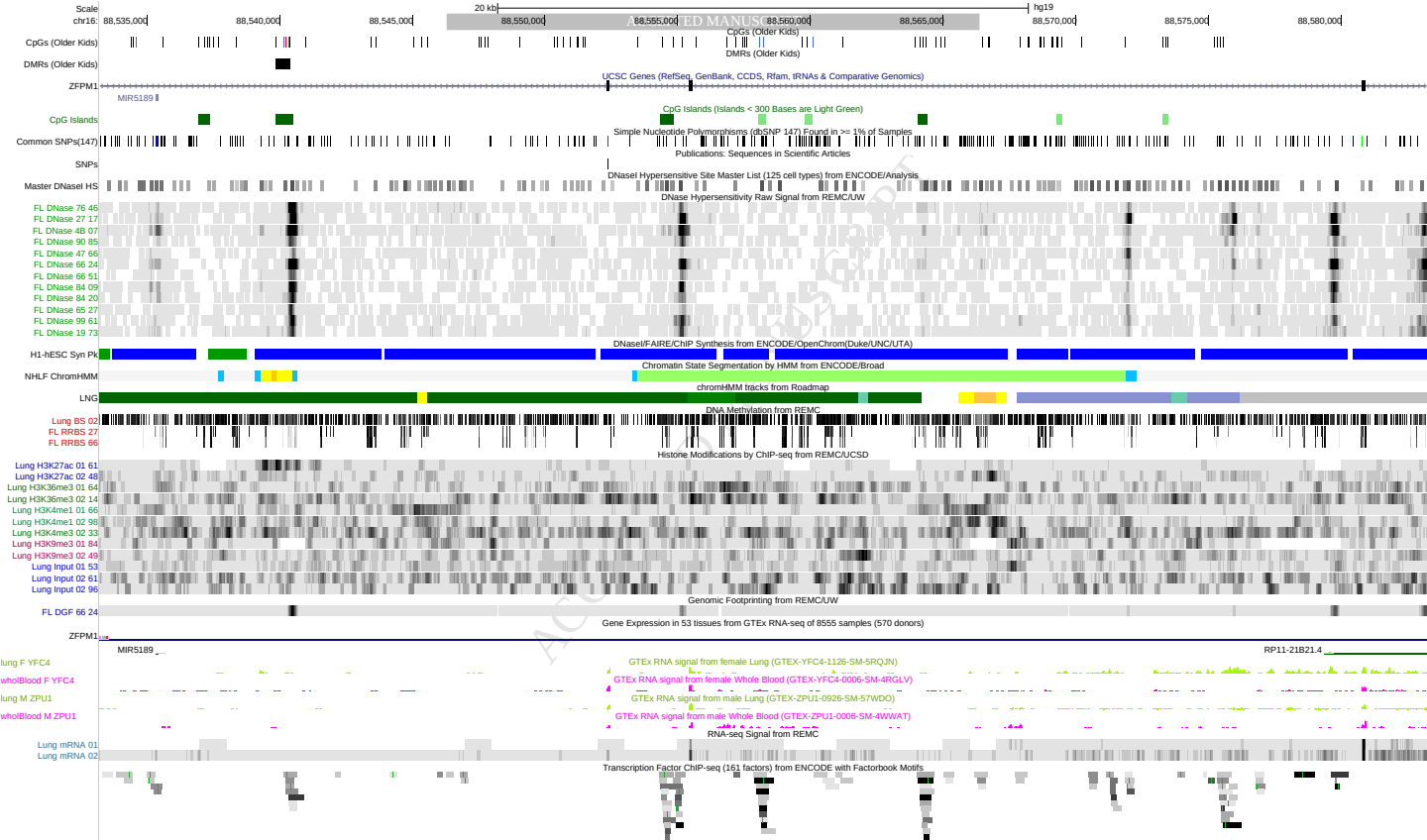

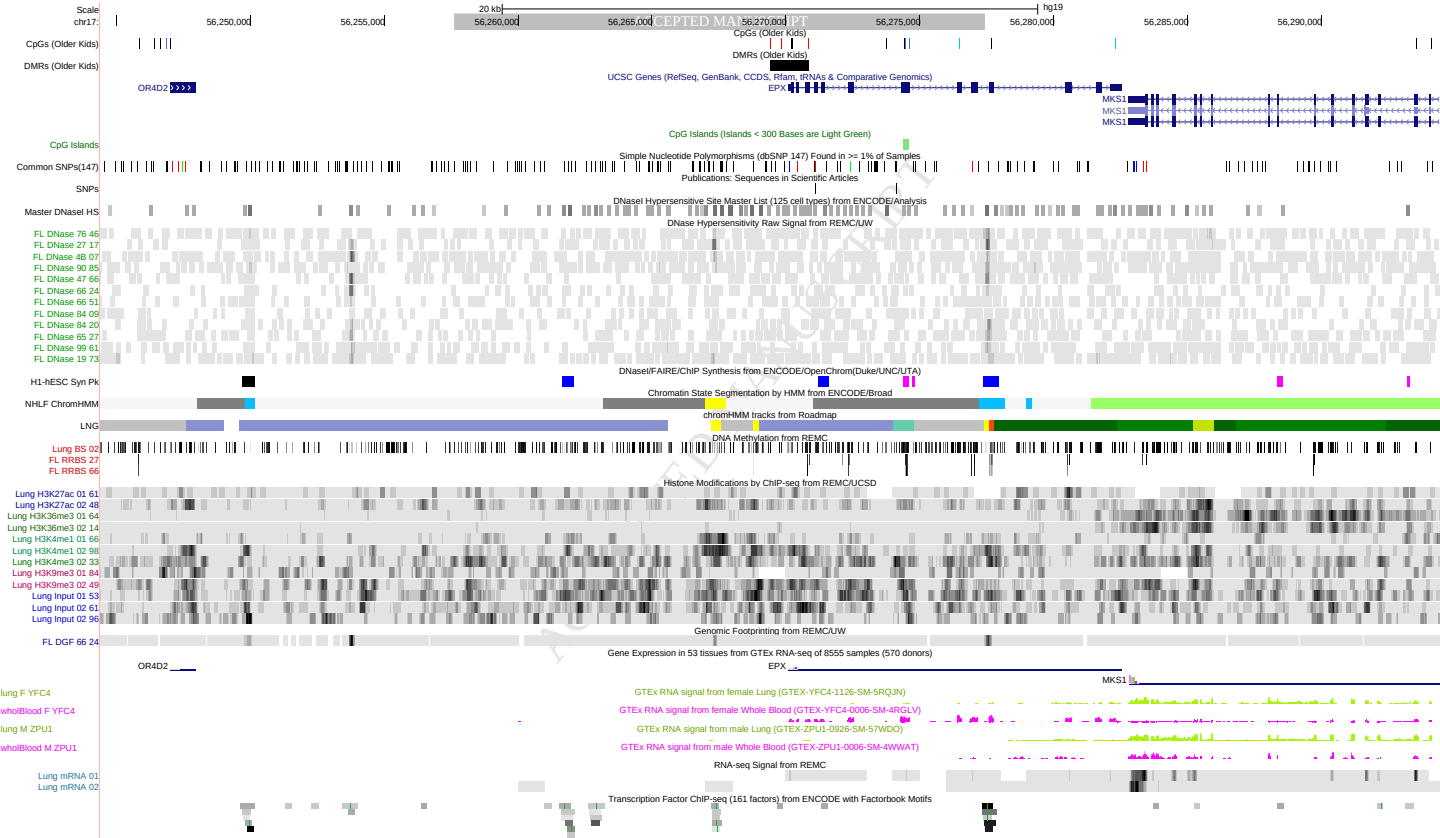
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CpGs (Older Kids)
DMRs (Older Kids)
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OR4D2
EPX
MKS1
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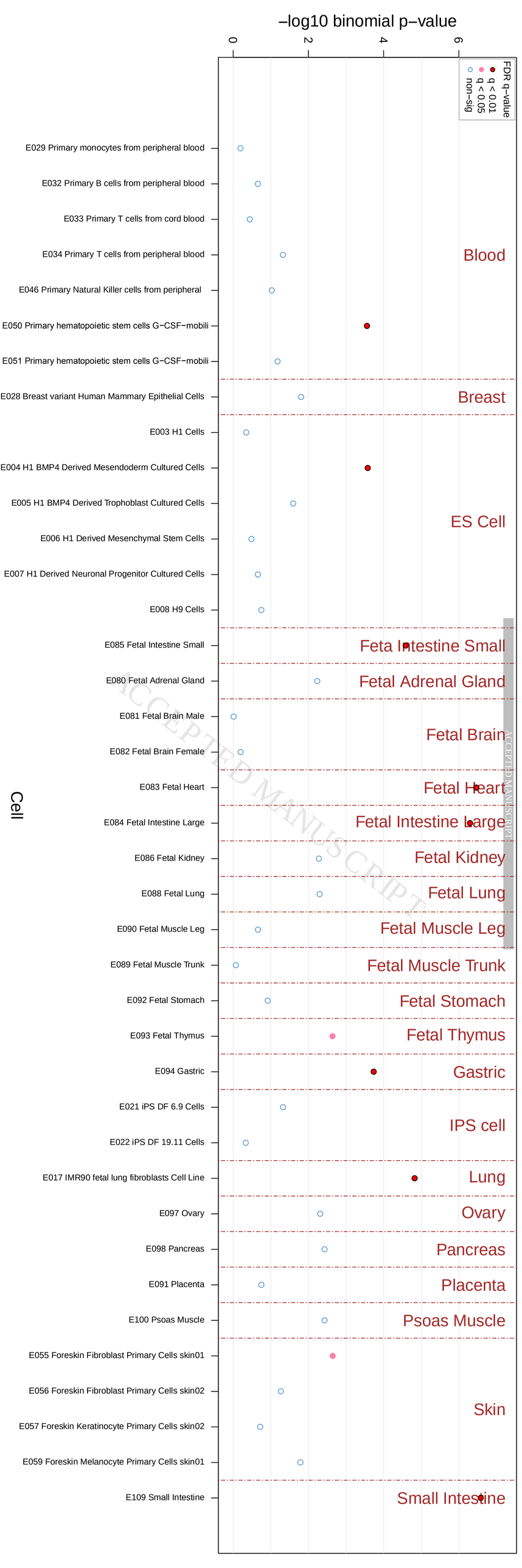

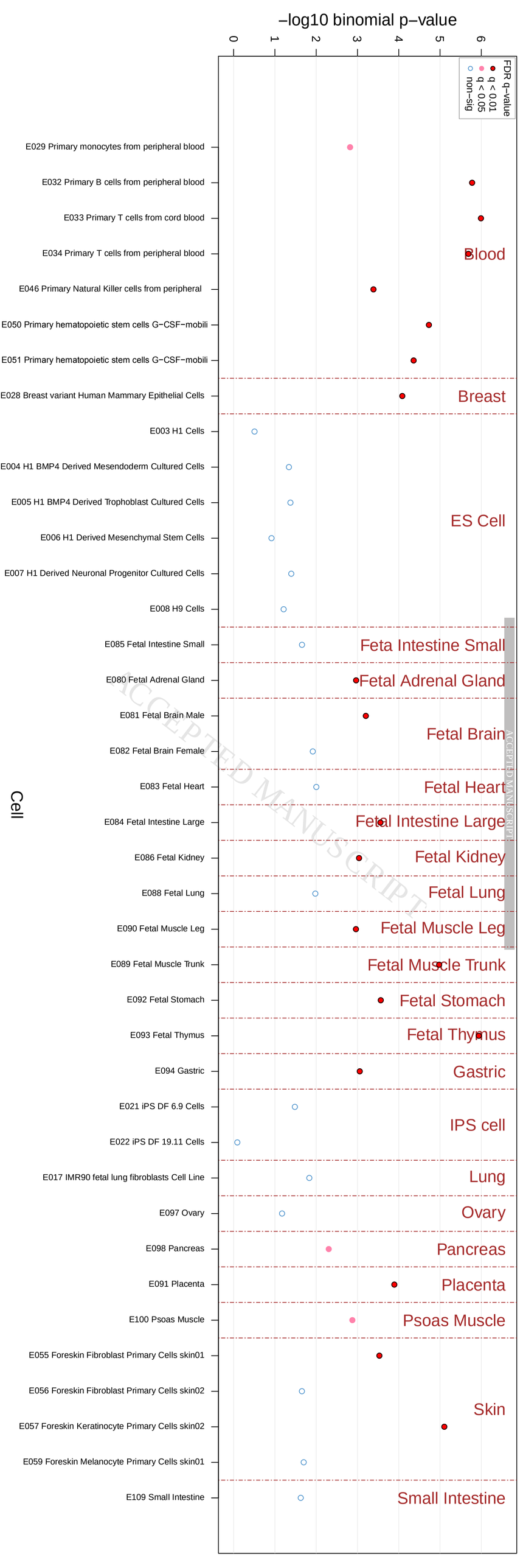
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E032 Primary B cells from peripheral blood
E033 Primary T cells from cord blood
E034 Primary T cells from peripheral blood
E046 Primary Natural Killer cells from peripheral
E050 Primary hematopoietic stem cells G−CSF−mobili
E051 Primary hematopoietic stem cells G−CSF−mobili
Blood
E028 Breast variant Human Mammary Epithelial Cells
Breast
E003 H1 Cells
E004 H1 BMP4 Derived Mesendoderm Cultured Cells
E005 H1 BMP4 Derived Trophoblast Cultured Cells
E006 H1 Derived Mesenchymal Stem Cells
E007 H1 Derived Neuronal Progenitor Cultured Cells
E008 H9 Cells
ES Cell
E085 Fetal Intestine Small
Feta Intestine Small
E080 Fetal Adrenal Gland
Fetal Adrenal Gland
E081 Fetal Brain Male
E082 Fetal Brain Female
Fetal Brain
E083 Fetal Heart
Fetal Heart
E084 Fetal Intestine Large
Fetal Intestine Large
E086 Fetal Kidney
Fetal Kidney
E088 Fetal Lung
Fetal Lung
E090 Fetal Muscle Leg
Fetal Muscle Leg
E089 Fetal Muscle Trunk
Fetal Muscle Trunk
E092 Fetal Stomach
Fetal Stomach
E093 Fetal Thymus
Fetal Thymus
E094 Gastric
Gastric
E021 iPS DF 6.9 Cells
E022 iPS DF 19.11 Cells
IPS cell
E017 IMR90 fetal lung fibroblasts Cell Line
Lung
E097 Ovary
Ovary
E098 Pancreas
Pancreas
E091 Placenta
Placenta
E100 Psoas Muscle
Psoas Muscle
E055 Foreskin Fibroblast Primary Cells skin01
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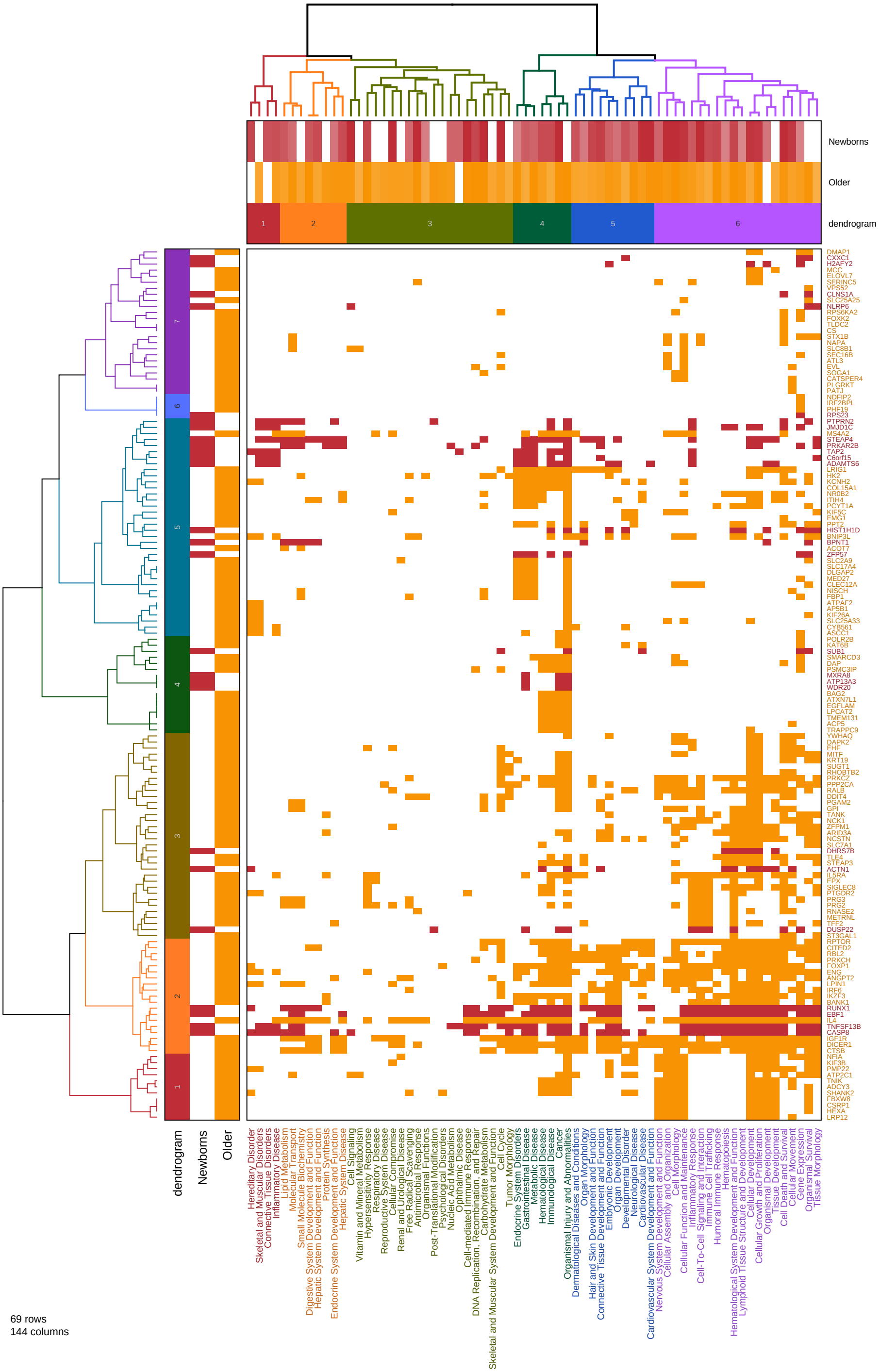
ACCEPTED MANUSCRIPT



