2 Incidence and Syndromes Associated with Congenital Anomalies of the Upper Limb

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Incidence

The best epidemiological studies of incidence of congenital anomalies are total population studies; there are four total population studies of congenital anomalies of the upper extremity (CAUE) in the literature (Table 2.1). A 5-year birth registry study of Edinburgh, Scotland by Rogala et al. found the prevalence of babies born with any limb anomalies to be 30 out of 10,000 live births, and the incidence of upper limb anomalies to be 22.5 out of 10,000 live births [1]. Of those with upper limb anomalies, 35 % had another non-upper limb anomaly. They used an older classification, that of Temtamy and McKusick [2], so direct comparisons to more recent studies are difficult. One striking finding in this study is the complete lack of isolated simple syndactyly, which in other studies was found to be relatively common.

An 11-year total population study of Western Australia found the prevalence of babies born with upper limb anomalies to be 19.76 in 10,000 live births [3]. Forty-six percent of those affected had another non-hand congenital anomaly. Fifty-one percent had bilateral hand anomalies, and 17 % had multiple different hand anomalies. The most common anomalies were failures of differentiation (35 %), duplications (33 %), and failures of formation (15 %). Congenital upper limb anomalies were more common in boys; preterm, post-term, and multiple births; and older mothers. No significant differences in prevalence or frequency of anomalies were found between whites and nonwhites, left and right sides, and in babies that survived and those who died shortly after birth.

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Similarly, an 11-year total population study of the Stockholm region of Sweden found a recorded incidence of congenital anomalies of the upper limb of 21.5 per 10,000 live births [4]. Fifty-four percent of the children with congenital anomalies of the upper limb were boys. The anomalies affected the right side only in 30 %, the left side only in 33 %, and both sides in 37 %. Non-hand anomalies were recorded in 23 % of the children with congenital anomalies of the upper limb, most commonly in the lower limbs. In 17 % of the affected children, there was a known occurrence among relatives. Failure of differentiation was the most common category (47 %) followed by duplication (26 %), failure of formation (18 %), undergrowth (3 %), generalized abnormalities and syndromes (2.4 %), overgrowth (1.7 %), and constriction ring syndrome (1.5 %).

There are more total population studies of limb deficiency anomalies, for example: a 9-year total population study of the national incidence of upper limb deficiencies in Finland found an incidence of congenital deficiency anomalies of the upper limb of 5.26 per 10,000 live births [5]. These studies approximate the "failure of formation" category of complete CAUE population studies (Table 2.2).

Incidence figures derived by extrapolation from surveys of patients presenting for treatment show slightly lower incidence: an estimated 16–18 per 10,000 births [9–11]. It is thought that these population studies may underestimate incidence, as the milder deformities may never present for treatment. A comparison of a population-based study and clinic registry of Swedish children with CAUE showed an underestimation of incidence by 6 % in the clinic registry, and a low degree of correlation of classification of anomalies [12].

The IFSSH classification is a useful tool for classifying most CAUE and enables comparison between studies, but is based on theories of embryological failure and is subject to some differences of interpretation. Ambiguities in the categorization of anomalies may then lead to differences of incidence of certain classifications [13]. For instance, the IFSSH classification could classify polydactyly with complex syndactylies as duplication, but for clinical purposes it fits better

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into the category of failure of differentiation. Miura et al. [14] and Ogino [15, 16] suggested that a common teratological mechanism causes cleft hand, syndactyly, and polydactyly and that they should be put into a new category: failure of induction of digital rays. Classifying congenital absence of digits is also ambiguous; the distinctions between brachysyndactyly, symbrachydactyly (atypical cleft hand), and transverse arrest are not clearly defined.

In the Stockholm study thumb hypoplasia was categorized as failure of formation, longitudinal arrest, and radial ray deficiency, whereas in the study from Western Australia, thumb hypoplasia was categorized as undergrowth. The Stockholm study showed a much lower frequency of undergrowth as a result. There was also a surprisingly large disparity between the categories of transverse arrest and symbrachydactyly regarding associated non-hand anomalies. Other differences in relative frequencies are also likely caused by other differences of interpretation of classification strategies.

Epidemiologic studies are important for health care planning, detecting changes in incidence over time, and comparing differences among regions. These two total population studies of CAUE agree on total incidence figures. These population studies are slightly higher than the estimated 0.16–0.18 % incidence for CAUE of in surveys of patients presenting for treatment (Table 2.3) [9, 10, 17–19]. It is assumed that this is due to the fact that milder deformities may never present for treatment.

These studies do, however, reveal the difficulties in comparing studies owing to different classification strategies and weaknesses within the IFSSH classification. For example, two studies of CAUE in Edinburgh, UK [2, 10] and two studies from Japan [17, 18] show markedly different relative frequency of incidence of duplication; presumably such a finding in ethnically similar populations is due to differences in classification (see Table 2.3). We hope that the ongoing discussion of classification systems for CAUE (see Chap. 1) will inspire improvements in registration and population studies.

