# Supplemental Information

## VACTERL questionnaire for participating registries

**Personal information:**

Registry : ……

Country: ……

Name : ……

Email: ……

Date: ……

**Diagnosis of the VACTERL association**

1. What is considered as VACTERL association within your registry?

   **Multiple answers might apply**

*VACTERL is an acronym for the association that includes vertebral defects (V), anorectal malformations (A), cardiac malformations (C), esophageal atresia with or without tracheooesophageal fistula (TE), renal anomalies (R) and (radial) limb anomalies (L).*

   - A diagnosis of VACTERL made in the clinic
   - Three or more anomalies part of the VACTERL association
   - Three or more anomalies part of the VACTERL association, but other congenital anomalies not part of the VACTERL association might be present
   - Other, please specify:

   ……

   ……

2. Sometimes, patients with VACTERL malformations also have features that belong to another syndrome / association. How would these patients be registered?

   a. VACTERL patients with a clinical diagnosis of caudal regression syndrome:
      - Registered as VACTERL association
      - Registered as caudal regression syndrome
      - Registered as both VACTERL association and caudal regression syndrome

   b. VACTERL patients with a clinical diagnosis of MURCS association:
      - Registered as VACTERL association
      - Registered as MURCS association
      - Registered as both VACTERL association and MURCS association

3. Are genetic tests routinely carried out to rule out other diagnoses with overlapping features?

- Yes
- No

4. What is the profession of the person who is making the VACTERL diagnosis in the clinic?
   - Clinical geneticist
   - Pediatrician
   - Nurse
   - Researcher
   - Other, please specify: ……

5. Are children with 3 or more anomalies part of the VACTERL association, **<u>without</u> any notification of VACTERL in the medical files,** listed with the VACTERL code within your registry?
   - Yes
   - No, we only register the individual congenital anomalies

6. Are children with 3 or more anomalies part of the VACTERL association, **<u>with</u> the notification of VACTERL in the medical files,** listed with the VACTERL code within your registry?
   - Yes
   - No, we only register the individual congenital anomalies

7. Does your registry code all individual anomalies of a person that are part of the VACTERL association?
   - Yes → go to question 8
   - No → go to question 9
8. For which birth years:
   ……

9. Is single umbilical artery (Q270, 7475) routinely registered within your registry?
   - Yes
   - No

**Additional comments:**

……
……
……
……

## Rationale for inclusion of the major and minor VACTERL features

Vertebral anomalies:

We included segmentation defects, vertebral fusions, costo-vertebral defects, and supernumerary or absent vertebrae as major vertebral VACTERL components [9,10]. Vertebral anomalies are often accompanied by rib anomalies or spinal curvatures without specification of bony malformations [9,10]. Therefore, we included the spinal curvatures, without specification of bony malformations, and rib anomalies as minor vertebral VACTERL features.

Patients with anorectal malformations (ARM) often have dysplastic sacral vertebrae, but it still remains unclear whether these sacral vertebral anomalies should be included as components of the VACTERL association [9]. Therefore, we decided to include the sacral vertebral defects as minor vertebral VACTERL features. When the location of the vertebral defects was not specified, we included the vertebral anomalies as minor vertebral VACTERL features, as we were not able to make a distinction between sacral and non-sacral vertebral anomalies. When the vertebral anomaly was not specified but rib anomalies were also present in the patient, we assumed that the vertebral defect was not located in the sacral region. Therefore, unspecified vertebral anomalies accompanied by rib anomalies were included as a major vertebral VACTERL feature.

Klippel Feil syndrome (OMIM #118100, #214300, #613702, and #616549) is characterized by segmentation defects of the cervical vertebrae. As this is a distinct syndrome, we decided to include Klippel Feil as a minor vertebral VACTERL feature, although the vertebral defects are in the non-sacral region. Patients with Klippel Feil were not excluded from the dataset, as this syndrome only explains the cervical vertebral anomalies, but not other congenital anomalies that are part of the VACTERL association.

Anorectal anomalies:

All types of anorectal malformations were considered to be major component features of the VACTERL association [9]. Based on the clinical expertise of some of our co-authors, we decided that the complex cloacal malformations (persistent cloaca and cloacal exstrophy) are not typically seen in VACTERL patients. Therefore, these cloacal anomalies were included as minor anorectal VACTERL features.