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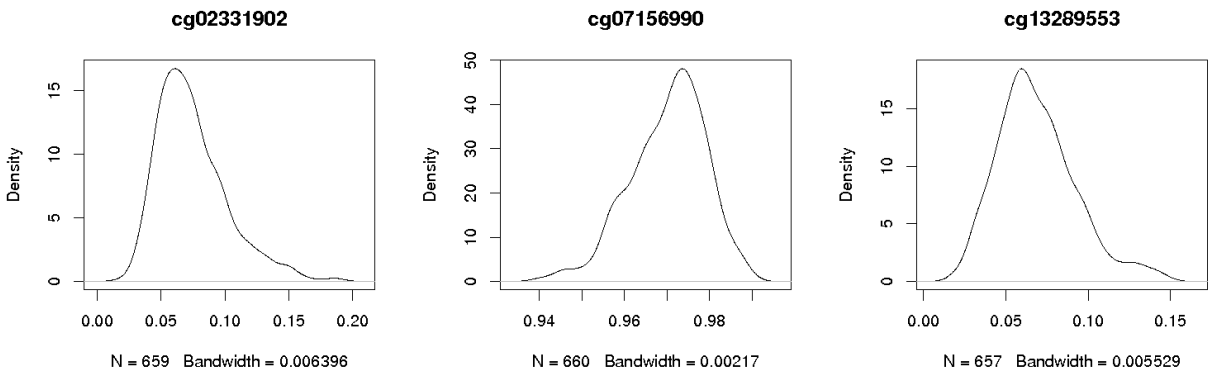
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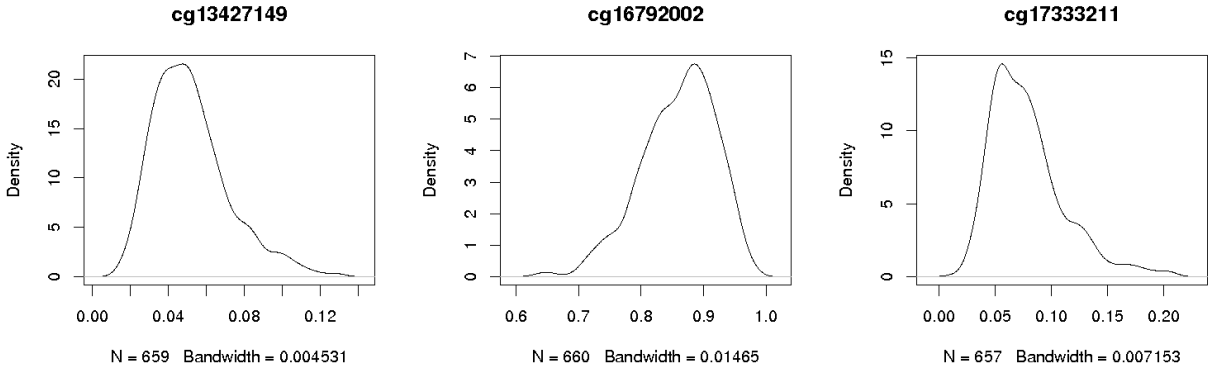
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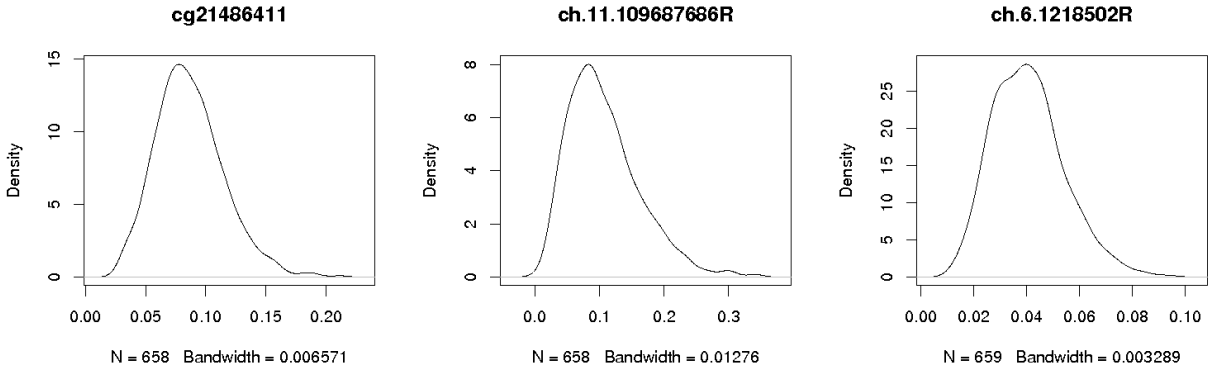
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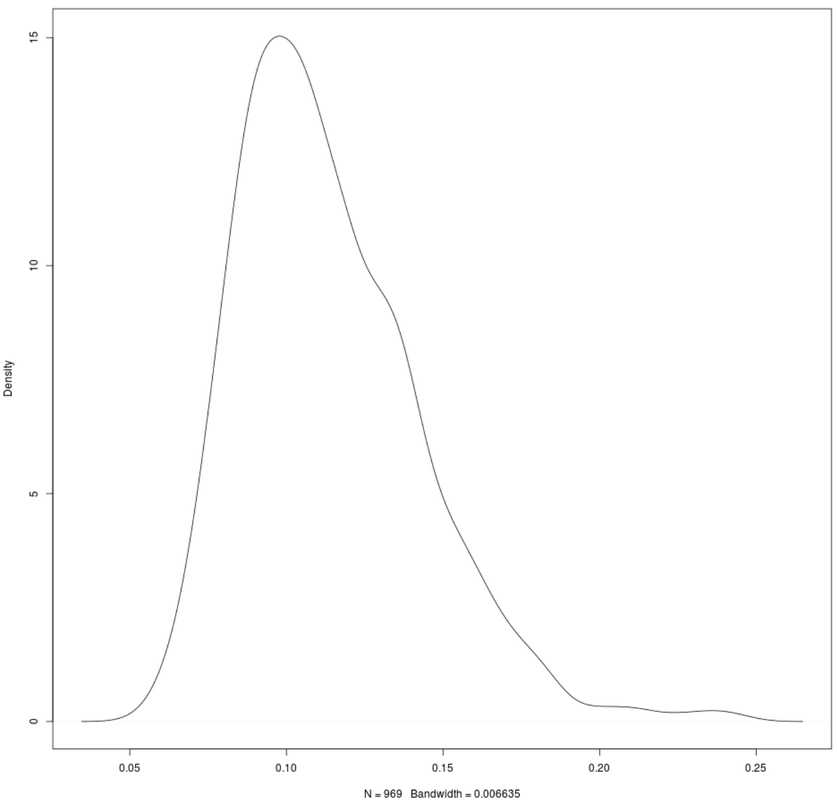
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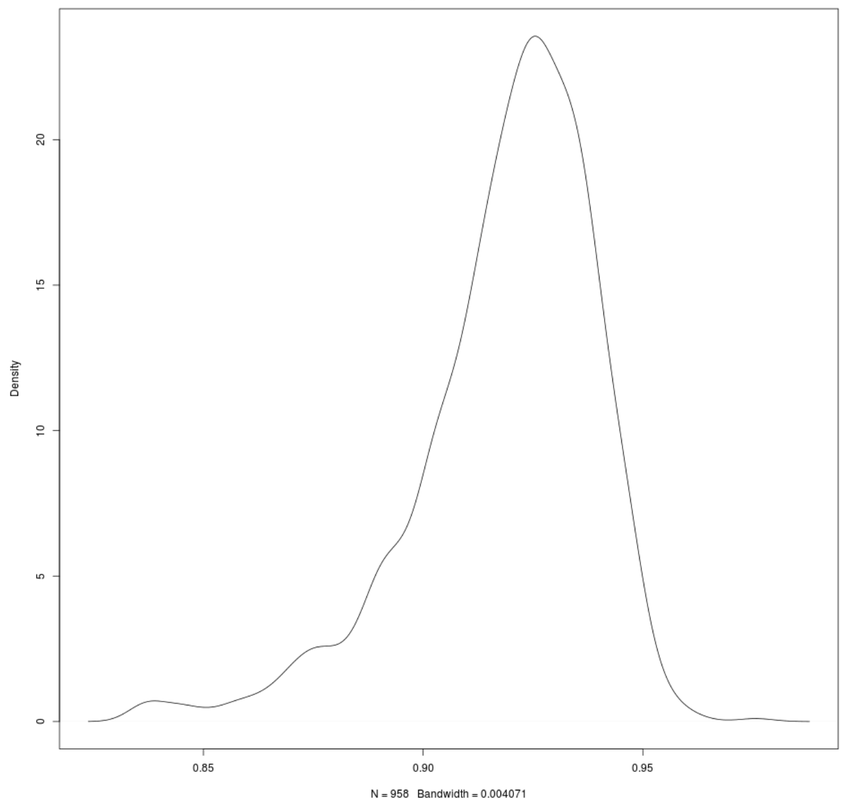
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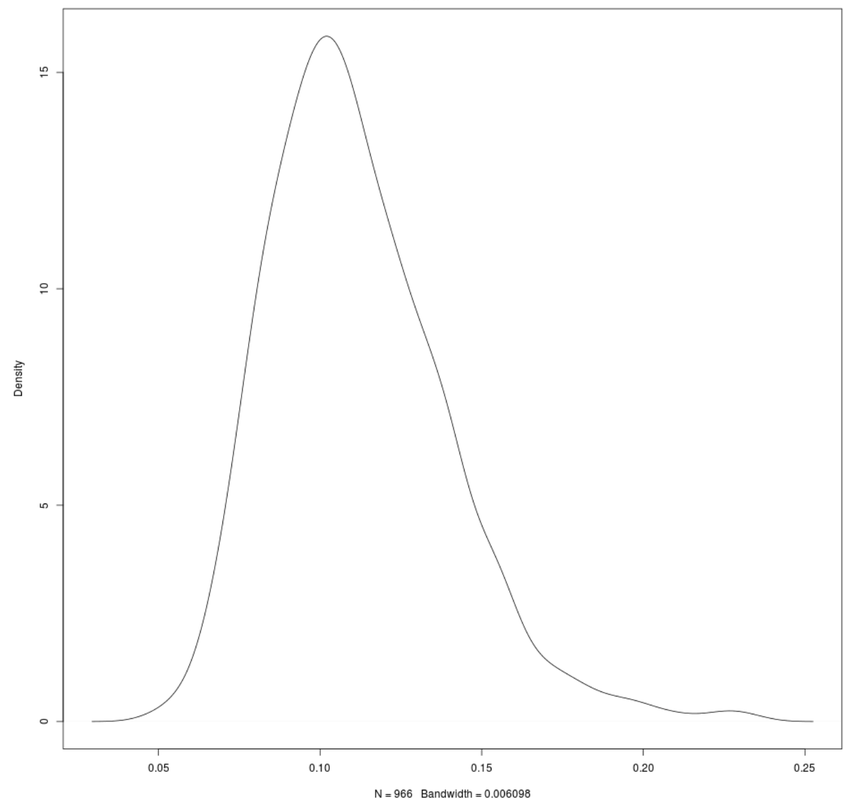
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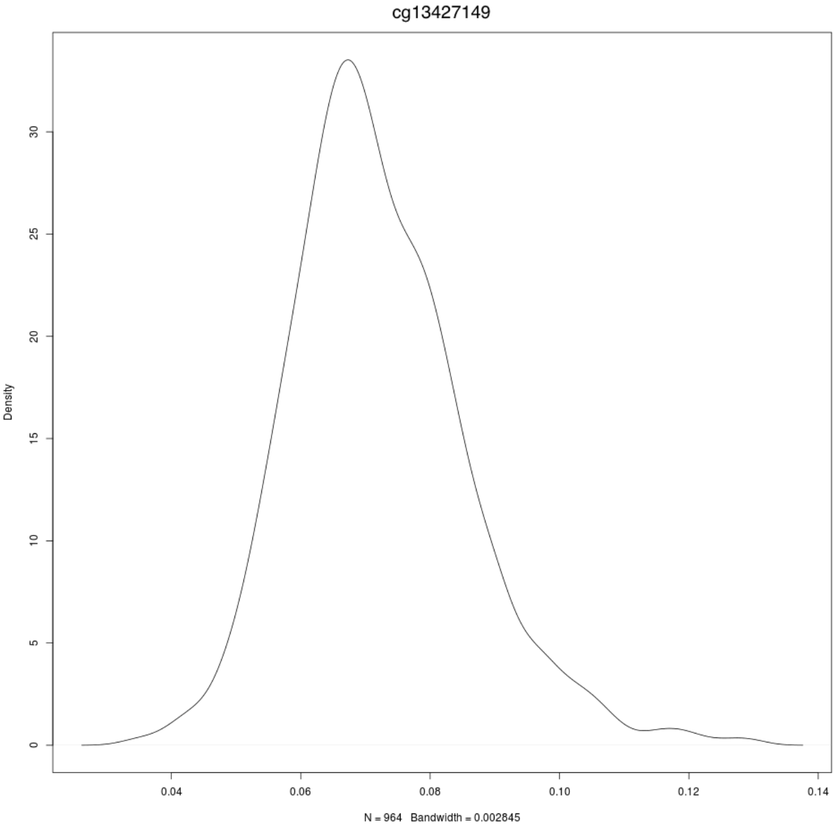
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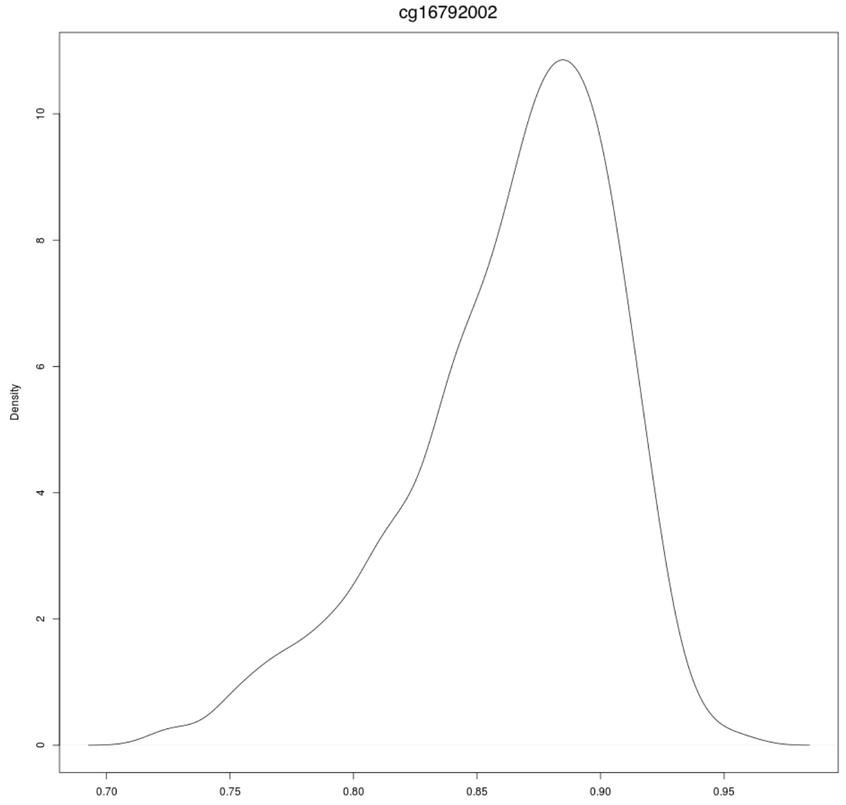
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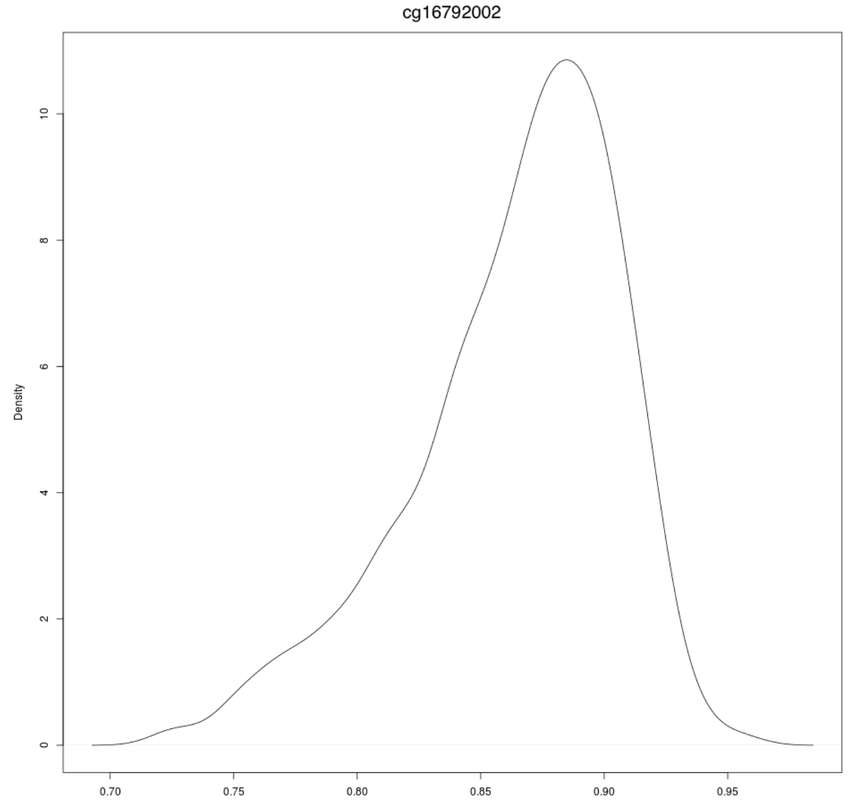
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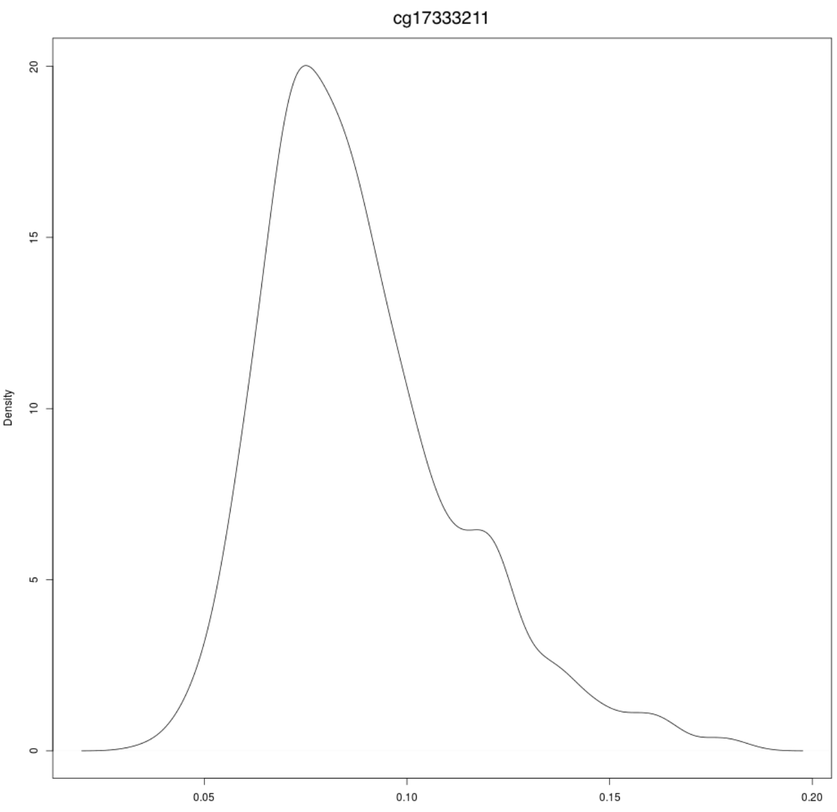
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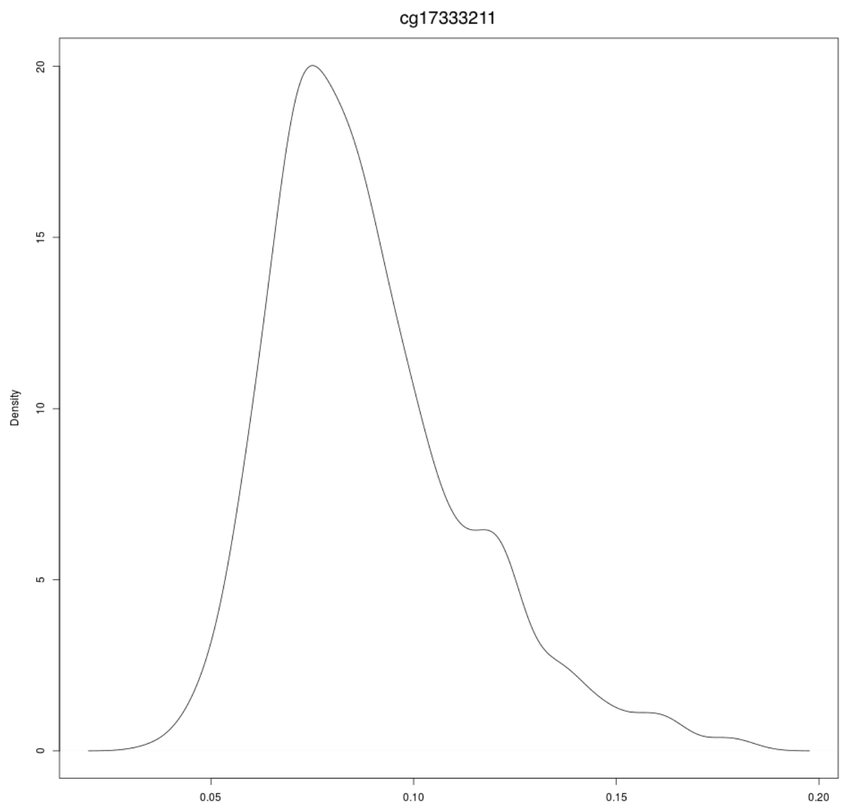
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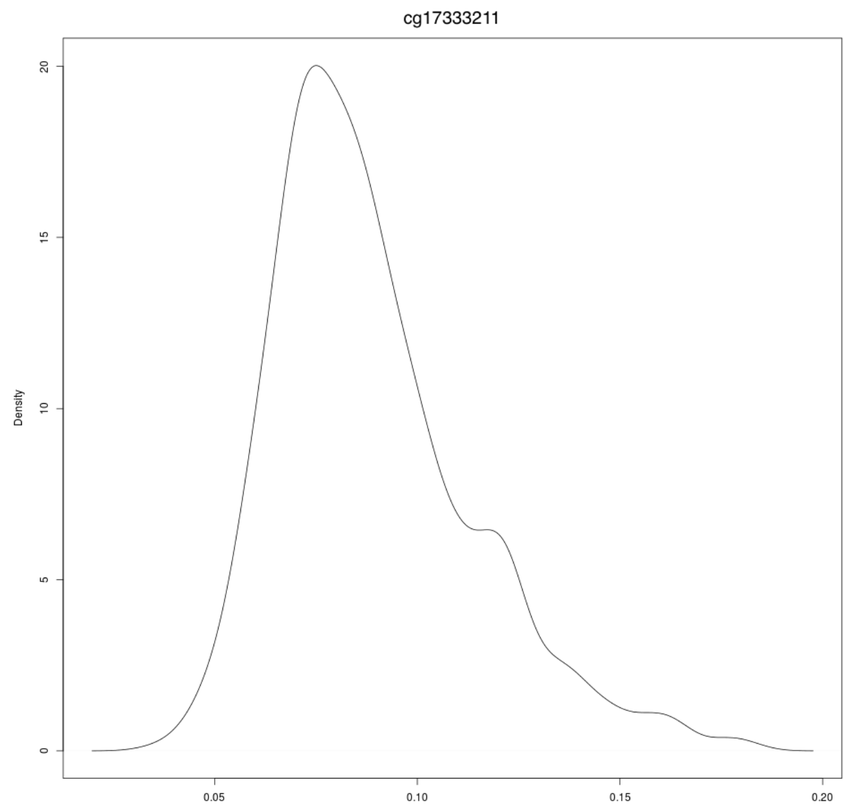
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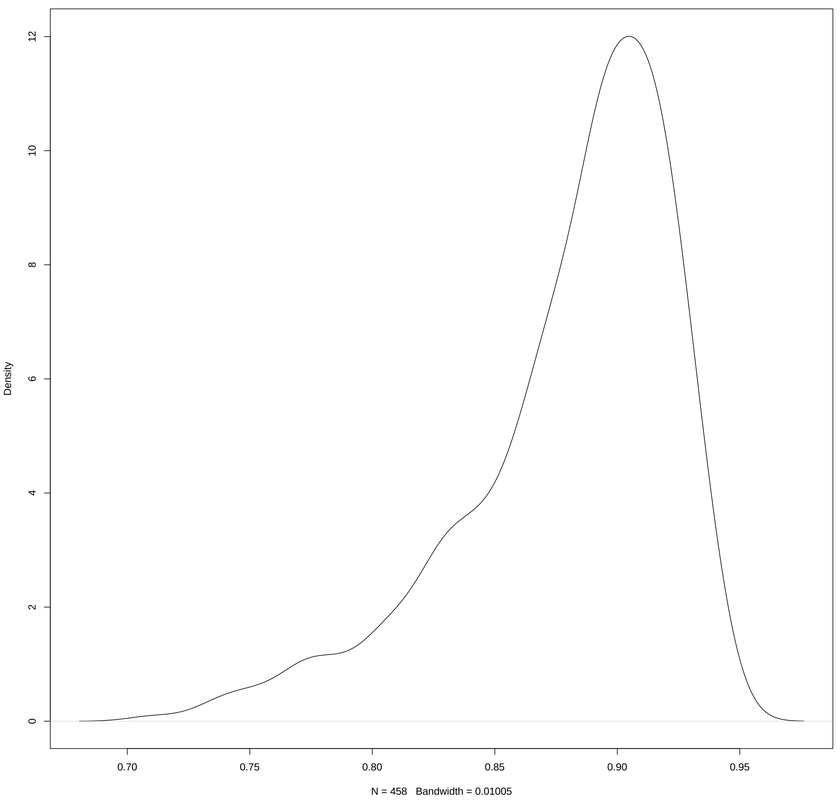
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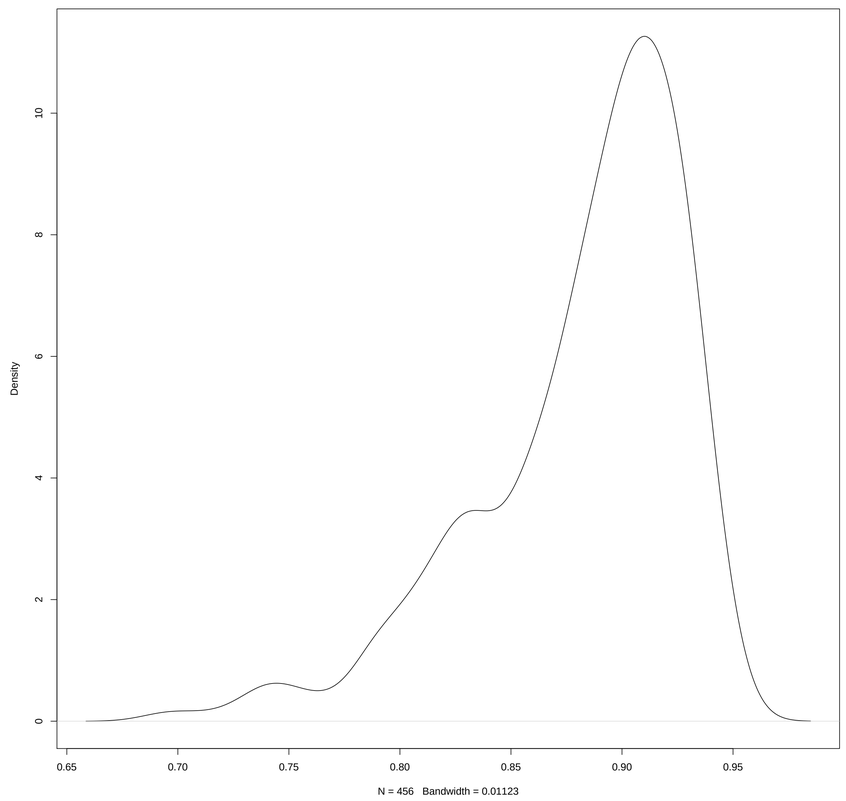
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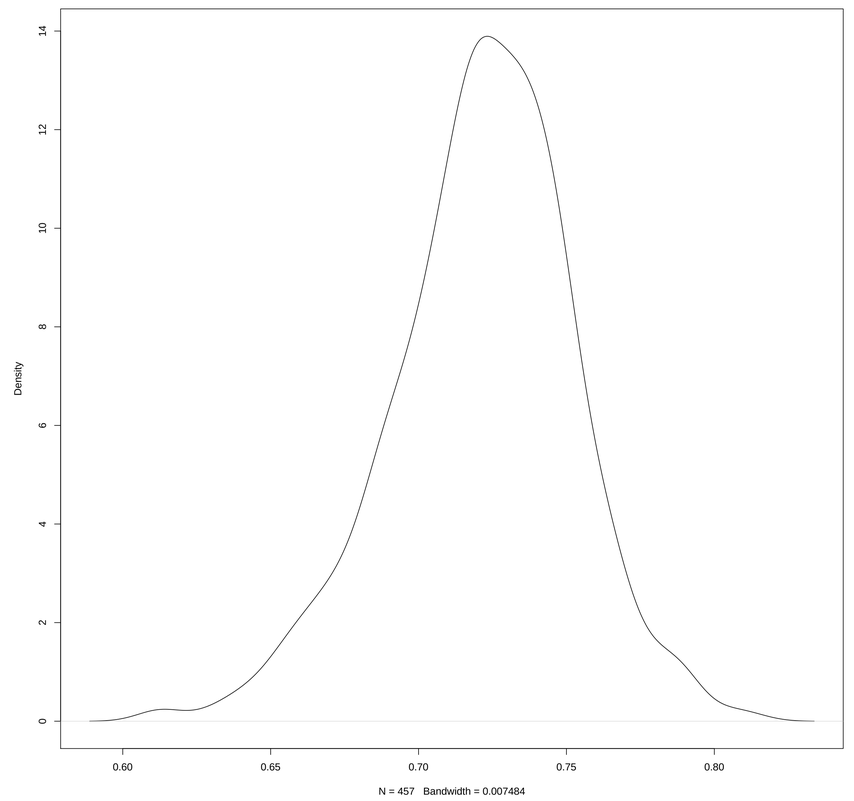
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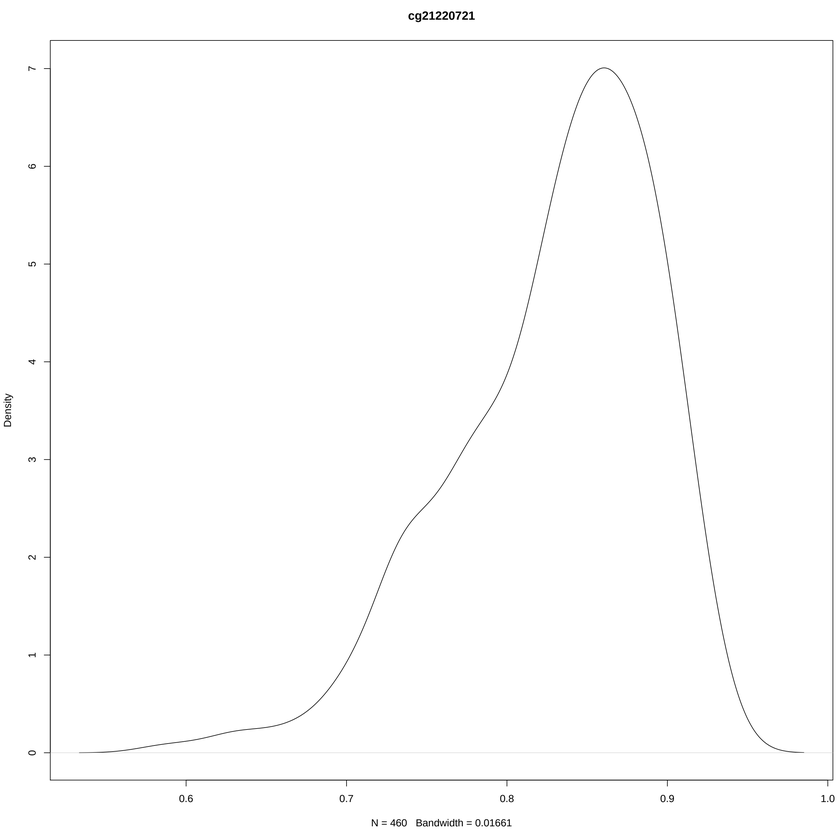
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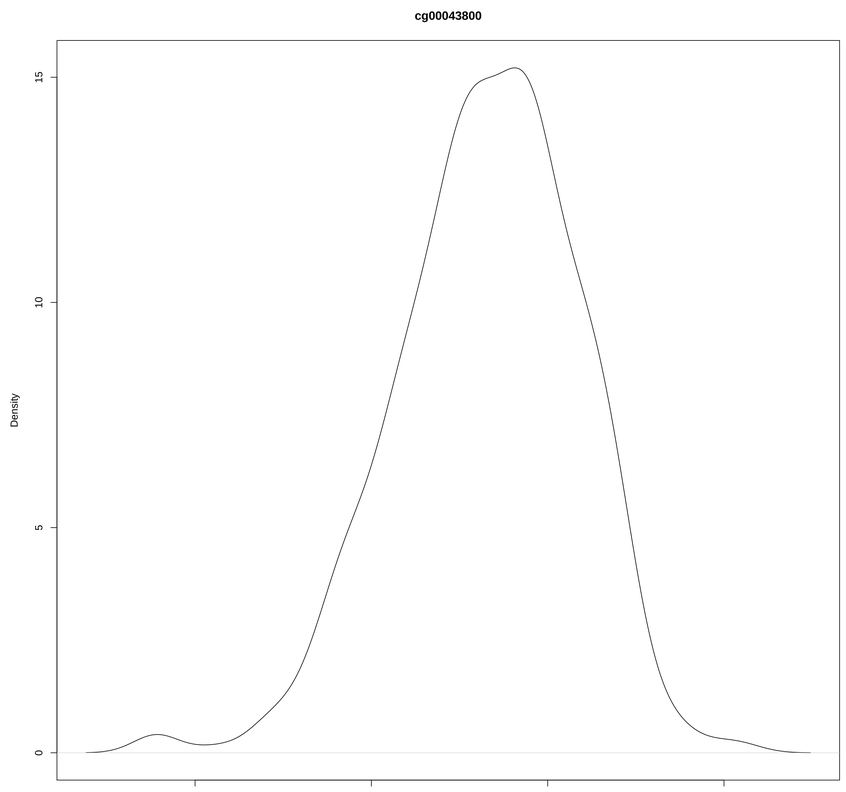
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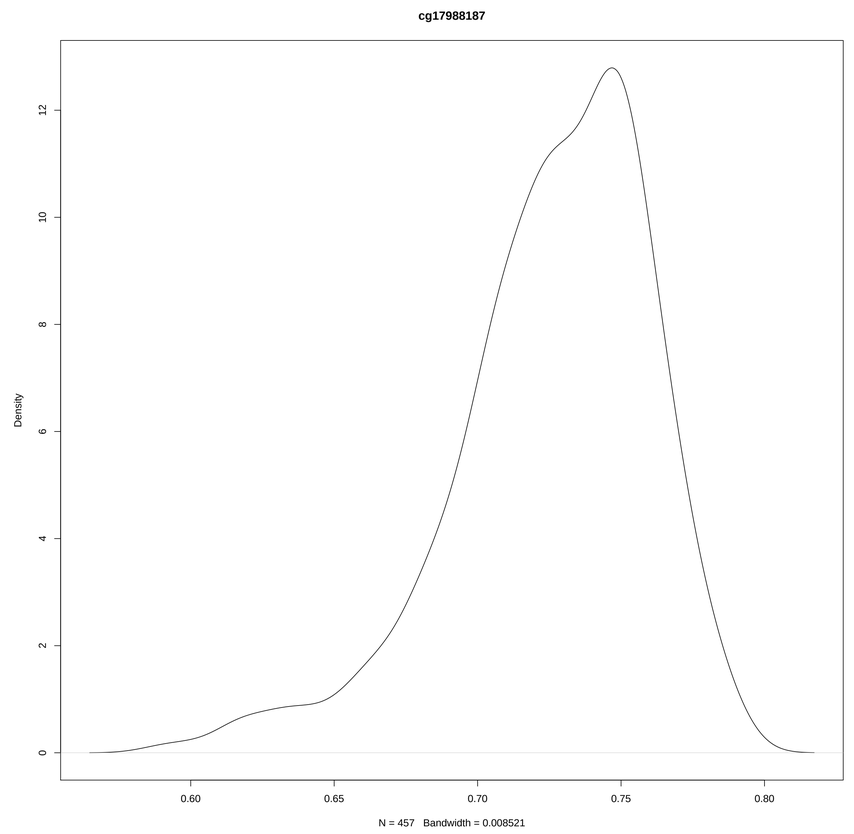
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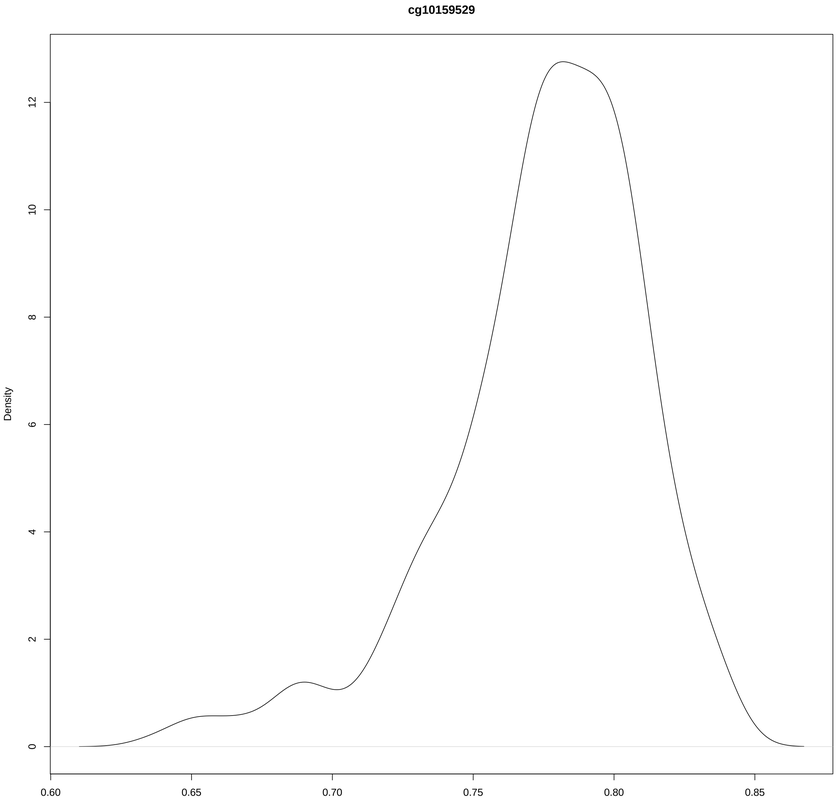
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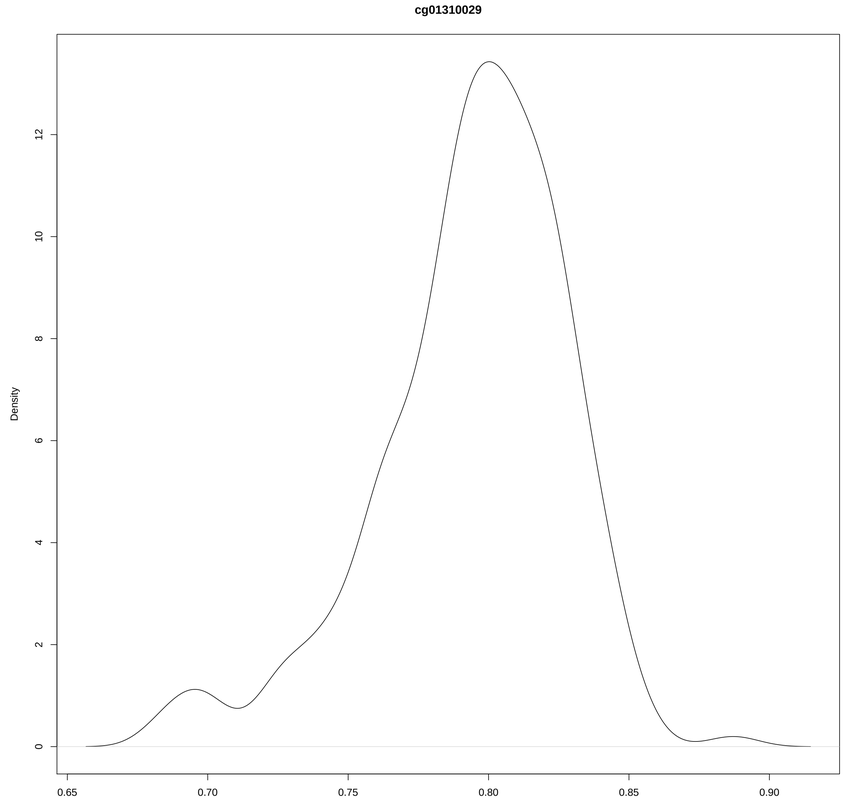
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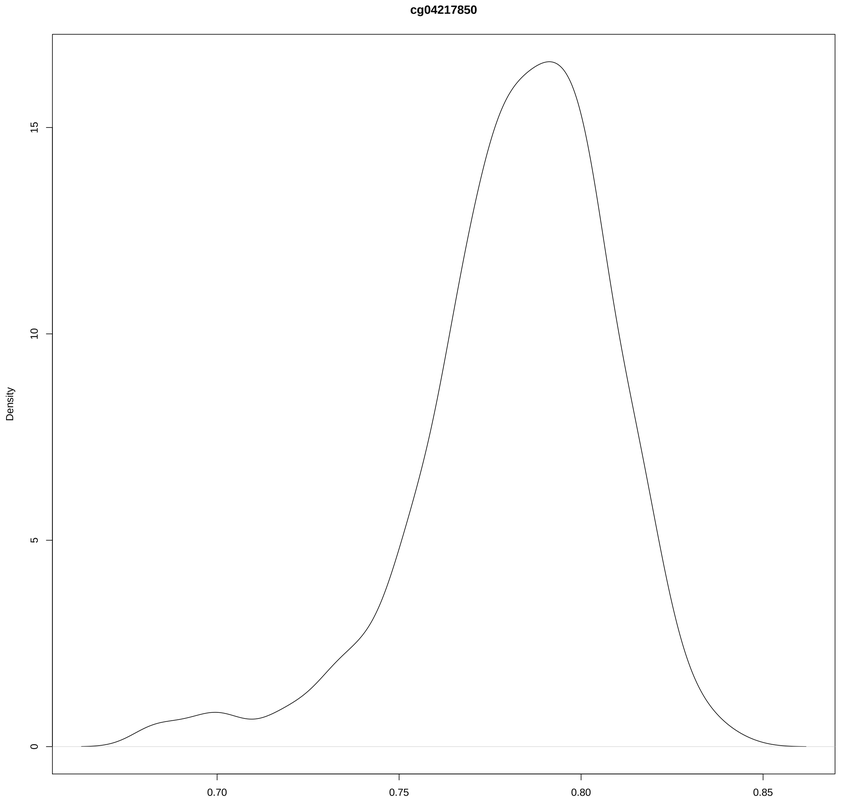
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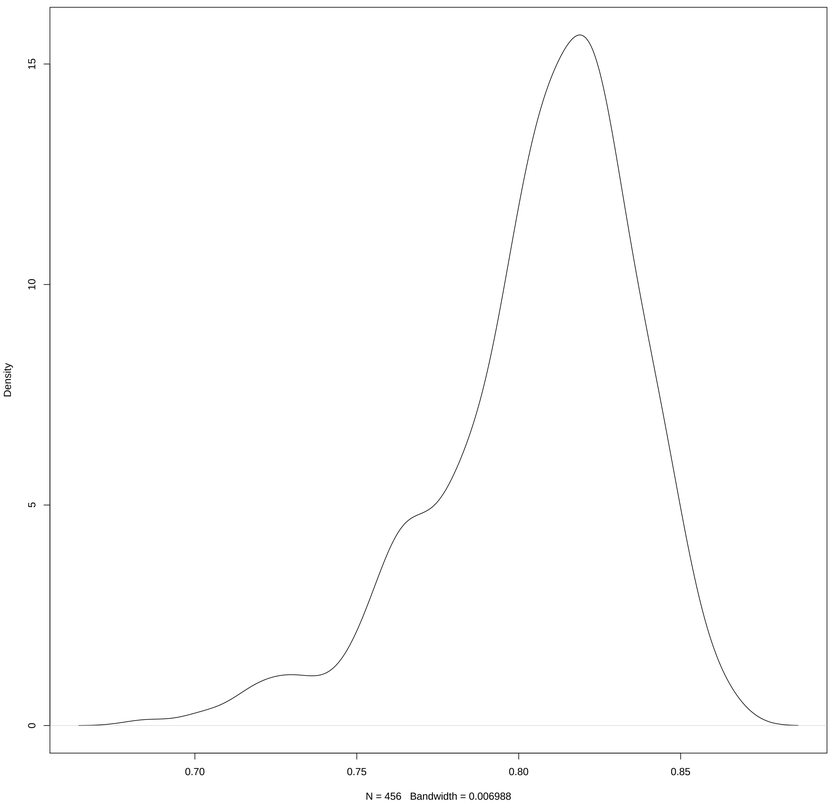
cg07410597