Table 2.1 Incidence and classification of congenital anomalies of the upper extremity (CAUE) in total population studies

Study	Ekblom et al. [4]	Giele et al. [3]	Rogala et al. [1]
Country	Sweden	Australia	Scotland
Years of survey	1997–2007	1980–1990	1964–1968
Incidence (per 10,000 live births)	21.50	19.76	16.00
Non-hand anomaly present (%)	23	46	15[a]
Failure of formation (%)	18	15	35
Duplication (%)	26	33	38[a]
Overgrowth (%)	2	1	35[a]
Undergrowth (%)	3	10	1[a]
Constriction ring (%)	1	3	2[a]
Generalized (%)	2	3	2[a]

[a]Author's interpretation: classification system differs

Associated Conditions

The genetics of hand formation have already been reviewed (Chap. 1). The genetic pathways were originally elucidated through chick and mouse studies. Genetic studies of human malformations and malformation syndromes have provided further insight. Congenital hand malformations can be categorized using a number of different criteria. A common classification scheme uses the broad designations of polydactyly, syndactyly, brachydactyly, and oligodactyly or reduction defects. Hand malformations can occur in isolation or as a part of a larger pattern of malformation. Although there are over a hundred recognized syndromes with hand anomalies as a part of their expression, this review will concentrate on only those syndromes for which the hand malformation is a cardinal or defining feature.

1. Syndromes with polydactyly
2. Syndromes with syndactyly
3. Syndromes with brachydactyly
4. Syndromes with oligodactyly
5. Syndromes with reduction defects

Syndromes with Polydactyly

Polydactyly was classified in 1978 by Temtamy and McKusick [20] into the following categories:

Postaxial type A—Postaxial extra digits that are well developed

Table 2.2 Incidence of upper limb deficiency anomalies in total population studies

Study	Koskimies et al. [5]	Giele et al. [3]	Kallen et al. [6]	Rogala et al. [1]	Aro et al. [7]	Froster and Baird [8]
Country	Finland	Australia	Sweden	Scotland	Finland	Canada
Years of survey	1993–2005	1980–1990	1965–1979	1964–1968	1964–1077	1952–1984
Incidence (per 10,000 live births)	5.25	5.12	4.00	6.70	4.00	3.40

Table 2.3 Comparison of classification of relative frequency of CAUE in population studies and large case series

Study	Ekblom et al. [4]	Giele et al. [3]	Flatt [9]	Ogino et al. [18]	Cheng et al. [19]	Lamb et al. [10]	Rogala et al. [2]	Yamaguchi et al. [17]
Country	Sweden	Australia	USA	Japan	China	UK	UK	Japan
Years of compilation	1997–2007	1980–1990	1960–1994	1968–1984	1976–1986	1976–1978	1964–1968	1961–1972
Failure of formation (%)	21.50	15	15	11	11	18	28	16
Failure of differentiation (%)	23	32	41	52	30	41	21	28
Duplication (%)	18	38	15	19	40	20	40	26
Overgrowth (%)	26	1	1	1	1	1	–	1
Undergrowth (%)	2	8	9	9	2	14	8	14
Constriction ring (%)	3	3	2	5	5	4	3	1
Generalized (%)	1	3	4	3	4	–	–	–
Unclassified (%)	2	–	13	1	3	–	–	14

Table 2.4 Primarily craniofacial syndromes associated with postaxial polydactyly

Syndrome	Other cardinal features	Inheritance/OMIM Gene/locus
Oral-facial-digital II, Mohr (OFD II)	Preaxial polysyndactyly of the feet, cleft tongue, midline partial cleft lip, hypertrophic frenulae, hamartomas of the tongue, conductive deafness	AR/252100
Oral-facial-digital III (OFD III)	See-saw winking of eyelids, oral frenulas, hamartomas of the tongue, supernumerary teeth, intellectual disability	AR/258850
Oral-facial-digital V (OFD V)	Hypertelorism, midline cleft of the upper lip, lobulated tongue, intellectual disability	AR/174300 DDX59/1q32.1
Oto-palato-digital, type II	Hypertelorism, micrognathia, cleft palate, overlapping fingers, dense bones	XLR/304120 FLNA/Xq28

Postaxial type B—Pedunculated postminimus
Preaxial type I—Duplication of thumbs/great toes
Preaxial type II—Triphalangeal thumbs/duplication of great toes
Preaxial type III—Absent thumbs, one or two extra preaxial digits
Preaxial type IV—Broad thumbs, preaxial polysyndactyly, postaxial postminimus

In 1998, Castilla reported on the congenital hand malformations using a study of Latin American Collaborative Study of Congenital Malformations [20]. He reviewed 5,927 consecutively born polydactyly cases. Castilla divided the polydactylies into *postaxial*, *preaxial*, and *rare*, a group in which he included *mesoaxial* and combinations of digits. These groups were then further subdivided into *isolated* or *associated*, depending upon whether there were other anomalies present. The *associated* category was then further subdivided into *combined*, if the other anomaly was a limb anomaly, *syndromic*, if the polydactyly occurred in a combination of anomalies representing a syndrome, and *MCA*, or multiple congenital anomalies, if the anomalies did not fit a recognizable pattern or syndrome.

From Castilla's study, several patterns emerged. Postaxial is the most common type of polydactyly and the most likely to be isolated. The rare polydactylies, that is, not clearly only postaxial or only preaxial, are the most likely to be associated with an underlying syndrome. Trisomy 13, Meckel syndrome, and Down syndrome accounted for 75 % of the syndromic polydactyly cases in this study. In both Meckel and Trisomy 13 syndromes, postaxial polydactyly is a cardinal feature of the syndrome. For Down syndrome, although preaxial polydactyly can be seen in Down syndrome with a higher frequency than in the general population, it would not be considered a cardinal feature of Down syndrome. For the purposes of this chapter, only the syndromic category will be included, as the isolated forms are reviewed in other chapters.

Syndromes in which polydactyly is a cardinal feature can be subdivided using the classification of postaxial, preaxial, mesoaxial and combined, and further subdivided by the other common findings or by a common aspect of development.

