Osteoarthritis and Cartilage 30 (2022) 1385–1389

Osteoarthritis and Cartilage

Brief report

The genetic contribution to hand osteoarthritis

K. Magnusson † ‡ *, A. Turkiewicz †, I.K. Haugen §, M. Englund †

† Lund University, Faculty of Medicine, Department of Clinical Sciences Lund, Orthopaedics, Clinical Epidemiology Unit, Remissgatan 4, 221 85 Lund, Sweden
‡ Norwegian Institute of Public Health, Cluster for Health Services Research, Sandakerveien 24C, 0473 Oslo, Norway
§ Diakonhjemmet Hospital, Division of Rheumatology and Research, Diakonveien 12, 0370 Oslo, Norway

ARTICLE INFO

Article history:
Received 11 January 2022
Accepted 18 June 2022

Keywords:
Hand OA
Genetics
Epidemiology

SUMMARY

Objective: To estimate the genetic contribution to doctor-diagnosed hand osteoarthritis (OA).
Methods: Using data from the Swedish Twin Registry and National Patient Register, we conducted a 20-year population-based longitudinal cohort study including 59,970 twins aged 35 years or older. We studied inpatient and outpatient doctor-diagnosed hand OA using ICD-10 codes from 1997 until 2016, including both the distal/proximal interphalangeal (DIP/PIP) joints and/or the first carpometacarpal (CMC-1) joints. We calculated intra-pair correlation, estimated the heritability (i.e., the percentage variation in hand OA that can be explained by genetic factors) as well as a genetic risk.
Results: Among 59,970 included persons, 936 had a hand OA diagnosis registered during the study period. The heritabilities of hand OA (any joint), CMC-1 OA and DIP/PIP OA were ~87%, 86% and 48%, respectively, yet the two latter should be interpreted with care due to low numbers. Hand OA in any joint in both twins in a pair occurred more frequently in identical twins (54/554 = 9.7%, intra-pair correlation = 0.54, 95% CI = 0.44–0.63) than in fraternal twins (18/1,246 = 1.4%, intra-pair correlation = 0.10, 95% CI = −0.01–0.22). Identical twins who were diagnosed with hand OA in any joint had a far higher risk than fraternal twins with hand OA to also have their co-twin diagnosed with hand OA in any joint (Hazard Ratio = 6.98, 95% CI = 3.08–15.45).
Conclusion: The genetic contribution to hand OA is high and likely varying between 48% and 87%. Potential differential heritability by hand OA phenotypes should be further explored.

Introduction

Osteoarthritis (OA) in the closest family has previously been reported to increase the risk of future hand OA[1]. Whereas familial clustering including genetic factors contributing to hip and knee OA has been thoroughly studied in large scale population-based twin registry studies[2–5], such studies are lacking for hand OA. Twin studies are useful in disentangling the genetic vs environmental contribution to joint diseases by allowing for the estimation of heritability. The heritability, or genetic contribution, is the percentage of the variance in a trait that can be ascribed to genetic factors.

In smaller surveys and clinical twin studies, the genetic contribution seems to be greater for hand OA than for hip and knee OA[6,7]. For example, the heritability of hand osteophytes and finger joint space narrowing was reported to be 59% (95% CI = 49–70%) in a British study of 250 twins, whereas the heritability was 39% (95% CI 26–52%) for knee osteophytes and knee joint space narrowing in the same study sample[6]. Familial factors also seem to be of relevance in other types of family-based studies of hand OA[8,9]. Findings from Iceland imply that the familial influence on hand OA increases with the disease severity of both distal/proximal interphalangeal (DIP/PIP) and first carpometacarpal (CMC-1) involvement (9).

Existing studies are typically based on small samples with strict selection criteria, exploring the genetic contribution to radiographic and symptomatic hand OA definitions separately. With the knowledge that the impact of genetic factors may be different for radiographic features and joint pain[10,11], more knowledge is needed regarding the genetic contribution to combined pain and structural features in a clinically relevant hand OA diagnosis in a population-based sample. Thus, to gain new insights into the etiology of clinically-relevant hand OA, our aim was to estimate the genetic contribution to doctor-diagnosed hand OA in ~60,000 Swedish twins.

