SYNDACTYLY AND POLYDACTYLY

PHENOTYPES

Syndactyly (ie, digit fusion, typically via webbing) is a common inherited and clinically heterogeneous malformation.1 It can be syndromic, comprising more than 300 distinct anomalies,1 or nonsyndromic, existing as 1 of 9 nonsyndromic forms.2 It also varies phenotypically between families. Even a single patient’s phenotype may be severe or mild, unilateral or bilateral, symmetrical or asymmetrical, complete or incomplete, cutaneous or bony, and involving many distinct bones, with inter-limb phenotypic variation.1

Polydactyly is another hereditary limb malformation, characterized by supernumerary digits (ie, more than 5 digits per limb). Like syndactyly, polydactyly is phenotypically variable2 in terms of the limb affected (hand or foot),3 its severity, and its syndromicity or lack thereof.3

Though syndactyly and polydactyly are phenotypically well understood, their genetic bases have not been synthesized in writing and remain unclear for some types. This study reviews the current knowledge on the genetics of these anomalies.

SYNDACTYLY AND POLYDACTYLY

GENETICS

Given the aforementioned morphological variation, it is not surprising that the genetic bases of syndactyly and polydactyly are diverse, polygenic,2 and as yet unclear in some cases. New causative genes and mutations are being discovered with advances in sequencing technology. The genes involved in syndactyly and polydactyly tend to affect specific bodily regions, including the zone of polarizing activity (ZPA): an area that controls limb structure and positional identity.6–9 The ZPA disappears by day 44 of embryonic development, after which time the phalanges form.10 Aside from the ZPA, which is on the posterior embryo and produces fibroblast growth factor 8 (FGF8), the apical ectodermal ridge, which is on the dorsal-ventral margin and produces FGF8, also aids in limb development.
The HOX genes, hedgehog pathways [Sonic Hedgehog (SHH) and Indian hedgehog (IHH)], FGFs, bone morphogenetic proteins (BMPs), and cartilage-derived morphogenetic proteins are also involved.11

Thirty-nine HOX genes exist in humans; the HOXA and HOXD clusters have been associated with syndactyly and polydactyly.12 Genes within the HOXD cluster and locus chr2q31 seem to be involved in syndactyly13; the HOXD13 gene, for example, is linked to syndactyly type V (SD5) and a brachydactyly-syndactyly syndrome.14

The SHH signaling pathway plays key roles in limb development.15 SHH is affected by—or affects—several transcription factors, namely HAND2, GLI3, ALX4, and certain BMP antagonists (formin and gremlin), changes to which have led to syndactyly and polydactyly.10 If disrupted, as if ZPA activity is impacted, then SHH cannot lead to normal limb development; this often results in syndactyly.16

The IHH signaling pathway may influence later development, considering its roles in chondrocyte differentiation and ossification.17 Further, IHH is repressed by fibroblast growth factor (FGF) receptors,18 functioning at a different time than WNTs and FGFs, which are involved in the final stages of mesenchymal ossification; later, in the last stage of digit formation, there is down-regulation of gremlin and restriction of FGF8 expression.20

Wingless-type mouse mammary tumor virus integration sit family members 6 and 10B (WNT6, WNT10B) are involved in the developing limb bud and related to the chr2q35 region [a locus implicated in syndactyly type I (SD1)].21 BMPs and their antagonist noggin (NOG), when blocked, also lead to syndactyly;10 GLI3 may also contribute;22 it is involved in a range of syndromes, and a GLI3 missense mutation led to syndactyly and polydactyly.23 N-Myc and zinc-finger transcription factors have caused soft-tissue syndactyly in mice.24

Syndactylies and polydactylies also vary in their patterns of inheritance. Most syndactyly types follow autosomal dominant inheritance,25 but SD7 and SD9 are autosomal recessive,1 and SD5 is X-linked recessive.30 Generally, autosomal dominant phenotypes are less severe with variable expressivity and incomplete penetrance.