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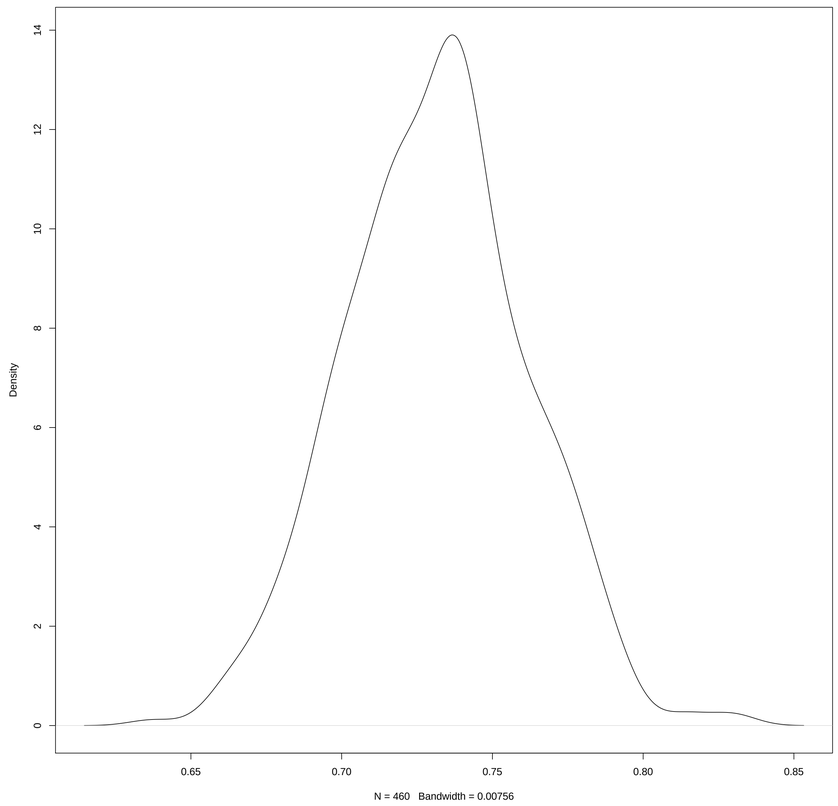