* Address correspondence and reprint requests to: K. Magnusson, Clinical Epidemiology Unit, Orthopaedics, Department of Clinical Sciences Lund, Lund University, Remissgatan 4, Wigerthuset, 221 85 Lund, Sweden. Tel.: 47-991-16-463.
E-mail address: karin.magnusson@med.lu.se (K. Magnusson).

https://doi.org/10.1016/j.joca.2022.06.011

Material and methods

Using data from the world's largest twin registry (the Swedish Twin Registry linked with the National Patient Register of inpatient and outpatient specialist care (individual level)), we conducted a 20-year population-based longitudinal cohort study including 59,970 twins born in 1911–77. A twin pair (only those with known zygosity: monozygotic/identical (MZ) and dizygotic/fraternal (DZ)) was included from the year they turned 35 years or older and when both twins in the pair were alive and had at least 1 year of follow-up (before e.g., moving, dying or being censored at study end). Thus, singletons were excluded (i.e., twins in pairs were only one twin was alive at baseline).

Outcome

We studied doctor-diagnosed hand OA using ICD-10 codes from 1997 until 2016, including OA codes both for the CMC-1 joint (M18) as well as for the DIP/PIP joints (M15, M19.0D, M19.1D or M19.2D). We categorized the codes into three study outcomes: 1) Hand OA, including both DIP/PIP OA and CMC-1 OA, 2) CMC-1 OA only, and 3) DIP/PIP OA only. A concordant twin pair is a pair in which both twins have the outcome. Thus, as an example for the first outcome (hand OA), a concordant twin pair could consist of one twin with DIP/PIP OA and the other twin with CMC-1 OA, but also of pairs with both twins having OA at the same joint sites. For the two latter outcomes (DIP/PIP OA and CMC-1 OA), we required both twins in the pair to have OA at the specific joint site in order to be counted as a concordant twin pair. Data from the Swedish Patient Register has been found to be high for most diagnoses, with a positive predictive value of 85–95%.

Statistical analyses

We first described individual characteristics of our study sample as well as the number of concordant pairs and discordant pairs, for MZ and DZ twins (discordant pairs are pairs in which only one twin has the diagnosis in question). We secondly estimated the intra-class correlation coefficient (ICC) of hand OA for MZ and DZ twins. If genetic effects are important, we would expect MZ twins to be more concordant and correlated for hand OA than DZ twins. Based on the ICCs, we also estimated the heritability (Falconers formula, $2(ICC_{MZ} - ICC_{DZ})$.). We did not estimate any classical twin models (e.g., ACE or ADE model), in order to avoid too many modelling assumptions and lack of comparability across the included diagnoses (for example, that an ACE model was the best fitting for one outcome, and an ADE model the best fitting for another outcome). Finally, we used zygosity as a proxy for genetic risk (MZ = 1, DZ = 0 (reference category)) and studied the time from the first twin was diagnosed with hand OA, until the second twin was diagnosed with hand OA (0–20 years and only studying the "at-risk" for concordance pairs), using the cumulative incidence function (where death and end of study were censoring events) and using Cox regression model adjusted for age, sex, education level (four levels), marital status (married or registered partner yes/no) and the mean annual income, all registered in years 1997–2015 (choosing the earliest record). Socioeconomic factors are closely related to health-seeking behavior, which was needed for the patient to have a hand OA diagnosis. Such factors are often more shared within MZ pairs than within DZ pairs, and we adjusted for the selected covariates to avoid an inflated genetic risk (i.e., crude measures of genetic risk may be inflated by shared environmental factors). All analyses were run in STATA MP v. 17.

Results

Among 80,740 twins and singletons registered in the Swedish Twin Register, we identified 59,970 twins in complete pairs, i.e., where both twins could be observed for at least 1 year after follow-up. Thus, we excluded 10,810 singletons as well as 6,442 twins in pairs where at least one of the twins died or emigrated during the first year of follow-up.

Among the 59,970 included persons, 936 had a hand OA diagnosis registered during the study period. Persons who had a hand OA diagnosis during the follow-up period tended to be older, more often women, more often married and have a lower education and income than observed in the total sample (Table I).

The genetic contribution to hand OA in any joint

The heritability of hand OA in any joint was ~87% (Table I). Thus, hand OA in both twins in a pair occurred more frequently in identical twins (54/554 = 9.7%, intra-pair correlation = 0.54, 95% CI = 0.44–0.63) than in fraternal twins (18/1,246 = 1.4%, intra-pair correlation = 0.10, 95% CI = −0.01–0.22), which is indicates a strong genetic component in hand OA. We observed only four fraternal female pairs and 0 fraternal male pairs with both twins having hand OA, respectively, and thus, intra-pair correlations could not be compared and sex differences could not be calculated. Identical twins who were diagnosed with hand OA in any joint had a far higher risk than fraternal twins with hand OA to also have their co-twin diagnosed with hand OA in any joint, when adjusted for environmental factors (Fig. 1).