NONSYNDROMIC DACTYLIES: PHENOTYPES AND GENETICS

Syndactyly

Nonsyndromic syndactyly manifests itself as 9 distinct types; at least 11 loci and 8 relevant genes have been identified27 (Fig. 1).

Syndactyly Type I

SD1 is one of the most common nonsyndromic syndactylies28 and is associated with the third and fourth fingers or the second and third toes.28 SD1 is so diverse that it can be divided into 4 subtypes.28 Subtype 1 (Weidenreich type or zygodactyly) accounts for 70% of nonsyndromic syndactyly cases29; it is bilateral, symmetrical, found exclusively in the feet, and free of bone involvement. Subtype 1 is associated with the 3p21.31 locus, but no disease-causing gene has been identified. It has been explored in a large Pakistani family.29 Subtype 2 (Lueken type, type Ib) is usually bilateral, in both the hands and feet, and can be either bony or cutaneous. It is associated with the chr2q34-q36 locus and has been studied in German and Iranian families.30 The disease-causing gene has not been identified. Subtype 3 (type Ic, Montagu type) involves the third and fourth fingers, is typically bilateral, and can be either bony or cutaneous. It is linked to the chr2q31-q32, and mutations p.R306Q and p.R306G in HOXD13. It has been studied in 2 Chinese families.31 Finally, subtype 4 (type I-d, Castilla type) involves the fourth and fifth toes and is typically bilateral and cutaneous.3 Little is known about its genetic basis, but it is typically inherited in an autosomal dominant manner.29,30

Syndactyly Type II

Syndactyly type II (SPD) is one of the most heterogeneous nonsyndromic types.1,10,29 Like SD1, SPD tends to involve the third and fourth fingers.3 However, unlike SD1, SPD is also associated with the fifth toe.10 SPD manifests itself in 3 types: SPD1 (Vordingborg type), SPD2 (Debeer type), and SPD3 (Malik type). In SPD1, both the HOXA and the HOXD clusters are involved; often, a polyalanine expansion on HOXD13 is present.32 The locus affected is usually chr2q31 on HOXD13. In SPD2, it is usually fibulin-1 (FBLN1) on chromosome 12 that is modified, and the locus involved is usually chr22q13.3.28 The mutations responsible for SPD2 are usually missense mutations or deletions. Finally, in SPD3, the chr14q11.2-q15 locus is affected. SPD as a whole is characterized by incomplete penetrance and high variability and has been studied in Turkish,32 Greek, Pakistani, Chinese, and Belgian families,30 as well as in mice.33 SPD is inherited in an autosomal dominant manner with reductive penetrance.1

Syndactyly Type III

Syndactyly type III (SD3; Johnston-Kirby type, 4/5 fingers or 3/4/5 fingers fusion) usually involves soft tissue and only the hands: specifically, there is complete, bilateral syndactyly between the fourth and fifth fingers, the fifth finger is often shortened, and the middle digit may be missing or underdeveloped.10 SD3 usually involves the connexin-43 (GJA1) gene at the chr6q21-3 and sometimes chr6q22-24 loci.34 SD3 has been studied in a Pakistani family.35 This type exhibits autosomal dominant inheritance with complete penetrance.1

Syndactyly Type IV

Syndactyly type IV (SD4; Haas type1) is very rare.54 It is complete and bilateral; often, polydactyly is associated.10 No associated conditions of the feet or bone fusion have been mentioned.54 SD4 involves a range of genes, including the SHH signaling pathway, limb development membrane protein 1 (LMBR1), and the zone of polarizing activity (ZPA) regulatory sequence (ZRS) locus at chr7q36.3.30 It can also further be divided into 2 subtypes: SDTY4 (Haas type) and Andersen-Hansen type. The former usually involves the ZRS locus and LMBR1, while the genetic basis of the latter is not known.30 This syndactyly has been studied in Chinese families.35 SD4 is autosomal dominant.1
Fig. 1. Summary of nonsyndromic and selected syndromic syndactyly with their known causal genes.
 Syndactyly Type V

Syndactyly type V (SD5; Dowd type) is another rare form of syndactyly. This syndactyly is usually complete and involves fusion of both cutaneous and bony tissue. Soft-tissue syndactyly affects the third and fourth fingers and the second and third toes; conversely, the metacarpals and metatarsals are most commonly fused in the case of the fourth and fifth or third and fourth digits. Sometimes, this syndactyly exists without metatarsal fusion, but in this case, there are usually other foot abnormalities. SD5, like SD1 and SPD, usually involves HOXD13 (namely a c.950A>G mutation or a polyalanine expansion as per SPD). The locus affected is usually chr2q31. This syndactyly has been studied in a Han Chinese family. SD5 is inherited in an autosomal dominant manner.