Anorectal malformations are frequently observed in combination with genitourinary (GU) anomalies (Solomon 2014). As these organ systems partly have a shared embryology [23], we decided that GU anomalies in combination with anorectal or renal anomalies were not included as anomalies outside the VACTERL spectrum.

Tethered cord can occur especially in patients with caudal features, such as ARM and GU anomalies [10]. Therefore, we decided that tethered cord in combination with ARM was not included as an anomaly outside the VACTERL spectrum.

Cardiac anomalies:

We included all structural cardiac malformations that affected the cardiac chambers and connections as major VACTERL features [9, 24], except for Q206, isomerism of atrial appendages, which was considered a minor cardiac VACTERL feature.

In addition, all structural cardiac defects affecting the septa were included as major VACTERL features [3, 9, 24]. Congenital malformations affecting the aorta were also included as major cardiac VACTERL features [3, 12, 24]. Patent ductus arteriosus was included as major cardiac VACTERL

feature when it was present in a patient born at a gestational age ≥37 weeks. When it was present in a preterm born baby, the anomaly was not included as major or minor cardiac component feature.

Based on the clinical expertise of our co-authors, we decided that all cardiac anomalies that affected the valves, pulmonary artery, and great veins were included as minor cardiac VACTERL features, as these are not typical for VACTERL. Dextrocardia was included as minor VACTERL feature as it does not always implicate a hemodynamic problem [3]. All other malformations affecting the heart were also included as minor cardiac VACTERL features.

Other circulatory anomalies, for example affecting the peripheral vascular system, were not considered as cardiac component features, as the heart itself or the great arteries/veins were not affected. However, they were not included as major congenital anomalies outside the VACTERL spectrum either, as they are part of the circulatory system to which most VACTERL cardiac component features also belong too.

Esophageal atresia/ trachea-esophageal fistula (EA/TEF):

Consistent with the literature, we included esophageal atresia and all types of tracheo-esophageal fistulas as major VACTERL component features [3, 10, 12, 24]. As this is a very specific component feature of the VACTERL association, no minor EA/TEF VACTERL features were defined.

Other congenital anomalies affecting the esophagus were not included as major or minor VACTERL component features as these are not specific for VACTERL, but they were not included as anomalies outside the VACTERL spectrum either.

Renal anomalies:

There is a wide range of severity and types of renal anomalies. We included renal agenesis and other reduction defects of the kidneys as major renal VACTERL features [3, 9, 12, 25]. In addition, we included dysplastic kidneys as major renal VACTERL features [3, 9, 12, 25]. Polycystic kidneys were not included as a VACTERL component as this anomaly often has a genetic etiology.

As hydronephrosis often occurs secondary to an obstructive defect of the ureter or urethra [25], it was considered as minor renal VACTERL feature, as was vesico-uretero-renal reflux (VUR). In addition, congenital obstructive defects of the renal pelvis and congenital anomalies of the ureter were included as minor renal VACTERL features. Additional anomalies of the kidneys were included as minor renal VACTERL features as well.

As renal anomalies are often accompanied by GU anomalies [9], we did not consider these GU anomalies separately when they occurred in combination with renal anomalies.

Limb anomalies:

We only included classical radial-ray anomalies, including thumb aplasia / hypoplasia, as major limb VACTERL features [3, 9, 12, 24]. All other upper limb defects were included as minor limb VACTERL features. Lower limb anomalies were not considered to be part of the VACTERL spectrum. However, lower limb anomalies were not included as congenital anomalies outside the VACTERL spectrum either, as these are sometimes considered as VACTERL components in the clinic, but also in epidemiologic studies [3, 9].