The genetic contribution to CMC-1 OA vs DIP/PIP OA

We also observed few pairs with both twins having CMC-1 OA, or both twins having DIP/PIP OA only (Table I). However, the estimates suggest a difference in genetic contribution for the two joint sites. Whereas the difference between MZ and DZ correlation was high, with non-overlapping 95% CIs for CMC-1 OA, the difference between MZ and DZ correlation was lower, with overlapping 95% CIs for DIP/PIP OA. Accordingly, the heritability was estimated to be 86% vs 48%, for CMC-1 OA and DIP/PIP OA, respectively.

Discussion

In this study of ~60,000 Swedish twins aged 35 years or older, we report a strong genetic component for hand OA, with a heritability of around 48–87%. This finding is high when compared to other OA sites and other diseases with known familial clustering. As an example, cancer (in general) has a heritability of 33% and eye color a heritability of 98%[12,13]. Potential sex differences in the heritability of hand OA and its different phenotypes (CMC-1 vs DIP/PIP OA) should be further explored.

To our knowledge, our study is the first population-based study of the genetic contribution to a clinically relevant hand OA diagnosis. Our findings confirm previous indications that the genetic contribution seems to be greater for hand OA than for hip and knee OA in smaller surveys and clinical studies[6,7]. For example, the heritability of clinically-relevant hand OA in any joint in our study sample was 87%, which is higher than the heritability of 53% for clinically-relevant knee OA in the same study sample[4]. Although results must be interpreted with great caution, we also found a potentially stronger genetic component in CMC-1 OA than in DIP/PIP OA. Previous studies have reported a more or less similar heritability for osteophytes at the CMC-1 joint vs IP joints, yet support that the genetics of hand OA should be studied in specific phenotypes[14]. Our findings imply that a phenotypic approach is

	Total	Hand OA (any joint)	CMC OA	DIP/PIP OA
Individual twins, n	59,970	936	542	470
Age at start of follow-up, mean (SD)	50.2 (13.4)	51.4 (9.3)	51.4 (9.4)	51.2 (9.1)
Women, *n* (%)	32,421 (54)	682 (73)	411 (76)	335 (71)
Education, 9 or fewer years, *n* (%)	18,094 (30)	262 (28)	158 (29)	126 (27)
Education, 10–12 years, *n* (%)	24,913 (42)	434 (46)	256 (47)	212 (45)
Education, 13–14 years, *n* (%)	7,118 (12)	108 (12)	71 (13)	49 (10)
Education, 15 or more years, *n* (%)	9,844 (16)	132 (14)	57 (11)	83 (18)
Married, *n* (%)	40,935 (68)	783 (84)	459 (85)	390 (83)
Annual income, mean (SD) 100,000 SEK	1.6 (1.5)	1.4 (1.2)	1.4 (1.2)	1.4 (1.2)
Twin pairs, n				
Identical twins	9,475			
Pairs without the outcome, n		9,198	9,314	9,330
Concordant pairs, n		27	14	5
Discordant pairs, n		250	147	140
Fraternal twins	20,510			
Pairs without the outcome, n		19,887	20,147	20,193
Concordant pairs, n		9	4	3
Discordant pairs, n		614	359	314
Genetic contribution measures				
Intra-pair correlation (rMZ) (95% CI)		0.54 (0.44–0.63)	0.56 (0.44–0.68)	0.38 (0.19–0.55)
Intra-pair correlation (rDZ) (95% CI)		0.10 (−0.01–0.22)	0.14 (−0.03–0.30)	0.13 (−0.05–0.31)
Heritability (2*[rMZ-rDZ])		87	86	48

* CMC, carpometacarpal; DIP, distal interphalangeal; PIP, proximal interphalangeal. Concordant pairs are pairs with both twins having the outcome. Discordant pairs are pairs with one twin having the outcome.