 Syndactyly Type VI

Syndactyly VI (SD6; mitten hand syndactyly) is perhaps the least researched type. It is typically unilateral, as its name suggests, it affects the second through fifth digits, generating a mitten-like appearance. The genetic basis of SD6 is unknown. It has an autosomal dominant mode of inheritance with reductive penetrance.

 Syndactyly Type VII

Syndactyly VII (SD7) is another very rare phenotype. It is similar to Apert syndrome but includes additional, severe shortening and fusion of the ulna and radius, as well as fusion of the metacarpals and disorganized phalangeal development. The SD7 syndactyly group appears to contain 2 phenotypes: one involving a “spoon hand,” and the other an oligodactyly. It is sometimes similar to SPD1. SD7 usually involves formin 1 (FMN1) and gremlin 1 (GREM1) on chr15q13.3 on, as well as low-density lipoprotein receptor–related protein 4 (LRP4) on chr11p12-p11.2. Specifically, SD7 can be subdivided into 2 types: Cenani-Lenz type (spoon-hand type) and oligodactyly type. The former is usually associated with LRP4 mutations, whereas the latter is usually associated with GREM1 and FMN1 mutations. This type has been studied in a Pakistani family. LRP4 mutations have been studied in cows, as well. This syndactyly type is autosomal recessive in inheritance, but sometimes also autosomal dominant.

 Syndactyly Type VIII

Syndactyly type VIII (SD8) is not common and involves fusion of the fourth and fifth metacarpals. It can be divided into 2 subtypes: Orel-Holmes type and Lerch type. SD8 is associated with chrXq26 and the split hand/foot malformation type 2 (SHFM2) gene. It has also been associated with 2 nonsense mutations p.R179X and p.S157X in exon 3 of the FGF16 gene on chrXq21.1. FGF16 is known to function in limb development. It has been studied in both Polish and German families. SD8 is autosomal dominant in inheritance.

 Syndactyly Type IX

Finally, syndactyly IX (SD9; mesoaxial synostotic syndactyly or Malik-Percin type) is another highly rare form and has only been described in 2 families. SD9 is associated with chr17p13.3. No causative gene has been pinpointed. It has been studied in Turkish and Pakistani families. SD9 is inherited in an autosomal recessive fashion.

Novel cases may necessitate expanded classification schemes. For example, Avina and Hernandez described a case they believe constitutes a new nonsyndromic syndactyly.

Polydactyly

Polydactyly is classified into 3 main phenotypes: preaxial, central, and postaxial (Fig. 2). Preaxial polydactyly (medial ray polydactyly) usually includes the thumb and can manifest itself in 1 of 4 types (types 1, 2, 3, and 4). It tends to be associated with GLI3 on chr7p13 and SHH on chr7q36. Central polydactyly (also “central ray” polydactyly) is associated with syndactyly and cleft hand. It dominantly appears syndromically. Finally, postaxial polydactyly (lateral ray polydactyly) is characterized by a hypoplastic or fully developed little finger, is often bilateral, can be simple or complex, and tends to be associated with foot deformations; it can also manifest in 2 types (types A and B). It is associated with GLI3 on chr7p13, and PAPA2 and PAPA3 on chr13q21-q32 and chr19p13.2-p13.1, respectively. It is also associated with SHH mutations, MI-POLI, and PITXI.