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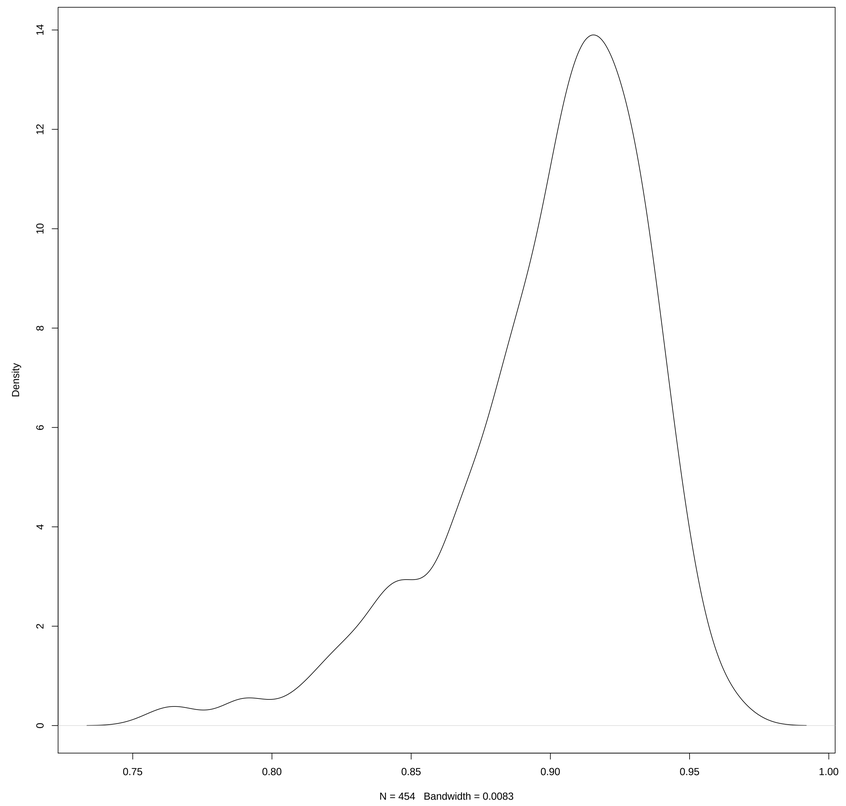