Table I

Osteoarthritis and Cartilage

Descriptive characteristics, intraclass correlation coefficients and genetic contribution measures

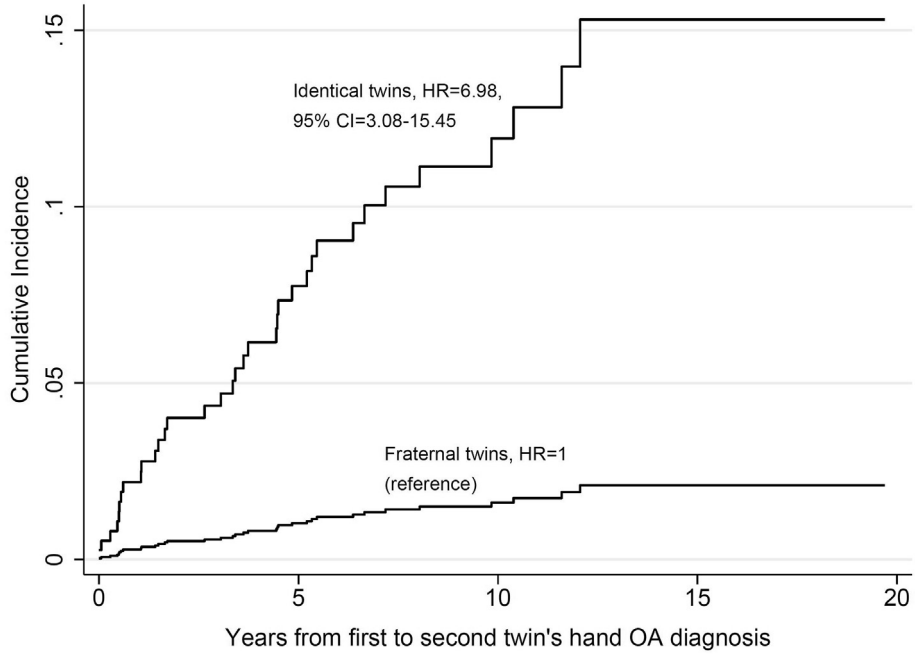

Fig. 1

Osteoarthritis and Cartilage

The cumulative incidence and hazard ratio (HR) of co-twin being diagnosed with hand osteoarthritis (OA) for index twins who were already diagnosed with hand OA. HRs were adjusted for age, sex, education status, marriage and mean annual income.

appropriate also in future studies of genetics of clinically-relevant hand OA. Such studies should include sex differences, as we had too low (site-specific) concordances for male and female twin pairs.

A number of important limitations should be mentioned. First, we studied hand OA diagnoses made in specialist care, which may imply we only captured the most severe or painful hand OA. Thus, we cannot infer whether our findings also apply to less symptomatic hand OA, which is often managed in primary care only. Differences in severity grade and subsequent healthcare use might explain the higher number of discordant than concordant twins with hand OA, i.e., it is possible that one twin in a pair went to specialist care whereas the other went to primary care. If so, our heritability estimates may be underestimates. Further, going to the specialist with hand OA may reflect an examination decision or treatment decision made by the general practitioner, and twins in a pair may share the decision to visit their doctor, despite one twin having more complaints from the finger joints than the other. Such shared behavior (which includes health-seeking behavior) may be more common in MZ twin pairs than in DZ twin pairs, and might have inflated our estimates of genetic risk. For example, MZ twins may be more likely than DZ twins to have similar jobs that entail mechanical hand stress, a known hand OA risk factor. Such potential violation of the equal environment assumption is a limitation of all twin studies and can only be avoided in studies of twins who were reared apart[15]. Twin adoptee studies are very seldom because of methodological challenges in obtaining sufficient sample sizes. Further, although such inflation of the heritability estimates may not be avoidable, we adjusted for socioeconomic factors as a proxy for shared socioeconomic factors. We also avoided running classical twin models (i.e., so-called ACDE-models, which are structural equation models estimating the percent of the variance explained by additive or dominant genetic factors (A or D), shared environmental factors (C) and unique environmental factors (E)). Instead, we present heritability as estimated by the Falconers formula. Although this formula may overestimate the heritability, we chose to rely on it here due to its simplicity and transparency[15]. As an important supplement, we report the risk of co-twin's diagnosis of hand OA, adjusted for a range of environmental factors that often are shared by twins.

Conclusion

The genetic contribution to hand OA is high and likely varying between 48% and 87%. Potential differences in the heritability of the different phenotypes in hand OA (CMC vs DIP/PIP OA) should be further explored.

Author contributions

Karin Magnusson had access to all of the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis. Karin Magnusson performed statistical analyses and drafted the manuscript. Aleksandra Turkiewicz, Ida K Haugen and Martin Englund contributed with acquisition of data, conceptual design, analyses and interpretation of results. All authors contributed in drafting the article or critically revising it for important intellectual content. All authors gave final approval for the version to be submitted.