SYNDROMIC DACTYLIES: PHENOTYPES AND GENETICS

Acrocephalosyndactyly

Acrocephalosyndactyly syndromes are characterized by craniosynostosis (early fusion of skull bones) alongside syndactyly and polydactyly. Apert syndrome is primarily characterized by craniosynostosis and syndactyly in which fingers and toes are either entirely fused or webbed. At minimum 5 digits on each hand and foot are fused together, though all digits can be fused. Polydactyly is less commonly found in Apert. Apert is associated with FGFR2 mutations on chr10q26.13 and autosomal dominant inheritance.

Carpenter syndrome is another manifestation of craniosynostosis, involving a pointed head (acrocephaly) and, severely, a cloverleaf skull. Typically, Carpenter syndrome involves cutaneous syndactyly between 2 or more fingers or toes, most commonly between the third and fourth fingers. Polydactyly most often occurs next to the first or second toe or fifth finger. Carpenter syndrome is typically associated with RAB23 at the chr6p11.2 locus and is primarily autosomal recessive.

Pfeiffer syndrome, a third kind of craniosynostosis, results in a misshapen head and face, and is most commonly associated with syndactyly. It is associated with FGFR1 on chr8p11.23 and FGFR2 on chr10q26.13 and presents with autosomal dominant inheritance.

Finally, Saethre-Chotzen syndrome is dominantly characterized by craniosynostosis but also involves syndactyly between the second and third fingers on each hand, and polydactyly involving a duplicated first toe. It is associated
with TWIST1 on chr7p21.1 and FGFR2 on chr10q26.13\(^9\) and presents with autosomal dominant inheritance.

**Bardet-Biedl Syndrome**

Bardet-Biedl syndrome (BBS) is associated with syndactyly and polydactyly in both the fingers and the toes. BBS can result from mutations in at least 20 genes. It is associated with CCDC28B on chr1p35.2, ARL6 on chr3q11.2, BBS1 on chr11q13.2, BBS6 (MKKS) on chr20p12.2, BBS10 on chr12q21.2, BBS9 (PTHB1) on chr7p14.3, BBS4 on chr15q24.1, BBS7 on chr4q27, BBS5 on chr2q31.1, MKS1 on chr17q22, BBS8 (TTC8) on chr14q31.3, SDCCAG8 on chr1q43-q44, LZTFL1 on chr3p21.31, WD-PCP on chr2p15, BBS4 on chr15q24.1, BBS12 on chr4q27, TMEM67 on chr8q22.1, CEP290 on chr12q21.32, TRIM32 on chr9q33.1, BBIP1 on chr10q25.2, chr22q12.3 on IFT27, and IFT172 on chr22p13.3. These syndromes typically present with autosomal recessive or digenic recessive inheritance.

**Greig Cephalopolysyndactyly Syndrome**

Greig cephalopolysyndactyly syndrome is another limb-anomaly-heavy disorder, involving the limbs, the head, and the face. Polydactyly of the finger or toes as well as cutaneous syndactyly are common. Greig cephalopolysyndactyly is associated with GLI3 mutations on chr7p14.1\(^50\) and is primarily autosomal dominant.

**McKusick-Kaufman Syndrome**

McKusick-Kaufman syndrome is characterized by 3 features: heart defects, genital abnormalities, and polydactyly. McKusick-Kaufman syndrome is associated with MKKS on chr20p12.2\(^31\) and autosomal recessive inheritance.
Pallister-Hall Syndrome

Pallister-Hall syndrome is characterized by an assortment of developmental defects, including polydactyly and cutaneous syndactyly. Pallister-Hall syndrome is associated with GLI3 on chr7p14.152 and autosomal dominant inheritance.

Poland Syndrome

Poland syndrome involves underdeveloped muscles and hand abnormalities, including syndactyly. The genetic basis of Poland syndrome appears to be unknown, but this syndrome exhibits autosomal dominant inheritance.