**Table 1. Specification of anomalies outside the VACTERL spectrum (based on the ICD10 coding for congenital anomalies). A distinction was made between major and minor congenital anomalies.**

| Organ system | Major congenital anomalies (including ICD 10 codes) | Minor congenital anomalies (including ICD 10 codes) |
|---|---|---|
| **Nervous system** | • Anencephaly and similar malformations (Q00)<br>• Encephalocele (Q01)<br>• Microcephaly (Q02)<br>• Congenital hydrocephalus (Q03)<br>• Other congenital malformations of the brain (Q04), **excluding** single congenital cerebral cyst (Q0461)<br>• Spina bifida (Q05)<br>• Other congenital malformations of spinal cord (Q06), including tethered cord (Q068)[a]<br>• Other congenital malformations of the nervous system (Q07), **excluding** Jaw-winking syndrome, Marcus Grunn's syndrome (Q0780) and crocodile tears (Q0782) | • Single congenital cerebral cyst (Q0461)<br>• Jaw-winking syndrome, Marcus Gunn's syndrome (Q0780)<br>• Crocodile tears (Q0782)<br>• Other minor congenital anomalies considered as minor anomalies by EUROCAT (without ICD 10 codes): anomalies of septum pellucidum, arachnoid cysts, asymmetric ventricles normal size, banana shaped cerebellum, cerebellar hypoplasia mild, cerebral atrophy, choroid plexus cysts, cyst of septum pellucidum, enlarged cistern Magana isolated, periventricular leukomalacia, thin or hypoplastic corpus callosum, ventriculomegaly < 15 mm |
| **Eye, Ear, Face, and Neck** | • Congenital ptosis (Q100), absence and agenesis of lacrimal apparatus (Q104), other congenital malformations of lacrimal apparatus (Q106), congenital malformation of orbit (Q107)<br>• Anophthalmos, microphthalmos and macrophthalmos (Q11)<br>• Congenital lens malformations (Q12)<br>• Congenital malformations of anterior segment of eye (Q13), **excluding** blue sclera (Q135)<br>• Congenital malformations of the posterior segment of eye (Q14)<br>• Other congenital malformations of eye (Q15)<br>• Congenital malformations of ear causing impairment of hearing (Q16)<br>• Webbing of neck (Q183) | • Congenital ectropion (Q101), congenital entropion (Q102), other congenital malformations of eyelid (Q103), Congenital stenosis and stricture of lacrimal duct (Q105)<br>• Blue sclera (Q135)<br>• Other congenital malformations of ear (Q17)<br>• Other congenital malformations of face and neck (Q18), **excluding** webbing of neck (Q183)<br>• Micrognatia (K070)<br>• Other minor anomalies considered as minor anomalies by EUROCAT (without ICD 10 codes):<br>  • Dysmorphic face: broad, prominent forehead, coarse facies, flattened face, frontal bossing / wide forehead, mid face hypoplasia, pointed facies, round head shape, sloping forehead, hypotelorism, epicanthus inversus, epicanthus folds, dystopia canthorum, short palpebral fissures, anteverted nares, bifid tip of nose, nasal root, bridge or septum anomalies, dysmorphic nose, underdeveloped nasal bones, philtrum anomalies, prominent jaw, short or broad neck<br>  • Ear: absent tragus, auricular pit, congenital absence of earlobe, narrow |