Syndromes with Postaxial Polydactyly: Craniofacial Anomalies as a Primary Feature

Polydactyly is a cardinal feature for a group of syndromes in which the major or defining features are craniofacial abnormalities (Table 2.4). These include the various types of oral-facial-digital (OFD) syndrome. Various reviewers have described the different types of OFD syndromes on their various oral, facial, and digital abnormalities, and many are now known to be genetically distinct. The primary findings of the OFD syndromes are polydactyly and a combination of oral anomalies, most prominently, abnormalities of the tongue and frenula.

Postaxial Polydactyly as a Feature in Ciliopathies

Ciliopathies are a group of conditions in which the genes code for proteins that are important in the cilium-centrosome complex (CCC). The function of the CCC is to sense a wide variety of intracellular signals that affect polarity, proliferation, differentiation, and tissue maintenance. Many of the syndromes in which postaxial polydactyly is a cardinal feature belong to a group of conditions known as the single-gene ciliopathies [21] and are in Table 2.5.

The single-gene ciliopathies with postaxial polydactyly include a group of skeletal dysplasias characterized by their narrow thoraces and short ribs: short rib polydactyly Types I, II, and IV, Ellis van–Creveld, and Jeune asphyxiating thoracic dysplasia, Type 1 and 2. The short rib polydactylies are characterized by early respiratory distress related to very small thoracic cages resulting in lung hypoplasia, and often, early infant death. Ellis–van Creveld, and Jeune Thoracic Dystrophy, also include short ribs as a defining feature, but have other distinctive features that separate them from the short rib polydactyly group. The configuration of the ribs is different in these last two conditions as well.

Ciliopathies also include Bardet–Biedl syndrome and Meckel–Gruber syndrome. Both of these syndromes can be caused by one of multiple genes, but all of the genes share the property that they encode proteins important in the CCC [21].

Bardet–Biedl is a multisystem disorder in which the primary features are retinal degeneration, cystic kidney disease or urinary tract malformation, intellectual disability, diabetes mellitus, obesity, infertility, and postaxial polydactyly. The delineation of the genetics of Bardet–Biedl syndrome helped establish ciliopathies as an important disease entity when it was shown that many of the proteins formed by genes responsible for BBS were expressed in the ciliated sensory neurons of the nematode *C. elegans* [22]. The polarization of cells required for the formation of the tubules in the kidney represent the action of these ciliary proteins that are affected by BBS gene mutations [21].

Both McKusick–Kaufman syndrome and Bardet–Biedl 6 (BBS6) are caused by mutations in the MKKS gene. McKusick–Kaufman is an autosomal recessive, multisystem condition with polydactyly, heart defects, and genital abnormalities, and is most common in the Old Order Amish community. MKKS codes for a protein important in centrosomal function, possibly acting as a chaperonin. Silencing of the transcript of that gene leads to multinucleate and multicentrosomal cells with cytokinesis defects [5].

Meckel–Gruber is a recessively inherited condition in which the cardinal features include central nervous system malformations, particularly occipital encephalocele, Arnold–Chiari malformation, absence of midline structures such as the corpus callosum and septum pellucidum, and cerebellar malformations. Other major findings include cystic changes in the kidneys and liver. The genes that cause Meckel–Gruber code for proteins that localize to the centrosome, pericentriolar region or to the cilium itself.

Oral-facial-digital syndrome, type 1 (OFD1) is an X-linked disorder in which the gene product has been shown to localize in the renal epithelial cells in the polarized region. Expression of OFD1 is necessary for primary cilia formation and left–right axis specification [21, 24], making OFD1 a ciliopathy syndrome as well. The hand findings in OFD1 are variable and primarily involve asymmetric shortening of the digits in the hands with variable syndactyly and preaxial polydactyly of the feet. However, postaxial and preaxial polydactyly of the hands has also been reported.

Other Syndromes with Polydactyly of Varying Types

Table 2.6 lists some of the many other syndromes associated with polydactyly. Grebe chondrodysplasia is a dwarfing condition in which all of the long bones are severely shortened, particularly the distal portions and is associated with postaxial polydactyly of the hands. Grebe chondrodysplasia is caused by mutations in the growth differentiation factor 5 (GDF5) gene, also known as the cartilage-derived morphogenetic protein 1 (CDMP1) gene. This gene has been found to be responsible for other types of chondrodysplasias including acromesomelic dysplasia, Hunter–Thompson type, Du Pan syndrome (fibular hypoplasia and complex brachydactyly), Multiple synostosis syndrome 2, as well as isolated heritable hand malformations including brachydactyly types A1, A2, and C and proximal symphalangism type 1B (OMIM gene 601146).

Greig cephalopolysyndactyly is a multiple malformation syndrome that is usually ascertained through the limb abnormalities, but includes craniofacial findings such as macrocephaly with an unusual head shape. In Greig, the hand and foot abnormalities are quite variable and include a combination of polydactyly and syndactyly. The polydactyly can be postaxial, preaxial, mesoaxial, or a mixture of all three, and can vary from limb to limb in the same individual. Greig is caused by mutations in the Gli-Kruppel Family member 3 (GLI3) gene on 7p13. GLI3 is a gene in the zinc finger gene family and is also the gene responsible for Pallister–Hall syndrome, a syndrome in which the polydactyly can be postaxial or mesoaxial and other cardinal features include hypothalamic hamartoma, pituitary dysfunction, and visceral malformations. Mutations in GLI3 are also found in some of the isolated heritable forms of polydactyly, including postaxial polydactyly types A1 and B, and preaxial polydactyly type IV [25, 26].