Short-Rib Polydactyly

Short-rib polydactyly syndromes are characterized by a narrow thorax as well as preaxial polydactyly. They include Jeune syndrome, Ellis van Creveld syndrome, Saldino-Noonan syndrome (Verma-Naumoff syndrome), and Majewski syndrome. These syndromes are largely phenotypically heterogeneous but are all characterized by polydactyly. Jeune syndrome is associated with ATD1 on chr15q13, and Ellis van Creveld syndrome is associated with LBN (EVC) on chr4p16.2. Saldino-Noonan and Majewski syndromes result from DYNC2H1 mutations on chr11q22.3. These syndromes are typically digenic and autosomal recessive.

Smith-Lemli-Opitz Syndrome

Smith-Lemli-Opitz syndrome is characterized by several affected body parts. Syndactyly primarily affects the second and third toes, and polydactyly affects either fingers or toes. This syndrome is associated with DHCR7 on chr11q13.4 and presents with autosomal recessive inheritance.

Triphalangeal Thumb-Polydactyly Syndrome

Triphalangeal thumb-polydactyly syndrome is a hand-foot malformation characterized by pre- and postaxial polydactyly, isolated syndactyly, complex polydactyly, and triphalangeal thumbs. Typically, the hands are more affected. This syndrome is associated with LMBR1 on chr7q36.3 and presents with autosomal dominant inheritance.

Fig. 3. The phenotypic manifestations of 2 of the 3 nonsyndromic polydactylies (preaxial and postaxial) and their subtypes. Adapted with permission from Hand Malformations [Internet]. Gainesville: University of Florida. Available at https://www.peds.ufl.edu/divisions/genetics/teaching/hand_malformations.htm.
DIAGNOSIS AND MANAGEMENT
Syndactyly and polydactyly are mostly diagnosed at birth.\textsuperscript{1} Management is surgical and postnatal and has remained unchanged for decades.\textsuperscript{10}

However, prenatal diagnostics also exist.\textsuperscript{56} Dysmorphology examinations (ie, examinations of structural abnormalities) can be conducted. Prenatal (in utero) surgery is still not viable: it presents more risks than benefits.\textsuperscript{50}

Whether prenatal diagnosis is possible depends upon the digits involved. Prenatal diagnosis of simple toe syndactyly is nearly impossible, whereas prenatal diagnosis of simple finger syndactyly is possible, though very difficult.\textsuperscript{56} Diagnosis is most readily carried out when syndactyly is both complete and complex, as this tends to result in prenatally detectable synchronous movements.\textsuperscript{56}

Where prenatal diagnoses is unclear, molecular/genetic methods can be complementary. First, DNA must be extracted from the fetus in utero via different methods.\textsuperscript{57} Next, the DNA is analyzed for relevant mutations via sequence analysis, deletion/duplication analysis, or cytogenetic/fluorescent in situ hybridization analysis.

The benefits of genetic diagnosis of syndactyly and polydactyly lie beyond the affected individual. The same genetic testing methods can also be generalized to adults to allow for carrier testing (ie, for detecting a carrier of an abnormal gene in a disease where the condition is not clinically expressed), which can aid in giving families preventative information.

SUMMARY
Syndactyly and polydactyly are both clinically and genetically complex. Phenotypically, the dactyli are diverse: 9 nonsyndromic syndactylies and a range of non-syndromic polydactylies exist. This intrinsic complexity is amplified by the fact that each dactylus can also exist in a range of syndromic manifestations: more than 300 distinct syndromic syndactylies\textsuperscript{58} and more than 300 distinct syndromic polydactylies exist.\textsuperscript{59}

This phenotypic complexity is paralleled by the dactyli’s varied genetic bases and patterns of inheritance. A range of genes—namely, the hedgehog pathways (SHH and IHH), WNTs, HOX genes (especially HOXD13), GJA1, LMBR1, FMN1, GREM1, LRPs, SHFM2, GLI3, FGFs, BMPs, and cartilage-derived morphogenetic proteins—have been implicated, but the genetic basis of certain syndactyly types, like nonsyndromic subtypes VI and IX, remains unknown.

This genetic complexity translates to great difficulty where genetic-based diagnosis and carrier testing are concerned. Although prenatal diagnosis via molecular and genetic methodologies exists, diagnosis is still largely postbirth, as not all genetic bases are effectively charted.

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