| | | |
|---|---|---|
| | | external auditory meatus, and Darwin's tubercle<br>• Nose: notched alas<br>• Eyes: anisocoria, oval shaped pupils<br>• Oral region: aberrant frenula, absent/hypoplastic depressor anguli oris (asymmetric crying face), alveolar crest, borderline small mandible / minor micrognathia, disturbances in tooth eruption, enamel hypoplasia, glossoptosis, malformed teeth, microglossia, mid-oral tongue position, neonatal teeth, ranula<br>• Neck: thymus involution, thyreoglossal cyst, hypoplasia/hyperplasia of thymus |
| **Circulatory system** | • Other malformations of peripheral vascular system (Q27), **excluding** single umbilical artery (Q270)<br>• Other congenital malformations of circulatory system (Q28) | • Single umbilical artery (Q270)<br>• Functional or unspecified cardiac murmur (R011)<br>• Cardiomegaly (I517)<br>• Cardiomyopathy (I429)<br>• Other minor congenital anomalies considered as minor anomalies by EUROCAT (without ICD 10 codes): absence of vena cava superior, deviation of heart axis, persistent right umbilical vein |
| **Nose** | • Congenital malformations of nose (Q30) | |
| **Respiratory system**[b] | • Congenital malformations of larynx (Q31), **excluding** laryngeal stridor, laryngomalacia and laryngeal stridor (Q314)<br>• Other congenital malformations of trachea (Q321), congenital stenosis of bronchus, other congenital malformations of bronchus (Q324)<br>• Congenital malformations of lung (Q33), **excluding** single cyst (Q3300), accessory lobe of lung (Q331), azygos lobe of lung (Q3310)<br>• Other congenital anomalies of respiratory system (Q34) | • Laryngeal stridor, laryngomalacia and laryngeal stridor (Q314)<br>• Tracheomalacia (Q320), and congenital bronchomalacia (Q322)<br>• Single cyst (Q3300), accessory lobe of lung (Q331), azygos lobe of lung (Q3310)<br>• Other minor congenital anomalies considered as minor anomalies by EUROCAT (without ICD 10 codes): pleural effusion, secondary pulmonary hypoplasia, relaxation of diaphragm, vocal cord palsy |
| **Cleft lip and palate** | • Cleft palate (Q35), **excluding** bifid / cleft uvula (Q357)<br>• Cleft lip (Q36)<br>• Cleft palate with cleft lip (Q37) | • Bifid / cleft uvula (Q357)<br>• Congenital malformations of palate, not elsewhere specified (Q385) |
| **Digestive system** | • Congenital malformations of lips (Q380), other congenital malformations of tongue (Q383), congenital malformations of salivary glands and ducts (Q384), other congenital malformations of mouth (Q386), | • Ankyloglossia (Q381), macroglossia (Q382)<br>• Pyloric stenosis (Q400), congenital hiatus hernia (Q401), functional gastro-intestinal disorders (Q4021)<br>• Meckel's diverticulum (Q430), and functional |

| | | |
|---|---|---|
| | pharyngeal pouch (Q387), and other congenital malformations of pharynx (Q388)<br>• Congenital stenosis and stricture of esophagus (Q393), esophageal web (Q394), congenital dilation of esophagus (Q395), diverticulum of esophagus (Q396), other congenital malformations of esophagus (Q398), congenital malformations of esophagus, unspecified (Q399)<br>• Other congenital malformations of upper alimentary tract (Q40), **excluding** pyloric stenosis (Q400), congenital hiatus hernia (Q401), functional gastro-intestinal disorders (Q4021)<br>• Congenital absence, atresia and stenosis of small intestine (Q41)<br>• Congenital absence, atresia and stenosis of other parts of large intestine (Q428), congenital absence, atresia and stenosis of large intestine, unspecified (Q429)<br>• Other congenital malformations of intestine (Q43) **excluding** Meckel's diverticulum (Q430), functional disorders of colon (Q432, Q4381, Q4382), ectopic anus (Q435), congenital fistula of rectum and anus (Q436), persistent cloaca (Q437)<br>• Congenital malformations of gallbladder, bile ducts and liver (Q44), **excluding** choledochal cyst (Q444)<br>• Other congenital malformations of digestive system (Q45), **excluding** congenital mesenteric cyst (Q4583) | disorders of colon (Q432, Q4381, Q4382)<br>• Choledochal cyst (Q444)<br>• Congenital mesenteric cyst (Q4583)<br>• Inguinal hernia (K409)<br>• Hepatomegaly (R160) and splenomegaly (R161)<br>• Other minor congenital anomalies considered as minor anomalies by EUROCAT (without ICD 10 codes): abdominal cyst not needing surgery, accessory spleen, congenital adrenal hypoplasia, congenital cholestasis, cyst of spleen, diastatis recti, dilatation of intestine, liver cyst, plica of anus, transient choledochal cyst, umbilical hernia |
| **Genital organs**[c] | • Congenital absence of ovary (Q500), other congenital malformations of ovary (Q503), embryonic cyst of fallopian tube (Q504), other congenital malformations of fallopian tube and broad ligament (Q506)<br>• Congenital malformations of uterus and cervix (Q51)<br>• Congenital absence of vagina (Q520), doubling of vagina (Q521), other congenital malformations of vagina (Q524), congenital malformation of clitoris (Q526), other specified congenital malformations of female genitalia (Q528), congenital malformation of female genitalia, unspecified (Q529)<br>• Hypospadias (Q54), **excluding** congenital | • Developmental ovarian cyst (Q501), congenital torsion of ovary (Q502), and embryonal cyst of broad ligament (Q505)<br>• Imperforate hymen (Q523), fusion of labia (Q525), and other congenital malformations of vulva (Q527)<br>• Undescended testicle (Q53)<br>• Congenital chordee (Q544)<br>• Bifid scrotum (Q5521), and retractile testis (Q5520)<br>• Hydrocele of testis (P835)<br>• Phimosis (N47)<br>• Testicular torsion (N44)<br>• Other minor congenital anomalies considered as minor anomalies by EUROCAT (without ICD 10 codes): |