Table 2.5 Ciliopathy syndromes associated with postaxial polydactyly

Syndrome	Other cardinal features	Inheritance/OMIM Gene/locus
Acrocallosal	Hypoplastic or absent corpus callosum, other brain abnormalities, preaxial polydactyly/syndactyly of the feet	AR/200990 KIF7/15q26.1
Bardet–Biedl	Obesity, intellectual disability, retinal dystrophy, renal anomalies, male hypogonadotrophic hypogonadism, complex female genitourinary malformations	AR
BBS1		BBS1/11q13.2
BBS2		BBS2/16q12.2
BBS3		ARL6/3q11.2
BBS4		BBS4/15q24.1
BBS5		BBS5/2q31.1
BBS6		MKKS/20p12.2
BBS7		BBS7/4q27
BBS8		TTC8/14q31.3
BBS9		BBS9/7p14.3
BBS10		BBS10/12q21.2
BBS11		TRIM32/9q33.1
BBS12		BBS12/4q27
BBS13		MKS1/17q22
BBS14		CEP290/12q21.32
BBS15		WDPCP/2p15
BBS16		SDCCAG8/1q43
Ellis–van Creveld	Atrial septal defect, short ribs, acromesomelic limb shortening, oral frenulae	AR/225500 EVC/4p16 EVC2, 4p16
Jeune asphyxiating thoracic dystrophy	Short ribs, brachydactyly, short stature, renal failure, hepatic and pancreatic fibrosis, retinal degeneration	AR/208500
ATD1		ATD1
Asphyxiating thoracic dystrophy 2	Narrow thorax, brachydactyly, short stature, shortened and bowed femora	AR/611263
(ATD2)		IFT80/3q25.33
McKusick–Kaufman	Mesoaxial polydactly, congenital heart disease, and hydrometrocolpos in females and genital malformations in males (most commonly hypospadias, cryptorchidism, and chordee)	AR/236700 MKKS/20p12.2
Meckel–Gruber	Encephalocele, cystic kidneys, microphthalmia, cleft lip/palate, hepatic fibrosis	AR/249000
MKS1		MKS1/17q22
MKS2		TMEM216/11q12.2
MKS3		TMEM67/8q22.1
MKS4		CEP290/12q21.32
MKS5		RPGRIP1L/16q12.2
MKS6		CC2D2A/4p15.32
MKS7		NPHP3/3q22.1
MKS8		TCTN2/12q24.31
MKS9		B9D1/17p11.2
MKS10		B9D2/19q13.2
Oral-facial-digital, type I (OFD I)	Syndactyly and asymmetric brachydactyly of hands with occasional pre- and postaxial polydactyly of hands, preaxial polydactyly of feet, midline cleft lip, cleft tongue, hamartomas of the tongue, hyperplastic frenulae, intellectual disability, polycystic kidneys	XLR/311200 OFD1/Xp22.2
Short rib polydactyly Type I	Short ribs, imperforate anus, urogenital abnormalities, congenital heart anomalies	AR/263530
Short rib polydactyly Type II	Short ribs, midline cleft of the upper lip, ovoid tibia	AR/263520 NEK1/4q32.3
Short rib polydactyly Type III	Short ribs, craniofacial abnormalities	AR/263510 DYNC2H1/11q21.22.1
Short rib polydactyly	Short ribs, acromesomelic hypomineralization and campomelia, laterality defects, and cystic kidneys	AR/614091
Type V		WDR35/2p24.3

Table 2.6 Other selected syndromes associated with polydactyly

Syndrome	Type	Other cardinal features	Inheritance/OMIM Gene/locus
Carpenter syndrome	Postaxial	Brachydactyly with clinodactyly and syndactyly, broad bifid thumbs, brachycephaly, craniosynostosis, intellectual disability	AR/201000 RAB23/6p11.2
Chondrodysplasia, Grebe type	Postaxial	Hypoplastic digits, severe shortening of long bones	AR/200700 CDMP1/GDF5/20q11.2
Greig cephalopolysyndactyly	Preaxial/postaxial	Preaxial polydactyly of feet, syndactyly, craniosynostosis, macrocephaly with frontal bossing, absence of corpus callosum	AD/175700 GLI3/7p14.1
Laurin–Sandrow	Preaxial/postaxial Mirror	Mirror polysyndactyly of hands and feet, ulnar and fibular dimelia, dysplasia or absence of the radius and tibia, cleft nares	AD/135750 14q13
Pallister–Hall	Postaxial/mesoaxial	Hypothalamic hamartoblastoma, hypopituitarism, imperforate anus, abnormal or absent epiglottis, early death	AD/146510 GLI3/7p14.1
Simpson-Golabi-Behmel	Postaxial	Brachydactyly, syndactyly, overgrowth, coarse facial features, intellectual disability	XL/312870 GPC3, GPC4/Xq26.2
Smith–Lemli–Opitz	Postaxial	2–3 syndactyly of toes, microcephaly, intellectual disability, hypospadias, cryptorchidism	AR/270400 DHCR7/11q13.4
Townes–Brocks	Preaxial	Distal deviation of thumbs, hypoplastic thumbs, microcephaly, ear anomalies and hearing loss, anal and intestinal atresias, genital anomalies, renal anomalies and kidney disease	AD/107480 SALL1/16q21.1
Ulnar–mammary	U	Postaxial polydactyly, apocrine abnormalities, hypopigmentation and hypoplasia of areola, nipple and breast, genital anomalies in males, delayed puberty	AD/181450 TBX3/12q24.21

Syndromes with Syndactyly

Syndactyly is harder to accurately study as mild cutaneous syndactyly is often not reported as a congenital anomaly. Significant cutaneous syndactyly and bony syndactyly is associated with a number of underlying syndromes. Complete syndactyly of the third and fourth digits of the hands, also called zygodactyly can be seen in fetuses with triploidy (karyotype with three copies of every chromosome) but can also occur as an isolated finding.

