Review

Polydactyly: phenotypes, genetics and classification

Polydactyly is one of the most common hereditary limb malformations featuring additional digits in hands and/or feet. It constituted the highest proportion among the congenital limb defects in various epidemiological surveys. Polydactyly, primarily presenting as an additional pre-axial or post-axial digit of autopod, is a highly heterogeneous condition and depicts broad inter- and intra-familial clinical variability. There is a plethora of polydactyly classification methods reported in the medical literature which approach the heterogeneity in polydactyly in various ways. In this communication, well-characterized, non-syndromic polydactylies in humans are reviewed. The cardinal features, phenotypic variability and molecular advances of each type have been presented. Polydactyly at cellular and developmental levels is mainly a failure in the control of digit number. Interestingly, GLI3 and SHH (ZRS/SHH enhancer), two antagonistic factors known to modulate digit number and identity during development, have also been implicated in polydactyly. Mutations in GLI3 and ZRS/SHH cause overlapping polydactyly phenotypes highlighting shared molecular cascades in the etiology of additional digits, and thus suggesting the lumping of at least six distinct polydactyly entities. However, owing to the extreme phenotypic and clinical heterogeneity witnessed in polydactyly a substantial genetic heterogeneity is expected across different populations and ethnic groups.

Conflict of interest

None.

The term ‘polydactyly’ (Gr. Poly = many; dactylos = digit), is ascribed to a Dutch physician Theodor Kerckring in the 17th century (1). Polydactyly or polydactylyism/polydactylia or bifid finger/toe or duplex or finger du/tri-plication or hexadactyly or hyperdactyly or hyperphalangism or intercalary digit or mirror-image duplication or pentadactyly or polymetacarpalia or polymetatarsalia, all refer to the occurrence of supernumerary digits or duplication of digital parts. Ambrose Parey in the 16th century described this situation as ‘superfluous fingers’ (2). Examples range in degree from a minor cutaneous protuberance on lateral aspects of a digit to doubling of a single phalanx, to complete duplication of a limb or part of a limb (3).

Polydactyly is the most frequently observed congenital limb anomaly noticed immediately at birth. Its prevalence is estimated to be 0.3–3.6/1,000 in live-births and 1.6–10.7/1,000 in general population. Males are twice as often affected as females (4, 5).

Phenotypically, polydactyly is a highly heterogeneous malformation (3). Generally, there is high predilection for the involvement of upper limbs than the lower, right hand than the left, and left foot than the right (5, 6). The duplication may involve any digit in the upper or lower extremities. Two most common presentations are pre-axial polydactyly (PPD) (i.e. superfluous digit attached on the first digit), and post-axial polydactyly (i.e. extra digit along the fifth digit) (5, 3). Meso-axial polydactylies involving second, third, or fourth digits are rare.

Phenotypic severity of polydactyly is defined by the extent of digit duplication and the number of skeletal
elements of the autopod involved in duplication. Morphogenetically, polydactyly can be considered as a process of bifurcation of digit ray(s) in the longitudinal axis progressing from distal to proximal end. The process of bifurcation occurs in numerous grades and consequently the deformity appears in many varieties ranging from a mere broadening of a distal phalanx, to complete duplication of one or several finger/toe rays with the involvement of carpals/tarsals (7, 8).

Most of the cases encountered in the medical practice are sporadic, which usually have unilateral presentations. Familial types are mostly bilateral and symmetrical (5, 6). Polydactyly as an isolated presentation is more frequent than syndromic appearance. Nonetheless, polydactyly manifests itself as an integral part or a common association with ~300 well-characterized syndromic malformations (9–11).

This article presents the current status of knowledge on isolated polydactyly and covers its various aspects including approaches to polydactyly categorization, the well-characterized phenotypes, inheritance patterns and known genetic factors for polydactyly, its association with syndactyly, and a brief overview of two genetic factors, \(GLI3\) and \(ZRS/SHH\), which cause various polydactylies.