| | | |
|---|---|---|
| | chordee (Q544)<br>• Other congenital malformations of male genital organs (Q55), **excluding** bifid scrotum (Q5521), and retractile testis (Q5520)<br>• Indeterminate sex and pseudohermaphroditism (Q56) | • External genitalia male: buried penis, curvature of penis, hypo/hyperplasia of penis, micropenis, seminal vesicle cyst, deficient or hooded foreskin or foreskin tethered to scrotum<br>• External genitalia female: cysts of vulva, enlarged clitoris, hypertrophy of hymen, prominent labia minora, transient ovary cyst, vaginal skin tag |
| **Urinary system**[c] | • Other congenital malformations of urinary system (Q64), **excluding** cloaca exstrophy (Q641) | • Congenital single renal cyst (Q610)<br>• Other minor congenital anomalies considered as minor anomalies by EUROCAT (without ICD 10 codes): enlarged/thickened bladder, nefrocalcinosis, hydronephrosis with pelvis dilatation < 10 mm |
| **Musculoskeletal system** | • Congenital dislocation of hip (Q650 – Q652) and other congenital deformities of hip (Q658-Q659)[d]<br>• Pectus excavatum and carinatum (Q676-Q677)<br>• Congenital deformity of sternocleidomastoid muscle (Q680), congenital deformity of knee (Q682), and other specified congenital musculoskeletal deformities (Q688)<br>• Other malformations of skull and face bones (Q75), **excluding** hypertelorism (Q752), macrocephalus (Q753)<br>• Congenital spondylolisthesis (Q762), congenital malformation of sternum (Q767), and other congenital malformations of bony thorax (Q768-Q769)<br>• Osteochondrodysplasia with defects of growth of tubular bones and spines (Q77)<br>• Other osteochondrodysplasias (Q78)<br>• Congenital malformations of the musculoskeletal system, not elsewhere classified (Q79) | • Congenital subluxation of hip (Q653-Q655), unstable hip (Q656)<br>• Facial asymmetry (Q670), Compression facies (Q671), dolichocephaly (Q672), plagiocephalie (Q673), other congenital anomalies of skull, face and jaw (Q674), shieldlike chest, other congenital deformities of chest (Q678)<br>• Hypertelorism (Q752), macrocephalus (Q753)<br>• Spina bifida occulta (Q760), sternum bifidum (Q7671)<br>• Sacral dimple (L059)<br>• Other minor congenital anomalies considered as minor anomalies by EUROCAT (without ICD 10 codes):<br>  • Skull: bony occipital spur flat occiput, metopic ridge, high metopic suture, third fontanel, skull, late closure, wormian bones<br>  • Skeletal: cubitus valgus, depressed sternum, genu recurvatum, genua valgum, genua varum, no ossification of os coccygis, ovoid configuration of vertebrae, prominent sternum, bipartite vertebrae, bifid ribs, incomplete clefts of vertebrae, cubitus valgus, depressed sternum, genu a valgum, genua varum, no ossification os coccyx, ovoid configuration of vertebrae, prominent sternum |
| **Upper limb** | | • Clinodactyly (5th finger) (Q6810)<br>• Enlarged hypertrophic nails (Q845) and other congenital malformations of nails (Q846)<br>• Other minor congenital anomalies considered as minor anomalies by EUROCAT |