Syndactyly can be found as a defining feature in a group of syndromes with craniosynostosis as a major feature, often called acrocephalosyndactylies (Table 2.7). Syndactyly of all the fingers into a mitten like extremity occurs in Apert syndrome, an MCA syndrome in which there is significant craniosynostosis involving multiple sutures.

Syndactyly is also seen in a number of other syndromes. It is a defining characteristic in only some of these, which are listed in Table 2.8.

Syndromes with Brachydactyly

Isolated Brachydactyly

Brachydactyly of the hands or shortened digits can be due to absent, underdeveloped, or abnormally shaped phalanges (brachyphalangy), or metacarpals (brachymetacarpia), or a combination of these. Brachydactyly can involve all of the digits or only some of the digits. Bell classified isolated brachydactyly in 1951 [2, 27] into Types A through E with subtypes.

Type A: Brachymesophalangy
Type A-1: Brachymesophalangy II–V; brachyphalangy I
Type A-2: Brachymesophalangy II
Type A-3: Brachymesophalangy V
Type B
Aplasia terminal phalanges, II–V
Hypoplasia middle phalanges, II–V
Broad distal phalanges, I
Type C
Brachymesophalangy II, III, V
Hypersegmentation, proximal phalanges, II, III
Type D
Short, broad thumb distal phalanx
Type E
Brachymetacarpia
Brachymetatarsia

Brachydactyly of one or all the digits can also be found as a feature of multiple syndromes (Table 2.9).

Brachydactyly is a common finding in more than 50 different skeletal dysplasias, but rarely is the defining characteristic. Chapter 26 reviews many of these, and Table 2.10 lists many of these skeletal dysplasias as well.

Table 2.7 Craniosynostosis syndromes associated with syndactyly

Syndrome	Digits involved on the hand	Other cardinal features	Inheritance/OMIM Gene/locus
Apert	1–5; can be osseous or cutaneous, often resulting in a "mitten" hand	Midface hypoplasia, cleft palate, hypertelorism, hyperhidrosis, variety of brain malformations, fusion of cervical vertebrae, intellectual disability, hearing loss	AD/101200 FGFR2/10q26.13
Carpenter syndrome	2–5	Postaxial polydactyly, brachydactyly with clinodactyly, broad bifid thumbs, brachycephaly, intellectual disability	AR/201000 RAB23/6p11.2
Pfeiffer	2–3	Syndactyly of toes, broad and medially deviated distal phalanges of thumb and great toe, brachymesophalangy hypertelorism, brachycephaly	AD/101600 FGFR1/8p11.23-p11.22 FGFR2/10q26.13
Saethre–Chotzen	2–3	3–4 syndactyly of toes, brachydactyly and clinodactyly, ossification defects and hyperostosis of skull, short clavicles, facial asymmetry	AD/101400 TWIST/7p21 FGFR2/10q26.13 FGFR3/4p16.3

Table 2.8 Other syndromes associated with syndactyly as a defining or significant feature

Syndrome	Digits involved	Other cardinal features	Inheritance/OMIM Gene/locus
Focal dermal hypoplasia (Goltz)	Primarily 3–4 but can include others	Ectrodactyly, oligodactyly, dermal hypoplasia, microphthalmia, other eye abnormalities, facial asymmetry, cleft palate	XL/305600 PORCN/Xp11.23
Fraser	1–5; can be osseous or cutaneous, often resulting in a "mitten" hand	Midface hypoplasia, cleft palate, hypertelorism, hyperhidrosis, variety of brain malformations, fusion of cervical vertebrae, intellectual disability, hearing loss	AD/101200 FGFR2/10q26.13
Greig cephalopolysyndactyly	1–5, variable	Preaxial polydactyly of feet, syndactyly of toes, macrocephaly with frontal bossing, absence of corpus callosum	AD/175700 GLI3/7p14.1
Laurin-Sandrow	1–5	Mirror polysyndactyly of hands and feet, ulnar and fibular dimelia, dysplasia or absence of the radius and tibia, cleft nares	AD/135750 14q13
Oculodentodigital (ODD)	4–5	Syndactyly of third and fourth toes, microcephaly, intellectual disability, hearing loss, brain abnormalities abnormalities, microphthalmia, cleft lip/palate, microdontia, enamel hypoplasia, hyperostosis of skull and vertebrae, palmoplantar keratoderma	AD/164200 GJA1/6p22.31
Oral-facial-digital II, Mohr (OFD II)	1–5	Preaxial polysyndactyly of the feet, cleft tongue, midline partial cleft lip, hypertrophic frenulae, hamartomas of the tongue, conductive deafness	AR/252100
Pallister–Hall	4–5	Postaxial/mesoaxial polydactyly, hypothalamic hamartoblastoma, hypopituitarism, imperforate anus, abnormal or absent epiglottis, early death	AD/146510 GLI3/7p14.1
Poland	Unilateral brachydactyly, syndactyly, oligodactyly	Aplasia of the pectoralis major, cardiac defects, rib anomalies, can be seen with Moebius	AD or sporadic/173800 Unknown

There are single reports of families in which brachydactyly occurs as a dominant trait with one or two other features, but the genetics of these conditions is not well defined. These single-family reports will not be included in this review. Numerous multiple malformation syndromes have brachydactyly as a prominent or cardinal feature. Some of the more common of these are listed in Table 2.11.