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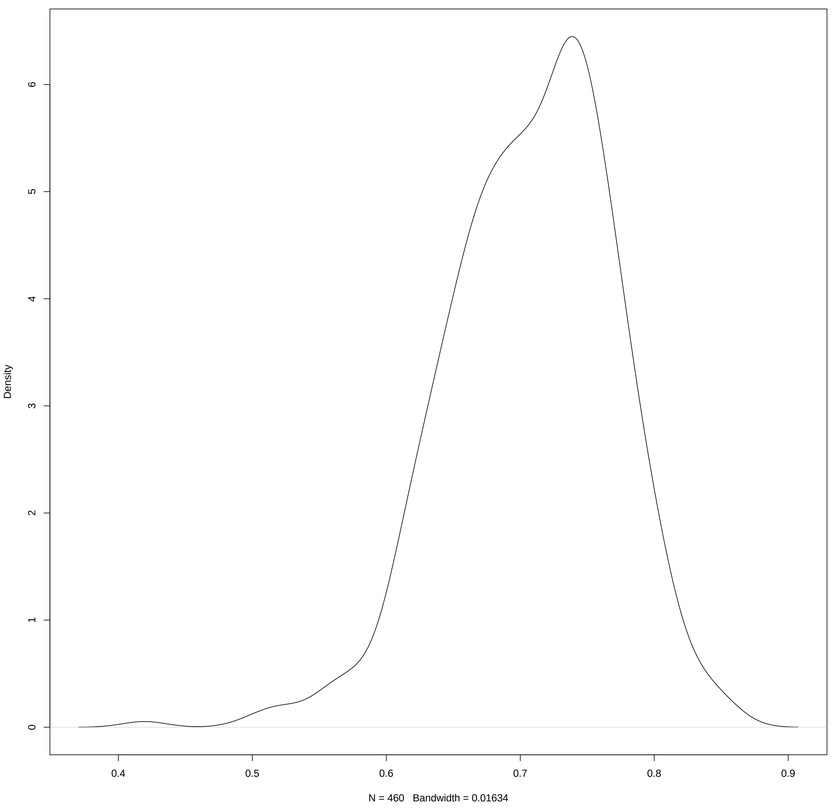

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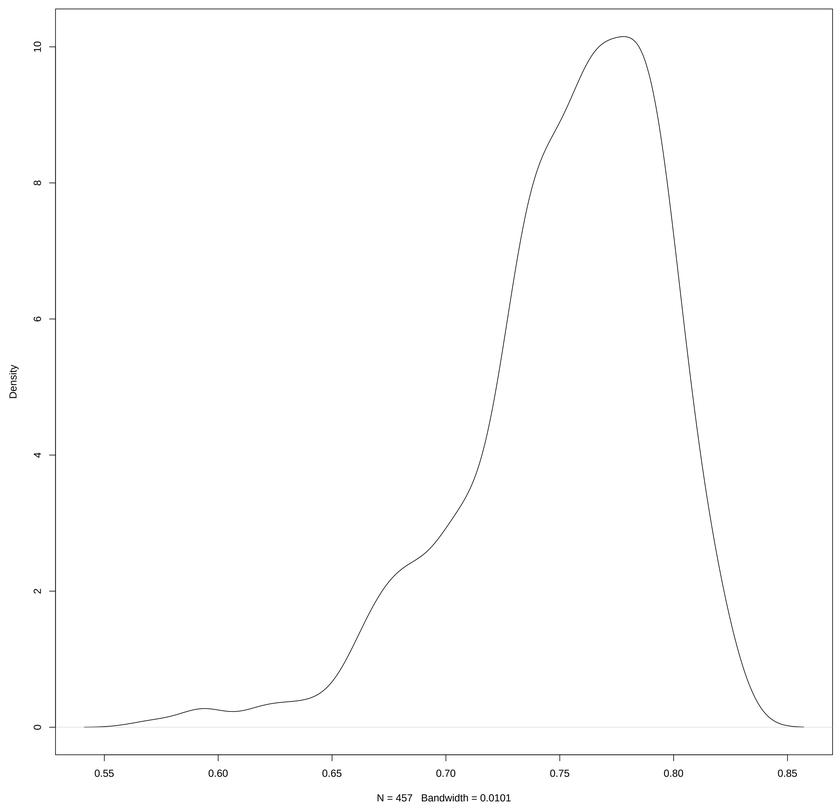