| | | |
|---|---|---|
| | | (without ICD 10 codes): arachnodactyly, duplication of thumbnail, overlapping fingers, short fingers, small fingers, subluxation of phalangeal bones, unusual dermatoglyphics, congenital bowing of upper limb |
| **Lower limb**[e] | • Talipes equinovarus, clubfoot (Q660)<br>• Accessory toe (Q692)<br>• Fused toes (Q702), webbed toes (Q703)<br>• Reduction defects of lower limbs (Q72)<br>• Congenital malformation of knee (Q741), Other congenital malformations of lower limb (Q742), arthrogryposis multiplex congenita (Q743), other specified malformations of lower limbs (Q748) | • Congenital deformities of feet (Q66), **excluding** talipes equinovarus (Q660)<br>• Congenital bowing of femur, fibula and tibia, long bones of leg, unspecified (Q683-685)<br>• Other minor congenital anomalies considered as minor anomalies by EUROCAT (without ICD 10 codes): bulbous toes, overlapping toes, gap between toes ($1^{st}$-$2^{nd}$), prominent calcaneus, recessed toes ($4^{th}$, $5^{th}$), rocker bottom feet, short great toe |
| **Other malformations** | • Congenital ichthyosis (Q80)<br>• Epidermolysis bullosa (Q81)<br>• Other congenital malformations of the skin (Q82), **excluding** congenital non-neoplastic naevus (Q825), and abnormal palmar creases (Q8280), accessory skin tags (Q8281)<br>• Congenital malformations of the breast (Q83), **excluding** accessory nipple (Q833)<br>• Other congenital malformations of integument (Q84), **excluding** enlarged and hypertrophic nails (Q845), and other congenital malformations of nails (Q846)<br>• Phakomatoses, not elsewhere classified (Q85)<br>• Other congenital malformations, not elsewhere classified (Q89), **excluding** unspecified (Q899) | • Congenital non-neoplastic naevus (Q825), and abnormal palmar creases (Q8280), accessory skin tags (Q8281)<br>• Accessory nipple (Q833)<br>• Other congenital malformations, unspecified (Q899)<br>• Other minor congenital anomalies considered as minor anomalies by EUROCAT (without ICD 10 codes):<br>  • Skin: angioma, cafe-au-lait spot, depigmented spot, epibulbar dermoid, hemangioma if no treatment is required, heterochromia of hair, lymphangioma, persistent lanugo, unusual place of nipples or wide spaced nipples<br>  • Head: aberrant scalp hair patterning |

Blue = congenital anomalies that are not considered as anomalies outside the spectrum of the VACTERL association. However, these are not specific enough to be incorporated in the major or minor VACTERL features either.

[a] As tethered cord is often observed in combination with ARM, it was not included as an anomaly outside the VACTERL spectrum when it occurred in combination with ARM.

[b] Respiratory system anomalies can often be explained by cardiac anomalies, EA/TEF, or renal anomalies. Therefore, respiratory system anomalies are considered secondary anomalies and consequently, they were not included as anomalies outside the VACTERL spectrum.

[c] As the embryology of the genitourinary (GU) system is partly shared with that of the anorectal and renal organ systems, GU anomalies were not considered as major congenital anomalies outside the VACTERL spectrum when they occurred in combination with ARM or renal anomalies.

[d] Congenital dislocation of hip and other congenital deformities of hip were not considered as major congenital anomalies outside the VACTERL spectrum, as these are very common congenital anomalies.

[e] Congenital anomalies affecting the lower limbs were not considered as major congenital anomalies outside the VACTERL spectrum either, as they are often included as limb component features for VACTERL in the clinic.

**Table 2. Frequencies of VACTERL component features and additional congenital anomalies for male and female patients separately, in the total group of VACTERL patients and in the VACTERL subtypes*.**