Cornelia de Lange, or Brachman de Lange, syndrome is a multiple malformation syndrome that was first described in severely affected cases in which there was moderate to severe intellectual disability and severely affected upper limbs with oligodactyly and ulnar deficiency. Short stature and microcephaly were often severe. The facial appearance was also striking, with high arched eyebrows and synophrys, a small upturned nose, and a long philtrum with thin lips and a crescent-shaped mouth with downturned edges. Most cases were sporadic. When the first gene was identified, NIPBL, the phenotype was found to be much more variable in

Table 2.9 Genetics of isolated brachydactyly

Classification	Description	Genetics OMIM
Type A1	Brachymesophalangy II–V; brachyphalangy I	AD/112500
		IHH/2q35
		BDA1B/5p13.3-p13.2
Type A2	Brachymesophalangy II	AD/112600
		BMPR1B/4q22.3
		BMP2/20p12.3
		GDF5/20q11.22
Type A3	Brachymesophalangy V	AD/112700
Type B	Aplasia terminal phalanges, II–V, hypoplasia middle phalanges, II–V, broad distal phalanges, I, symphalangism, syndactyly	AD/113000
		ROR2/9q22.31
Type C	Hypersegmentation of proximal and middle phalanges, II, III, brachymesophalangy II and III, ulnar deviation II and III	AD/113100
		GDF5/20q11.22
Type D	Stub thumb; short, broad thumb distal phalanx	AD/113200
		HOXD13/2q31.1
Type E	Brachymetacarpia, variable	AD/113300
		HOXD13/2q31.1
Sugarman	Brachydactyly with major proximal phalangeal shortening, duplicated first metacarpals	AR/272150
Temtamy type (Type A4, not classified by Bell)	Brachymesophalangy II and V	AD/112800

Table 2.10 Skeletal dysplasias with brachydactyly[a]

Achondrogenesis	Lenz–Majewski hyperostotic dwarfism
Achondroplasia	Metaphyseal chondrodysplasia (McKusick)
Acrodysostosis	Metaphyseal dysplasia with exocrine pancreatic
Acrodysplasia with retinitis pigmentosa and nephropathy	insufficiency and cyclic neutropenia metatropic dysplasia
Acromesomelic dysplasia, Campailla-Martielli	Moerman lethal short limb dwarfism with brain abnormalities
Acromesomelic dysplasia, Maroteaux	Multiple epiphyseal dysplasia
Acromicric dysplasia	Nance–Sweeney dwarfism
Asphyxiating thoracic dystrophy	Opsismodysplasia
Atelosteogenesis	Osebold–Remondini
Campomelic dysplasia	Osteoglophonic dwarfism
Cephaloskeletal dysplasia	Osteosclerosis, Stanescu
Chondrodysplasia punctata	Oto-palato-digital
Chondrodysplasia, Grebe type	Pseudoachondrodysplasia
Chondrodysplasia, Hunter–Thompson type	Pycnodysostosis
Cleidocranial dysplasia	Robinow
Cranioectodermal dysplasia	Ruvalcava
Deafness and metaphyseal dysplasia	Short rib-polydactyly
Dyggve–Melchior–Clausen	Spondyloepimetaphyseal dysplasia, Irapa type
Dyschonrosteosis	Spondyloepiphyseal dysplasia congenital
Dyssegmental dysplasia	Spondylometaphyseal dysplasia, Kozlowski
Ellis–van Creveld	Spondyloperipheral dysostosis
Enchondromatosis	Thanatophoric-clover leaf skull
Fibrochondrogenesis	Thanatophoric dysplasia
Geleophysic dysplasia	Thricho-rhino-phalangeal
Hypochondroplasia	Weill–Marchesani
Larsen	

[a]Adapted from Everman DB. Hands and feet. In: Stevenson RE, Hall JG, eds. Human malformations and related anomalies, 2nd edition. New York: Oxford University Press; 2006. By permission of Oxford University Press, USA