Role of the funder

This study was funded by the Swedish Research Council (E0234801), the Greta and Johan Kock Foundation, the Swedish Rheumatism Association, the Österlund Foundation, Governmental Funding of Clinical Research within the National Health Service (ALF) and the Faculty of Medicine, Lund University, Sweden.

The funding sources had no influence on the design or conduct of the study, the collection, management, analysis, or interpretation of the data, the preparation, review, or approval of the manuscript, or the decision to submit the manuscript for publication.

Conflict of interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgements

We would like to acknowledge The Swedish Twin Registry and Barbro Sandin and Patrik Magnusson for access to the data and data management. The Swedish Twin Registry is managed by Karolinska Institute and receives funding through the Swedish Research Council under the grant no 2017-00641.

References

1. Weldingh E, Johnsen MB, Hagen KB, Østerås N, Risberg MA, Natvig B, *et al*. The maternal and paternal effects on clinically and surgically defined osteoarthritis. Arthritis Rheumatol 2019;71(11):1844–8.
2. Magnusson K, Scurrah K, Ystrom E, Orstavik RE, Nilsen T, Steingrimsdottir OA, *et al*. Genetic factors contribute more to hip than knee surgery due to osteoarthritis - a population-based twin registry study of joint arthroplasty. Osteoarthritis Cartilage 2017;25(6):878–884016.
3. Skousgaard SG, Skytthe A, Moller S, Overgaard S, Brandt LP. Sex differences in risk and heritability estimates on primary knee osteoarthritis leading to total knee arthroplasty: a nationwide population based follow up study in Danish twins. Arthritis Res Ther 2016;18(1):46.
4. Magnusson KTA, Englund M. Nature vs. nurture in knee osteoarthritis – the importance of age, sex and body mass index. Osteoarthritis Cartilage 2019 Apr;27(4):586–92.
5. Skousgaard SG, Hjelmborg J, Skytthe A, Brandt LP, Moller S, Overgaard S. Probability and heritability estimates on primary osteoarthritis of the hip leading to total hip arthroplasty: a nationwide population based follow-up study in Danish twins. Arthritis Res Ther 2015;17:336.
6. Spector TD, Cicuttini F, Baker J, Loughlin J, Hart D. Genetic influences on osteoarthritis in women: a twin study. BMJ 1996;312(7036):940–3.
7. Kujala UM, Leppavuori J, Kaprio J, Kinnunen J, Peltonen L, Koskenvuo M. Joint-specific twin and familial aggregation of recalled physician diagnosed osteoarthritis. Twin Res 1999;2(3):196–202.
8. Riyazi N, Meulenbelt I, Kroon HM, Ronday KH, Hellio le Graverand MP, Rosendaal FR, *et al*. Evidence for familial aggregation of hand, hip, and spine but not knee osteoarthritis in siblings with multiple joint involvement: the GARP study. Ann Rheum Dis 2005;64(3):438–43.
9. Jonsson H, Manolescu I, Stefansson SE, Ingvarsson T, Jonsson HH, Manolescu A, *et al*. The inheritance of hand osteoarthritis in Iceland. Arthritis Rheum 2003;48(2):391–5.

10. Williams FM, Spector TD, MacGregor AJ. Pain reporting at different body sites is explained by a single underlying genetic factor. Rheumatology (Oxford) 2010;49(9):1753–5.
11. MacGregor AJ, Li Q, Spector TD, Williams FM. The genetic influence on radiographic osteoarthritis is site specific at the hand, hip and knee. Rheumatology (Oxford) 2009;48(3):277–80.
12. Mucci LA, Hjelmborg JB, Harris JR, Czene K, Havelick DJ, Scheike T, *et al*. Familial risk and heritability of cancer Among twins in nordic countries. JAMA 2016;315(1):68–76.
13. Bito LZ, Matheny A, Cruickshanks KJ, Nondahl DM, Carino OB. Eye color changes past early childhood. The Louisville Twin Study. Arch Ophthalmol 1997;115(5):659–63 (Chicago, IL: 1960).
14. Ishimori ML, Altman RD, Cohen MJ, Cui J, Guo X, Rotter JI, *et al*. Heritability patterns in hand osteoarthritis: the role of osteophytes. Arthritis Res Ther 2010;12(5):R180.
15. Mayhew AJ, Meyre D. Assessing the heritability of complex traits in humans: methodological challenges and opportunities. Curr Genom 2017;18(4):332–40.