| | Total Group | STRICT-VACTERL | VACTERL-LIKE | VACTERL-PLUS |
|---|---|---|---|---|
| **VACTERL component feature** | | | | |
| **Vertebral** **male** | | | | |
| *Major* | 81 (31.6) | 55 (41.4) | 4 (7.5) | 22 (31.4) |
| *Minor* | 86 (33.6) | 27 (20.3) | 32 (60.4) | 27 (38.6) |
| *Total* | 167 (65.2) | 82 (61.7) | 36 (67.9) | 49 (70.0) |
| **female** | | | | |
| *Major* | 49 (35.8) | 40 (50.6) | 2 (7.1) | 7 (23.3) |
| *Minor* | 44 (32.1) | 15 (19.0) | 15 (53.6) | 14 (46.7) |
| *Total* | 93 (67.9) | 55 (69.6) | 17 (60.7) | 21 (70.0) |
| **Anorectal** **male** | | | | |
| *Major* | 167 (65.2) | 94 (70.7) | 30 (56.6) | 43 (61.4) |
| *Minor* | 1 (0.4) | 1 (0.8) | - | - |
| *Total* | 168 (65.6) | 95 (71.4) | 30 (56.6) | 43 (61.4) |
| **female** | | | | |
| *Major* | 76 (55.5) | 53 (67.1) | 10 (35.7) | 13 (43.3) |
| *Minor* | 11 (8.0) | 1 (1.3) | 6 (21.4) | 4 (13.3) |
| *Total* | 87 (63.5) | 54 (68.4) | 16 (57.1) | 17 (56.7) |
| **Cardiac** **male** | | | | |
| *Major* | 138 (53.9) | 87 (65.4) | 15 (28.3) | 36 (51.4) |
| *Minor* | 20 (7.8) | 6 (4.5) | 6 (11.3) | 8 (11.4) |
| *Total* | 158 (61.7) | 93 (69.9) | 21 (39.6) | 44 (62.9) |
| **female** | | | | |
| *Major* | 89 (65.0) | 57 (72.2) | 14 (50.0) | 18 (60.0) |
| *Minor* | 6 (4.4) | 1 (1.3) | 2 (7.1) | 3 (10.0) |
| *Total* | 95 (69.3) | 58 (73.4) | 16 (57.1) | 21 (70.0) |
| **Tracheo-Esophageal** **male** | | | | |
| *Major* | 154 (60.2) | 87 (65.4) | 37 (69.8) | 30 (42.9) |
| **female** | | | | |
| *Major* | 91 (66.4) | 56 (70.9) | 16 (57.1) | 19 (63.3) |
| **Renal** **male** | | | | |
| *Major* | 137 (53.5) | 83 (62.4) | 14 (26.4) | 40 (57.1) |
| *Minor* | 44 (17.2) | 20 (15.0) | 14 (26.4) | 10 (14.3) |
| *Total* | 181 (70.7) | 103 (77.4) | 28 (52.8) | 50 (71.4) |
| **female** | | | | |
| *Major* | 64 (46.7) | 39 (49.4) | 7 (25.0) | 18 (60.0) |
| *Minor* | 18 (13.1) | 7 (8.9) | 8 (28.6) | 3 (10.0) |
| *Total* | 82 (59.9) | 46 (58.2) | 15 (53.6) | 21 (70.0) |
| | | | | |

| | | | | |
|---|---|---|---|---|
| **Limb** **male** | | | | |
| *Major* | 60 (23.4) | 34 (25.6) | 4 (7.5) | 22 (31.4) |
| *Minor* | 14 (5.5) | 5 (3.8) | 6 (11.3) | 3 (4.3) |
| *Total* | 74 (28.9) | 39 (29.3) | 10 (18.9) | 25 (35.7) |
| **female** | | | | |
| *Major* | 36 (26.3) | 28 (35.4) | 4 (14.3) | 4 (13.3) |
| *Minor* | 13 (9.5) | 4 (5.1) | 6 (21.4) | 3 (10.0) |
| *Total* | 49 (35.8) | 32 (40.5) | 10 (35.7) | 7 (23.3) |
| **Additional congenital anomalies[a] - male** | | | | |
| **Congenital anomalies outside the VACTERL spectrum** | 70 (27.3) | - | - | 70 (100.0) |
| **Tethered cord** | 4 (1.6) | 1 (0.8) | 2 (3.8) | 1 (1.4) |
| **Respiratory system anomalies** | 30 (11.7) | 13 (9.8) | 6 (11.3) | 11 (15.7) |
| **Genitourinary anomalies** | 42 (16.4) | 23 (17.3) | 6 (11.3) | 13 (18.6) |
| **Hip anomalies** | 5 (2.0) | 2 (1.5) | 1 (1.9) | 2 (2.9) |
| **Lower limb anomalies** | 33 (12.9) | 17 (12.8) | 6 (11.3) | 10 (14.3) |
| **Additional congenital anomalies[a] - female** | | | | |
| **Congenital anomalies outside the VACTERL spectrum** | 30 (21.9) | - | - | 30 (100.0) |
| **Tethered cord** | 5 (3.6) | 3 (3.8) | 1 (3.6) | 1 (3.3) |
| **Respiratory system anomalies** | 14 (10.2) | 5 (6.3) | - | 9 (30.0) |
| **Genitourinary anomalies** | 20 (14.6) | 14 (17.7) | 3 (10.7) | 3 (10.0) |
| **Hip anomalies** | 1 (0.7) | 1 (1.3) | - | - |
| **Lower limb anomalies** | 15 (10.9) | 9 (11.4) | 1 (3.6) | 5 (16.7) |