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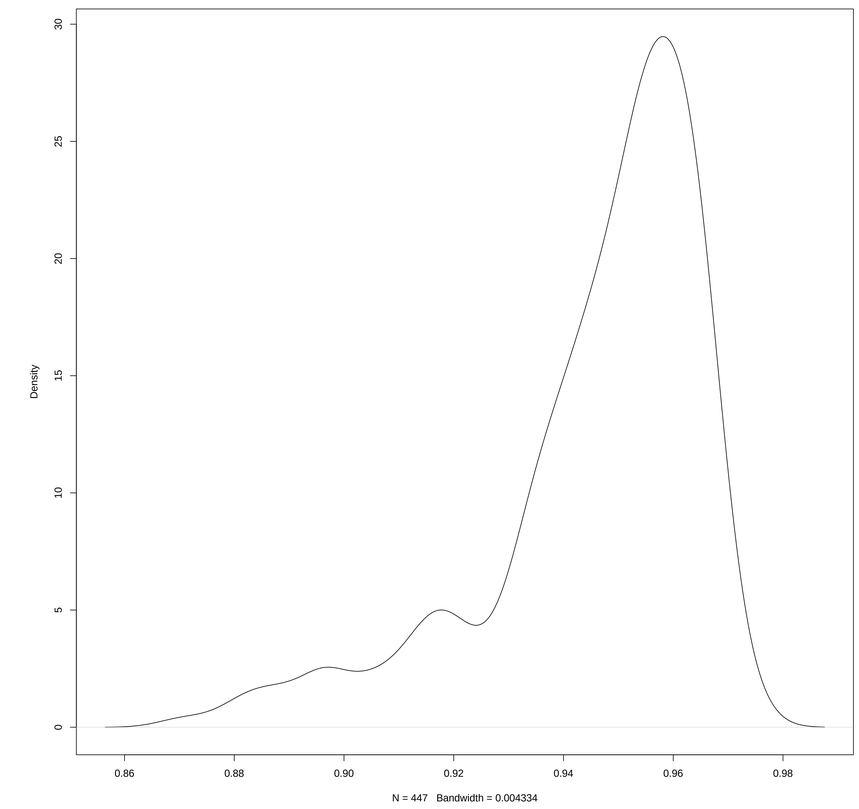

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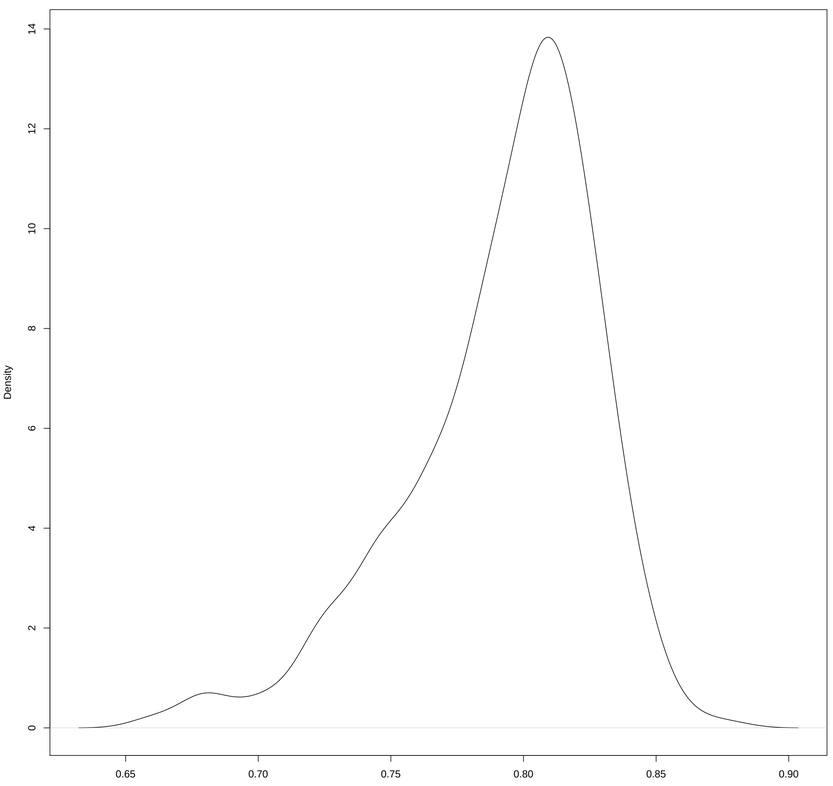

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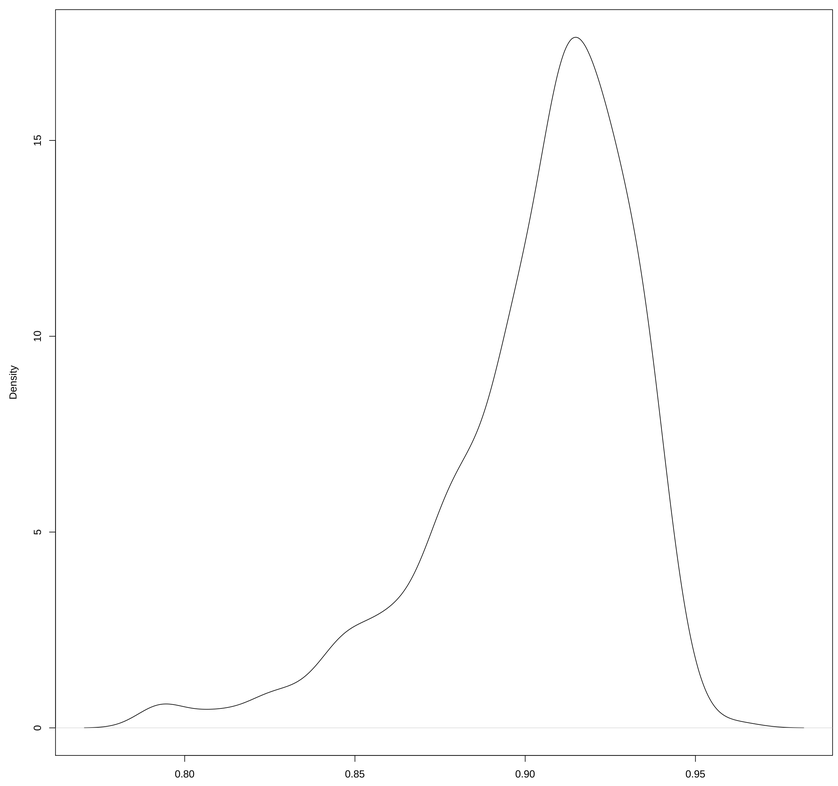

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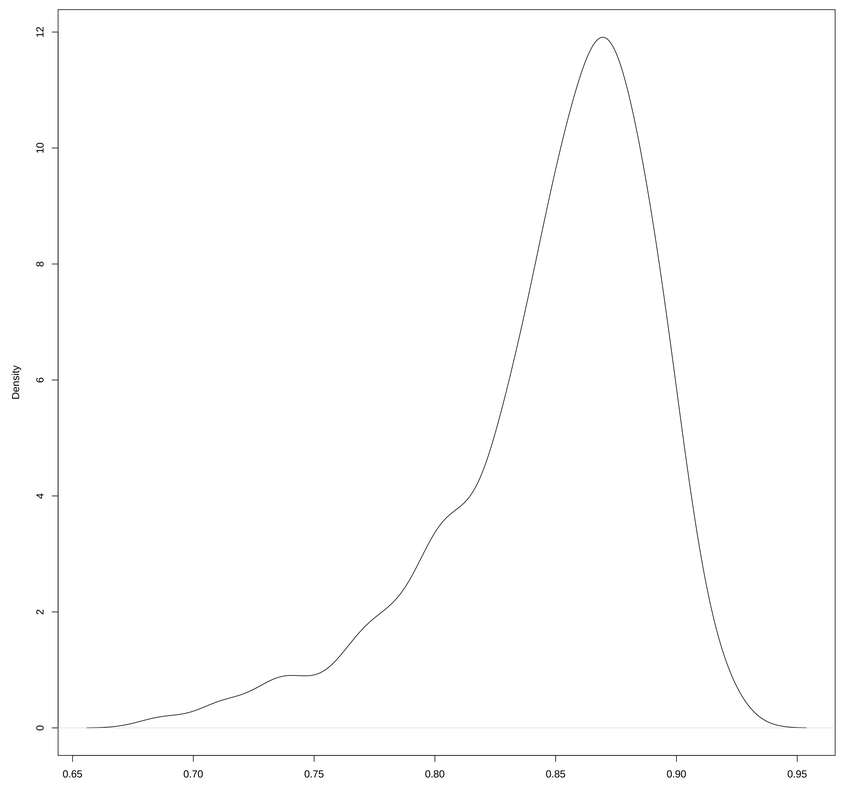

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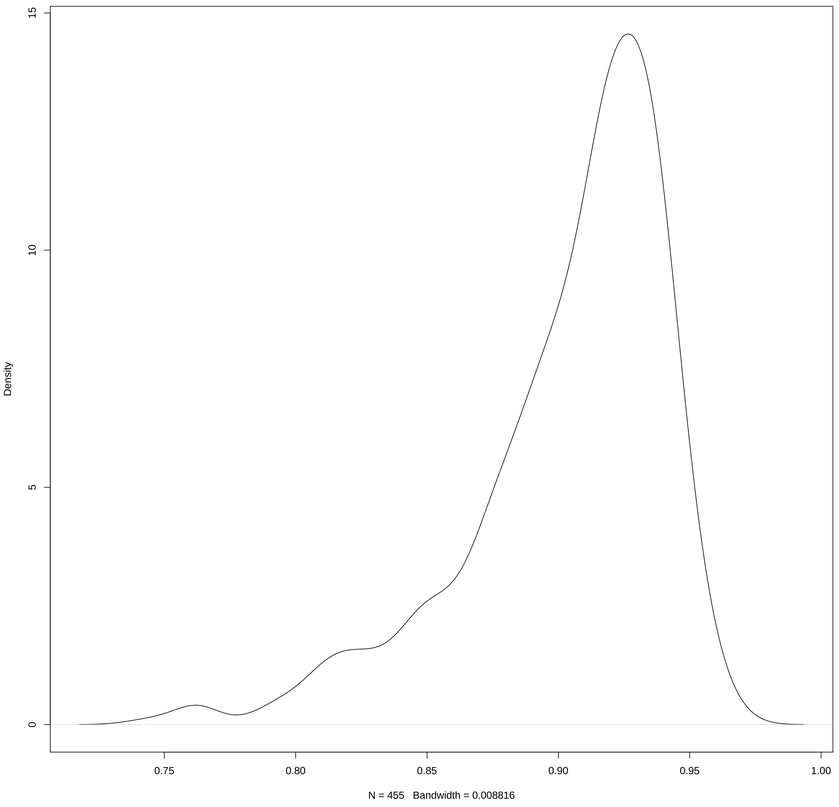

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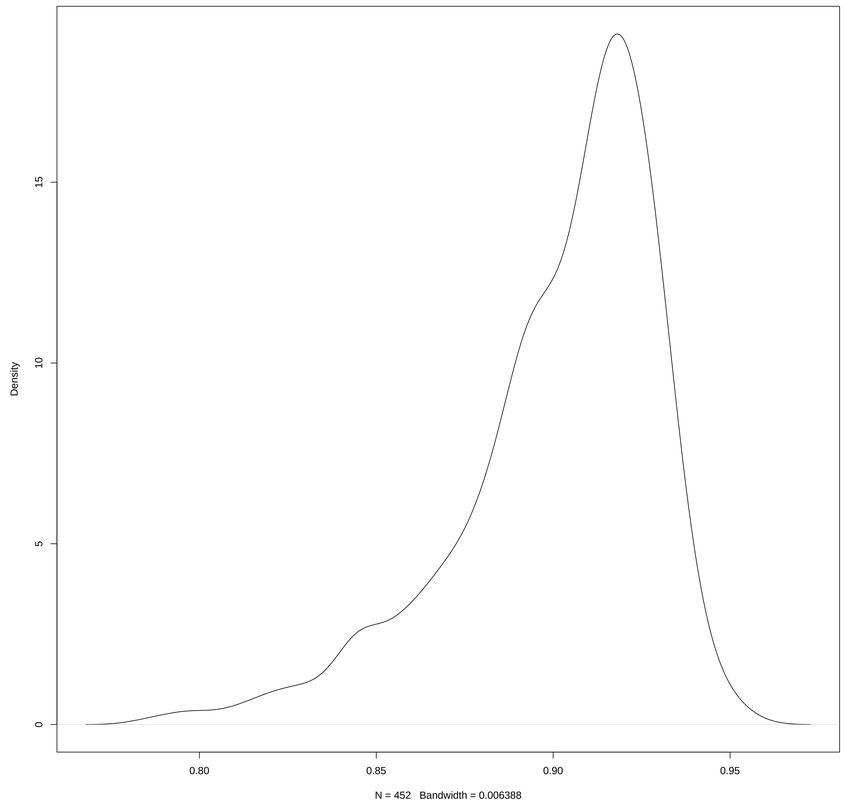

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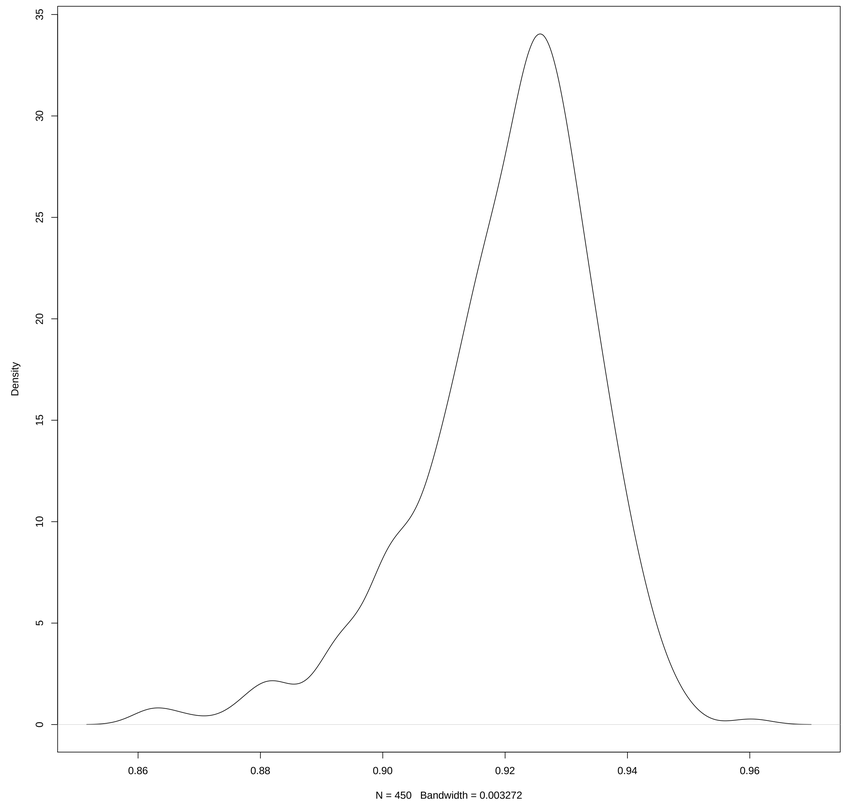