Table 2.11 Syndromes with brachydactyly as a major feature

Syndrome	Hand features	Other cardinal features	Inheritance/OMIM Gene/locus
Aarskog	Brachydactyly of all fingers with clinodactyly of fifth, unusual positioning of fingers on extension	Short stature, hypertelorism, shawl scrotum	XL/305400 FGD1/Xp11.21
Acrodysostosis	Brachyphalangia and brachymetacarpia	Brachymetatarsia	AD/101800
		Brachymelic short stature, saddle nose, intellectual disability	PRKARIA/17q24.2 PDE4D, 5q11.2-12.1
Adams–Oliver	Digits may be short or have terminal transverse defects	Cutis aplasia, terminal transverse defects of limbs, intellectual disability in recessive form	AD/100300 ARHGAP31, 3q13.33 AR/614219 DOCK6/19p13.2
Albright hereditary osteodystrophy	Short distal phalanx of thumb, brachymetacarpia (4 and 5)	Short stature, intellectual disability, obesity, round face, resistance to PTH, TSH, and GHRH, hypogonadism	AD/103580 GNAS1/20q13.2
Brachydactyly–ectrodactyly-fibular aplasia (Genuardi)	Brachydactyly, ectrodactyly	Fibular aplasia or hypoplasia	AD/113310
Brachydactyly-hallux varus-thumb abduction (Christian)	Brachymetacarpia (1), broad abducted thumbs	Hallux varus	AD/112450
Brachydactyly-hypertension	Brachyphalangy, brachymetacarpia	Hypertension	AD/112410 12p12.2-p11.2
Carpenter syndrome	Brachydactyly with clinodactyly, postaxial polydactyly, broad bifid thumbs, syndactyly (2–5)	Brachycephaly, craniosynostosis, intellectual disability	AR/201000 RAB23/6p11.2
Coffin–Lowry	Brachydactyly with tapering fingers, tufted drumstick appearance to distal phalanges on X-ray, small fingernails	Short stature, short bifid sternum with pectus deformities, coarse facial features, hypertelorism, scoliosis, hypodontia, rectal/uterine prolapse	XL/303600 RPS6KA3/Xp22.12
Coffin–Siris	Hypoplasia of 5th fingers (particularly distal phalanx), absence of 5th fingernail	Hypoplastic or absent toenails, short stature, sparse scalp hair, intellectual disability, coarse facial features, wide mouth with full lips, feeding difficulties, frequent infections	AR/135900 7q32-q34
Cohen	Brachymetacarpia, narrow hands	Short stature, obesity, prominent upper central incisors, intellectual disability	AR/2165500 COH1/8q22.2
Cornelia de Lange	Brachymetacarpia (1), clinodactyly (5), oligodactyly, ulnar deficiency	Short stature, microcephaly, intellectual disability, characteristic face with arched eyebrows, synophrys, down turned mouth and upturned nose, hirsuitism, variable phenotype	AD/122470+ NIPBL/5p13.2 RAD21/8q24.11 CSPG6/10q25.2 XL/300040+ SMC1A/Xp11.22 HDAC8/Xq13.1
Cranioectodermal dysplasia	Brachydactyly, single transverse palmar creases, clinodactyly (5) short, broad distal phalanges	Short stature, sagittal craniosynostosis, skeletal dysplasia, fine, sparse hair, lax skin, dental abnormalities, liver and kidney failure	AR/218330+ IFT122/3q21.3-q22.1 WDR35/2p24.1 IFT43/14q24.3 WDR19/4p14
DOOR	Hypoplastic or absent distal phalanges, triphalangeal thumbs	Sensorineural deafness, onychodystrophy, osteodystrophy, intellectual disability, seizures, visual impairment, microcephaly	AR/220500 TBC1D24/16p13.3
Floating Harbor	Brachydactyly, clinodactyly (5), broad thumbs	Short stature, severe speech and language delay, deep set eyes, bulbous nose, behavioral problems	AD/136140 SRCAP/16p11.2
Hand–foot–genital	Short, proximally placed thumbs, brachydactyly (5), ulnar deviation (2), clinodactyly (5), hypoplastic middle phalanges, delayed ossification of carpals, short 1st metacarpals, pseudoepiphyses	Absent/short halluces with medial deviation, brachydactyly, delayed ossification of tarsals, short first metatarsal, hypoplastic distal and middle phalanges of feet, genital defects (internal—female, external—male)	AD/140000 HOXA13/7p15.2

(continued)

Table 2.11 (continued)

Syndrome	Hand features	Other cardinal features	Inheritance/OMIM Gene/locus
Holt–Oram	Spectrum of upper limb defects, primarily involving the radial ray but can include the ulna, humerus, and the shoulder girdle; brachydactyly, oligodactyly, syndactyly	Cardiac defects include ventricular septal defect, atrial septal defect, and others	AD/142900 TBX5/12q24.1
Kabuki	Brachydactyly, short middle phalanges, short metacarpals (4 and 5), clinodactyly (5), prominent fingertip pads	Distinctive facial features with long palpebral fissures and lateral ectropion, ptosis, cleft palate, cardiac defects, hyperextensible joints, intellectual disability	AD/147920 MLL2/12q13.12 XL/300867 KDM6A/Xp11.3
Moebius	Brachydactyly, oligodactyly	Sixth and seventh nerve palsy, absent pectoral muscles, Klippel–Feil anomaly	AD/157900 Linked to several loci
Pfeiffer	Brachymesophalangy, syndactyly, broad and medially deviated distal phalanx of thumb	Syndactyly of toes, broad and medially deviated distal phalanges of great toe, craniosynostosis, hypertelorism, brachycephaly	AD/101600 FGFR1/8p11.23-p11.22 FGFR2/10q26.13
Poland	Unilateral brachydactyly, syndactyly, oligodactyly	Aplasia of the pectoralis major, cardiac defects, rib anomalies, can be seen with Moebius	AD or sporadic/173800 Unknown
Robinow	Brachydactyly, brachymetacarpia, bifid terminal phalanges, clinodactyly (5), hypoplastic/absent thumbs	Short stature, hypertelorism, costovertebral abnormalities, "fetal face"	AD/180700 WNT5A/3p14.3 AR/268130 ROR2/9q22.31
Rubinstein–Taybi	Brachydactyly, broad thumbs with radial deviation, clinodactyly (5)	Broad great toes, short stature, intellectual disability, microcephaly, downslanting palpebral fissures, narrow palate, beaked nose, grimacing smile	AD/180849 CREBBP/16p13.3 Deletion 16p13.3
Saethre–Chotzen	Brachydactyly, clinodactyly, 2–3 syndactyly	3–4 syndactyly of toes, craniosynostosis, ossification defects and hyperostosis of skull, short clavicles, facial asymmetry	AD/101400 TWIST/7p21 FGFR2/10q26.13 FGFR3/4p16.3
Schinzel–Giedion	Brachydactyly, brachymetacarpia (1), hypoplastic distal phalanges	Severe pes planus, short stature, intellectual disability, seizures, sclerotic skull and long bones, skeletal abnormalities, renal and genital anomalies	AD/269150 SETBP1/18q12.3
Smith–Magenis	Brachydactyly, broad hands	Brachycephaly, broad, flat midface, intellectual disability, sleep disturbance, characteristic behavior	AD/182290 RAI1/17p11.2 Deletion 17p11.2
Townes–Brocks	Distal deviation of thumbs, hypoplastic thumbs, preaxial polydactyly	Microcephaly, ear anomalies and hearing loss, anal and intestinal atresias, genital anomalies, renal anomalies and kidney disease	AD/107480 SALL1/16q21.1
Turner	Brachymetacarpia (4 and 5)	Short stature, webbed neck, ovarian failure, horseshoe kidney, coarctation of the aorta	Monosomy X