[a] All additional congenital anomalies were listed as major congenital anomalies outside the VACTERL spectrum, with five exceptions: tethered cord, respiratory system anomalies, genitourinary anomalies, hip anomalies, and lower limb anomalies.

*The numbers of male and female cases do not add up to the total group of VACTERL patients (main text Table 3) because of 4 cases with unknown gender.

**Table 3. Combinations of major VACTERL anomalies in the total group of VACTERL patients with three or more major VACTERL anomalies.**

| Triads | # | Tetrads | # | Pentads | # | Hexads | # |
|---|---|---|---|---|---|---|---|
| ACTE | 25 | ACTER | 14 | VACRL | 5 | VACTERL | 1 |
| ATER | 25 | VATER | 6 | VACTER | 5 | | |
| CTER | 20 | ATERL | 5 | ACTERL | 3 | | |
| ACR | 19 | ACTEL | 5 | VACTEL | 2 | | |
| VCTE | 19 | VCTEL | 5 | VATERL | 1 | | |
| VAR | 18 | VCTER | 5 | | | | |
| VAC | 10 | VACTE | 5 | | | | |
| CRL | 6 | VACR | 4 | | | | |
| CTEL | 6 | VARL | 3 | | | | |
| ATEL | 6 | ACRL | 3 | | | | |
| ACL | 6 | VCRL | 2 | | | | |
| VTER | 6 | VACL | 2 | | | | |
| VATE | 6 | CTERL | 1 | | | | |
| VRL | 5 | VTERL | 1 | | | | |
| ARL | 4 | | | | | | |
| VCR | 4 | | | | | | |
| VCL | 3 | | | | | | |
| VAL | 3 | | | | | | |
| TERL | 3 | | | | | | |
| VTEL | 2 | | | | | | |
| **Total** | **196** | | **61** | | **16** | | **1** |

V = vertebral anomalies, A = anorectal anomalies, C = cardiac anomalies, TE = Tracheo-esophageal anomalies, R = renal anomalies, L = limb anomalies

**Table 4. Combinations of major and minor VACTERL anomalies in the total group of VACTERL patients with three or more major VACTERL anomalies.**

| Triads | # | Tetrads | # | Pentads | # | Hexads | # |
|---|---|---|---|---|---|---|---|
| VAR | 27 | VACR | 25 | VACTER | 17 | VACTERL | 4 |
| VCTE | 26 | VATER | 20 | VACRL | 11 | | |
| CTER | 17 | ACTER | 18 | ACTERL | 5 | | |
| VAC | 15 | VCTER | 15 | VACTEL | 5 | | |
| ATER | 15 | VACTE | 8 | VATERL | 3 | | |
| ACR | 14 | VARL | 7 | VCTERL | 2 | | |
| ACTE | 13 | ATERL | 5 | | | | |
| VCR | 12 | VTERL | 5 | | | | |
| VATE | 11 | VCTEL | 5 | | | | |
| VTER | 10 | VACL | 5 | | | | |
| VRL | 8 | CTERL | 5 | | | | |
| CTEL | 7 | ACTEL | 4 | | | | |
| TERL | 6 | VCRL | 4 | | | | |
| VCL | 6 | VATEL | 3 | | | | |
| CRL | 5 | ACRL | 3 | | | | |
| VTEL | 5 | | | | | | |
| ATEL | 4 | | | | | | |
| ARL | 4 | | | | | | |
| ACL | 2 | | | | | | |
| VAL | 2 | | | | | | |
| **Total** | **209** | | **132** | | **43** | | **4** |

V = vertebral anomalies, A = anorectal anomalies, C = cardiac anomalies, TE = Tracheo-esophageal anomalies, R = renal anomalies, L = limb anomalies