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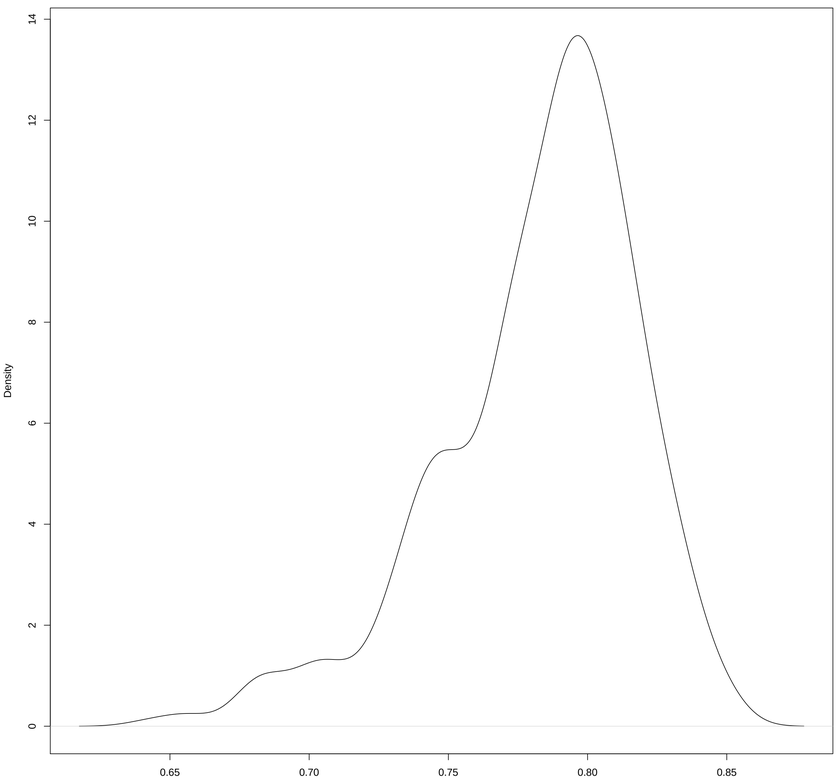

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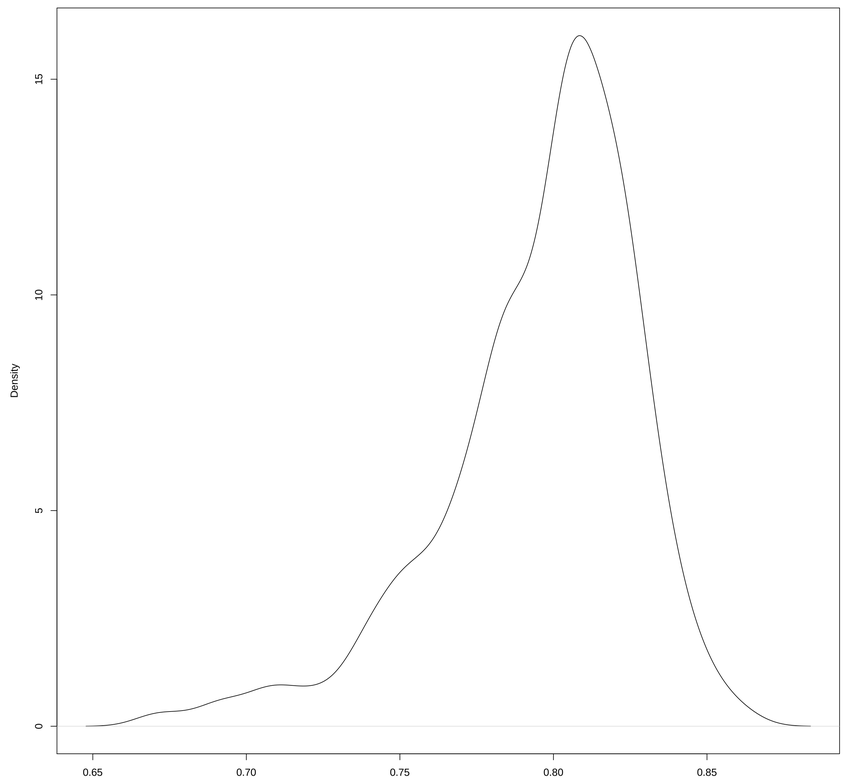

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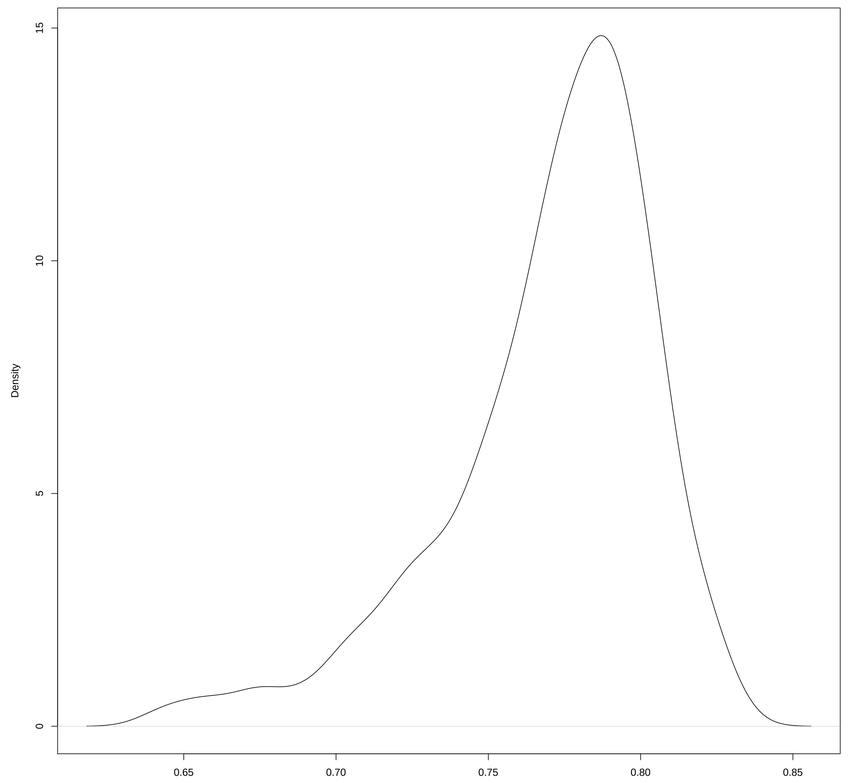

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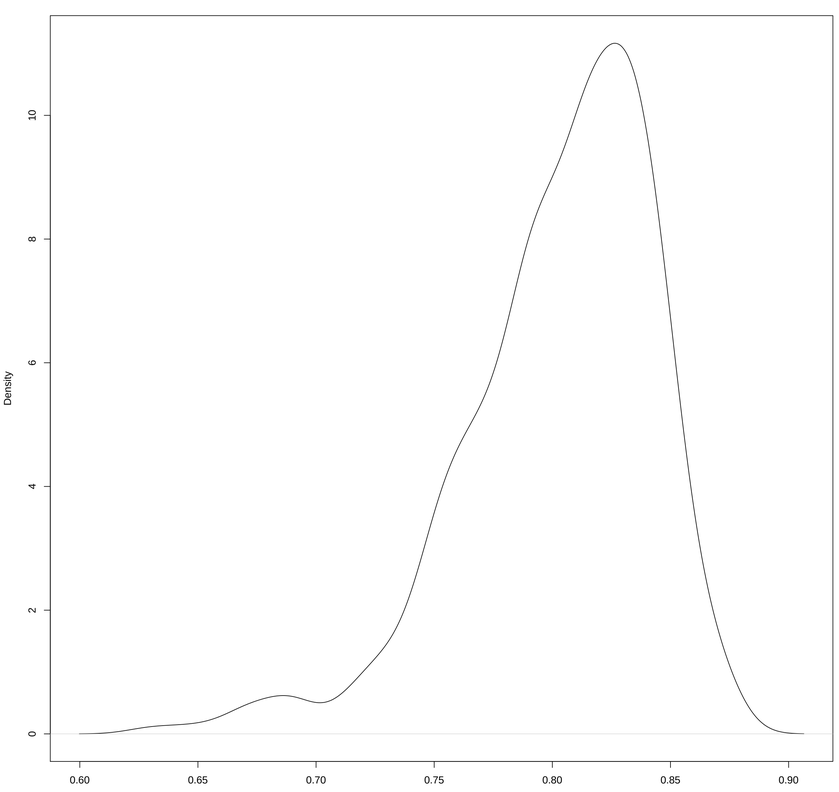

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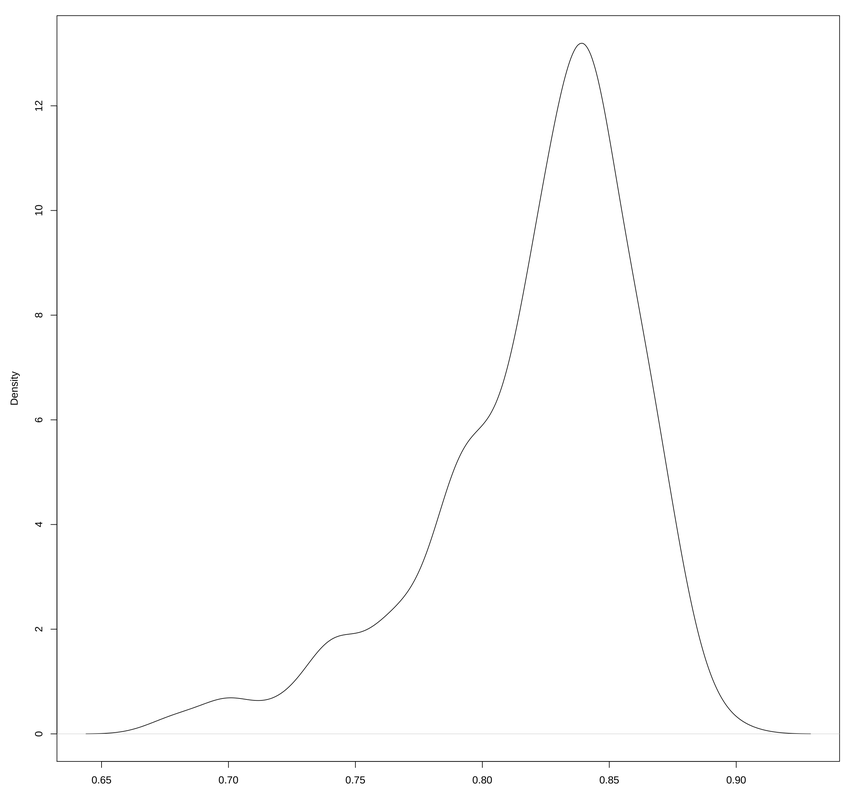

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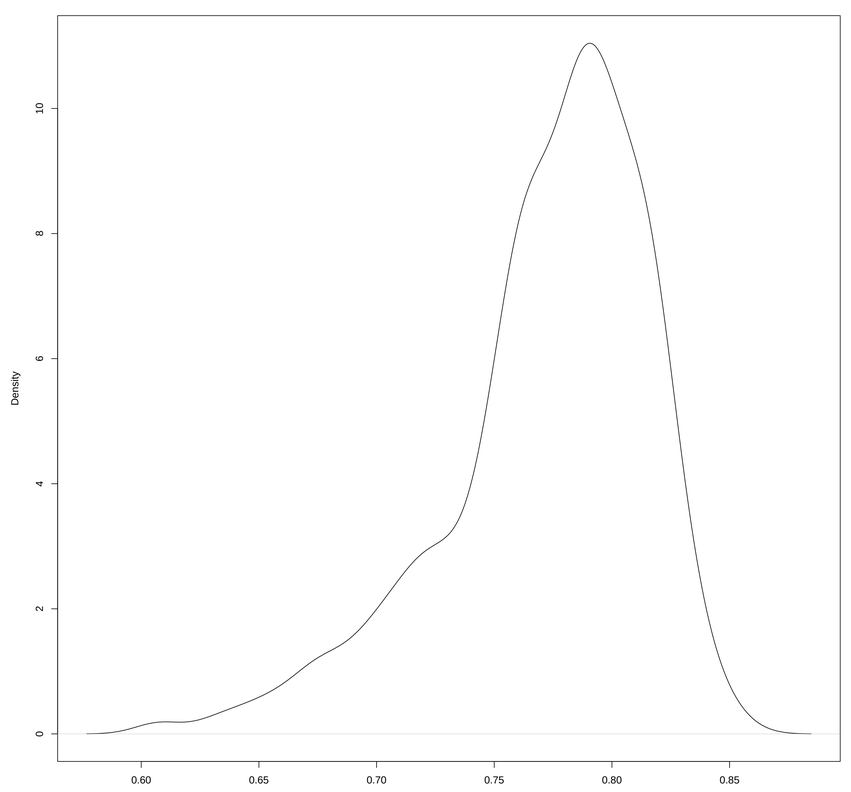