affected individuals. In particular the upper limb defects ranged from the classical findings of ulnar ray deficiency, to individuals with small hands, and individuals with brachydactyly. Following that, several more genes were identified that caused the same phenotype, confirming the inheritance as both autosomal dominant and X-linked.

Syndromes with Oligodactyly/Reduction Defects

The final category of syndromes with hand defects involves a group of syndromes in which the hands have reduction defects, resulting in either oligodactyly or adactyly (Table 2.12). Reduction defects are usually divided into those with radial ray defects and those with ulnar ray defects, and then a third category for conditions in which either or both rays might be involved. The reduction defects may just involve the digits, leading to oligodactyly, or may involve whole parts of the hand and/or upper extremity. They can be classified by the part of the hand structure that is involved.

Hand malformations are an important feature of many multiple malformation syndromes, and the genes involved give clues to the morphogenesis of the limbs as well as many other areas of development.

Table 2.12 Syndromes with oligodactyly or adactyly

Syndrome	Segment involved Radial (R), Ulnar (U), Middle (M), All (A)	Other cardinal features	Inheritance/OMIM Gene/locus
Adams–Oliver	R, M, U	Brachydactyly, cutis aplasia, intellectual disability in recessive form	AD/100300 ARHGAP31, 3q13.33 AR/614219 DOCK6/19p13.2
Brachydactyly–ectrodactyly-fibular aplasia (Genuardi)	M	Brachydactyly, fibular aplasia or hypoplasia	AD/113310
CHILD	M, U		XL/308050 NSDHL/Xq28
Cornelia de Lange	U, M	Short stature, microcephaly, intellectual disability, characteristic face with arched eyebrows, synophrys, down turned mouth and upturned nose, hirsuitism, variable phenotype	AD/122470+ NIPBL/5p13.2 RAD21/8q24.11 CSPG6/10q25.2 XL/300040+ SMC1A/Xp11.22 HDAC8/Xq13.1
Ectrodactyly–ectodermal dysplasia-clefting	M	Ectrodactyly of the feet, cleft lip/palate, light-colored and sparse hair, anodotia or oligodontia, tear duct anomalies, urinary tract abnormalities	AD/ TP63/
Fanconi anemia	R	Short stature, intellectual diability, renal anomalies, genital abnormalities, microcephaly, café au lait spots, deafness, cardiac defects, chromosomal breakage	AR/227650 PHF9/2p16.1 FANCD2/3p25.3 FANCE/6p21.31 XRCC9/9p13.3 FANCC/9q22.32 FANCF/11p14.3 BRCA2/13q13.1 FANCM/14q21.2 FANCI/15q26.1 SLX4/16p13.3 ERCC4/16p13.12 PALB2/16p12.2 FANCA/16q24.3 RAD51C/17q22 BRIP1/17q23.2 FAAP95/Xp22.2
Hand–foot–genital	R	Brachydactyly, clinodactyly (5), and ulnar deviation (2), abnormalities of the toes and metatarsals, primarily the great toe, brachydactyly of toes, genital defects (internal—female, external—male)	AD/140000 HOXA13/7p15.2
Holt–Oram	R	Brachydactyly, syndactyly, occasional involvement of shoulder girdle, cardiac defects include ventricular septal defect, atrial septal defect, and others	AD?142900 TBX5/12q24.1
Nager	R	Malar hypoplasia, downslanting palpebral fissures, partial absence of lower eyelashes, high nasal bridge, micrognathia, cleft palate, abnormal ears, radioulnar synostosis	AD/154400 SF3B4/1q21.2
Poland	Unilateral R	Unilateral aplasia of the pectoralis major with ipsilateral brachydactyly and syndactyly, cardiac defects, rib anomalies, can be seen with Moebius	AD or sporadic/173800 Unknown
Postaxial acrofacial dysostosis (POADS)—also known as Miller	U	Malar hypoplasia, downslanting palpebral fissures, eyelid coloboma, micrognathia, cleft lip/palate, abnormal ears, accessory nipples	AR/263750 DHODH/16q22.2

(continued)

Table 2.12 (continued)

Syndrome	Segment involved Radial (R), Ulnar (U), Middle (M), All (A)	Other cardinal features	Inheritance/OMIM Gene/locus
Roberts	U	Phocomelia, prenatal onset growth deficiency, microcephaly, ear, eye, heart and urogenital anomalies, intellectual disability	AR/268300 ESCO2/8p21.1
Robinow	R	Brachydactyly, short stature, hypertelorism, costovertebral abnormalities, "fetal face"	AD/180700 WNT5A/3p14.3 AR/268130 ROR2/9q22.31
Ulnar–mammary	U	Postaxial polydactyly, apocrine abnormalities, hypopigmentation and hypoplasia of areola, nipple and breast, genital anomalies in males, delayed puberty	AD/181450 TBX3/12q24.21
VACTERL	R	Vertebral defects, anal atresia, cardiac defects, renal defects, ear defects, tracheoesophageal atresia	

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