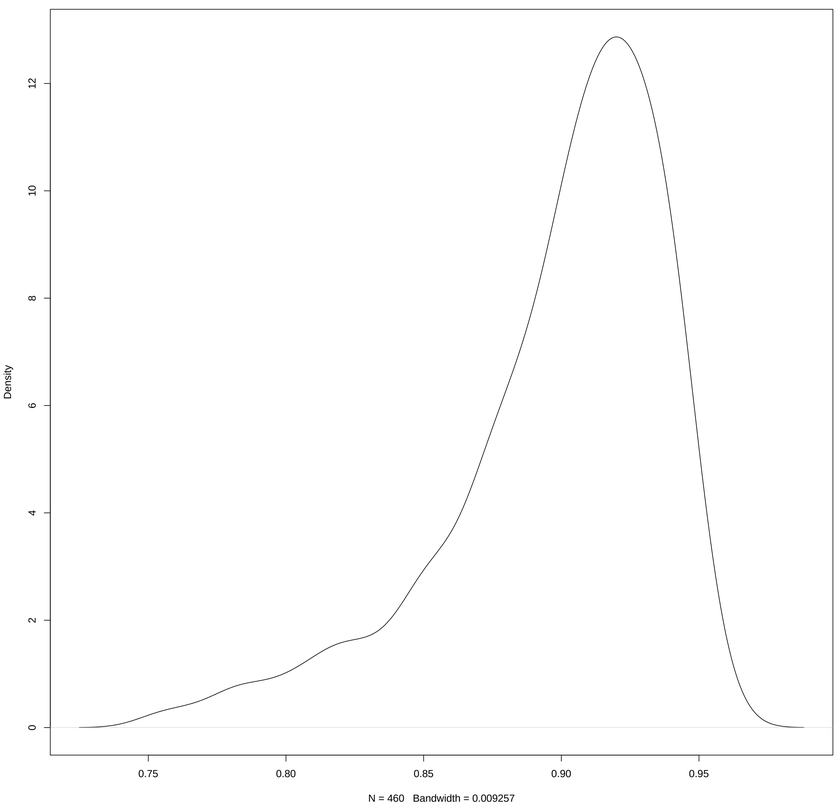
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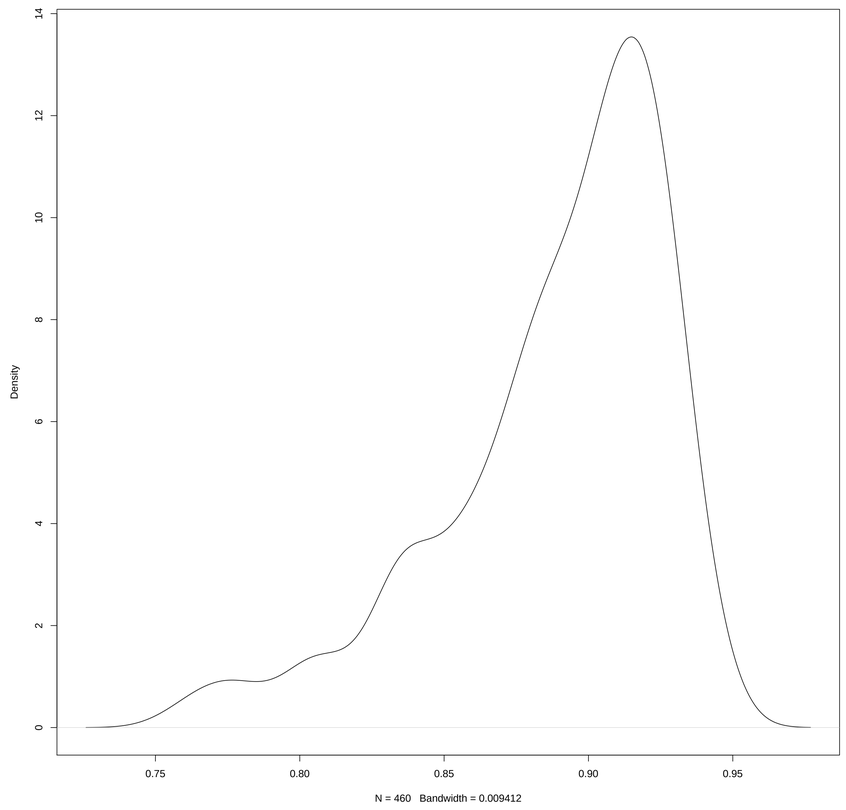
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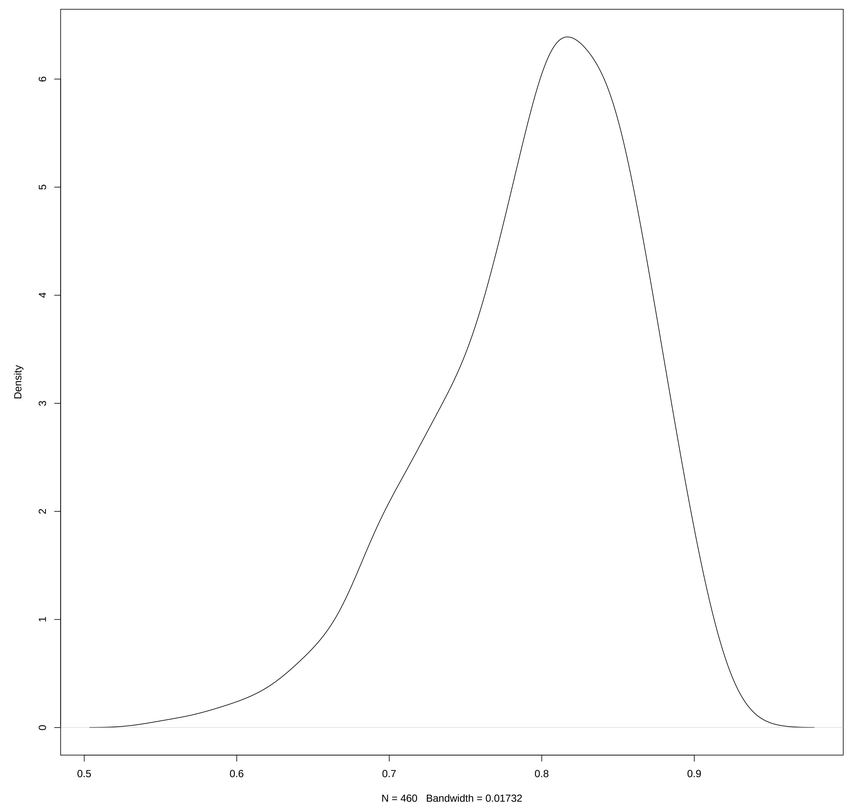
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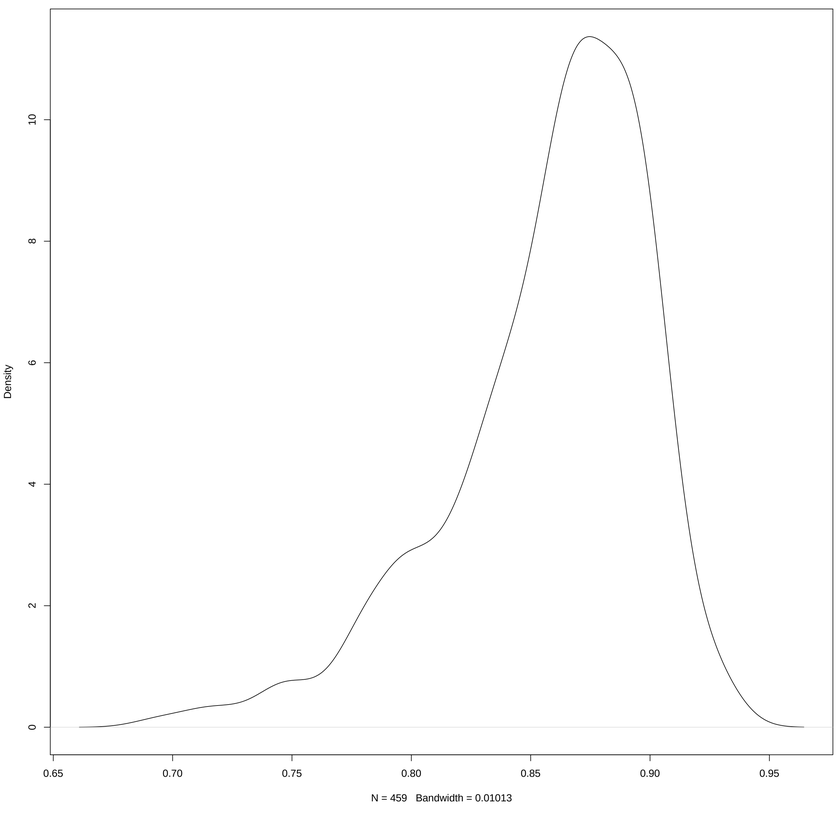
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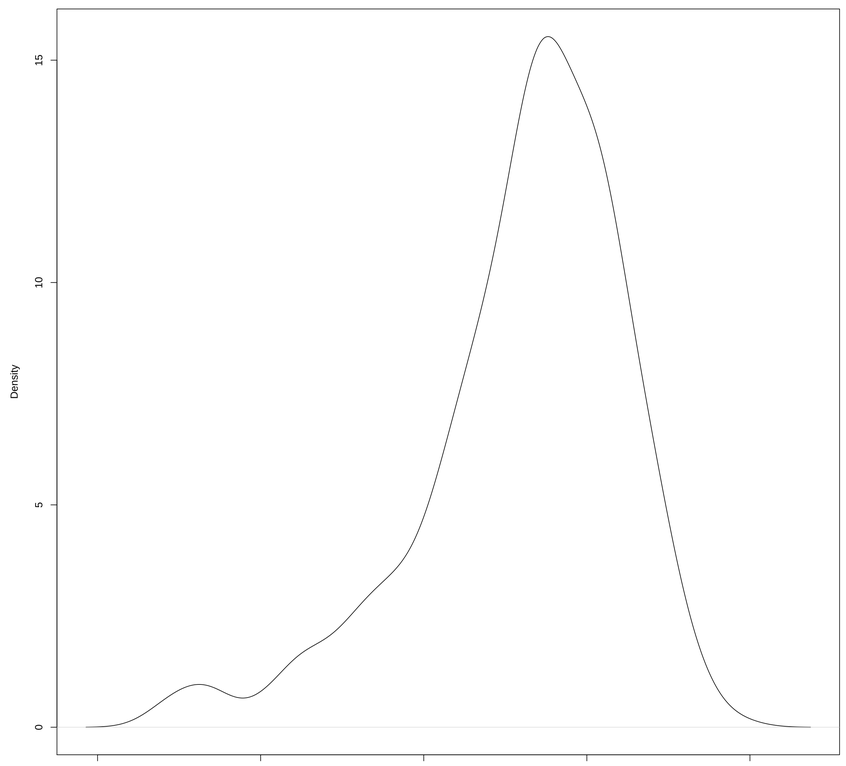
cg25173129
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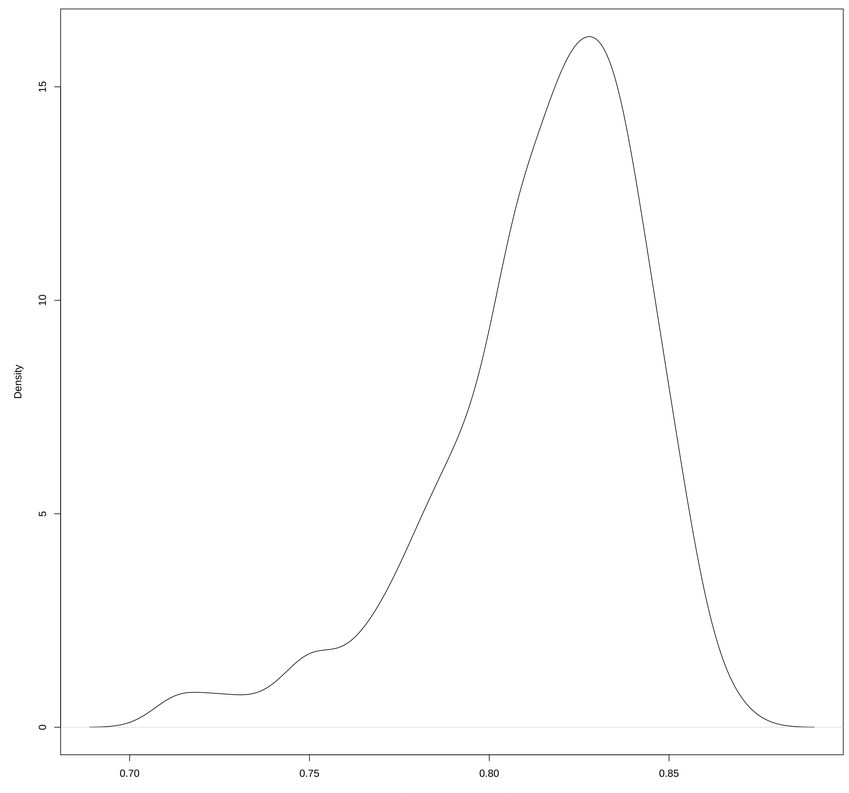
cg02970679
Density
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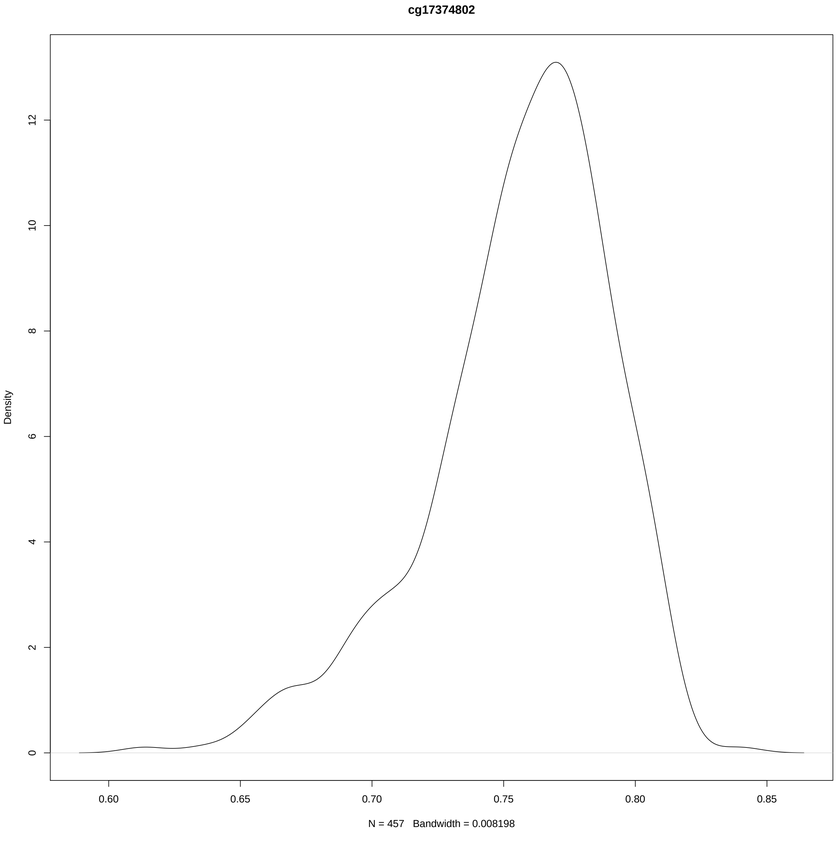
cg17374802
Density
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