**Approaches to polydactyly classification**

Being a rather common limb anomaly, the medical literature is rich in the description, illustration and categorization of polydactyly. As in the case of syndactyly, the classification systems proposed for polydactyly can also be lumped into three domains, depending upon the underlying approach: (i) topographic and morpho-anatomical systems; (ii) topographic but considering familial phenotypes and inheritance patterns; and (iii) embryological and molecular approaches. A comprehensive chronological compendium of publications on polydactyly highlighting the most significant contributions on its clinical and genetic aspects, is presented in Table S1.

**Topography and inheritance based approaches**

A number of observations of familial polydactylies with unique segregation patterns (i.e. transmission, penetrance, and expressivity) required an alternative approach to understand polydactyly. Thus, the Temtamy and McKusick (3) classification identified four pre-axial, two post-axial, and few high degrees/complex polydactylous entities, all of them segregating autosomally. Goldstein et al. (13) proposed an extension to the Temtamy–McKusick scheme by introducing subtypes (i.e. 10 pre-axial, 9 post-axial, 4 high-degrees, and 7 complex types; Table S1). Almost all of these types were suggested to segregate in autosomal dominant fashion with variable expression and incomplete penetrance. Castilla et al. (14) suggested that hand- and foot-post-axial polydactyly were two different entities. Likewise, Orioli and Castilla (15) proposed that thumb and hallux polydactylies were genetically heterogeneous (Table S1).

**Embryological and molecular approaches**

Considering the additional digit(s) as an embryological failure during limb development has been another approach to polydactyly categorization (16). The emergence of limb as a model of embryonic development has embarked much interest in this area and superfluous digit has been considered as a deviation from the normal anterior–posterior developmental plan during limb morphogenesis (10). However, only a few genetic factors have been discovered which have a potential role in the etiology of polydactyly. Talamillo et al. (17) suggested to group polydactyly types depending upon the ectopic expression of \(SHH\), one of the key morphogens in limb development. As the majority of genes involved in the etiology of polydactyly/limb malformations remain to be identified, a molecular classification or a unified categorization of polydactyly based upon genes and phenotypic presentation is currently not easy.

Interestingly, the morpho-anatomical, genetic and embryological systems of classification can be unified by the useful concept of ‘teratological sequence’ (18). All the anatomical variations from a collection of observations can be put into a logical order, i.e. from very mild to very extreme phenotype, and are interpreted as orderly changes occurring during the normal course of development with a common genetic etiology. This concept is popular among clinicians because the extent of the pathology often determines the function of the organ and provides a basis on which to guide treatment. This approach allows the lumping of diverse phenotypes and helps understanding their affinities and a likely common origin (7, 19).

**Recognizable phenotypes in polydactyly**

In the plethora of polydactyly classifications, the Temtamy–McKusick scheme (3) remains the most widely used among geneticists, dysmorphologists and genetic counselors. In this scheme, the three main
Polydactilies with further sub-types are pre-axial, post-axial, and complex types (3). Here, by integrating the recent clinical and molecular developments in each polydactyly, an update has been presented on this scheme (Table 1).

Pre-axial polydactilies

Tentamy and McKusick (3) identified four PPD types: thumb/hallux polydactyly (type I), polydactyly of triphalangeal thumb (TPT, type II), polydactyly of index finger (type III), and polysyndactyly or crossed polydactyly (CP, type IV) (Table 1; Fig. 1a–d).

Pre-axial type I

Thumb polydactyly (OMIM-174400)

This is a common presentation of polydactyly in which there is a duplication of one or more components of a biphalangeal thumb (Fig. 1a). Hands are preferentially affected, only hands are affected in bilateral cases, and the right hand is more commonly involved than the left (6). There is a high preponderance of affected males and low frequency of familial recurrence (15, 6).

The phenotypic spectrum form milder to severe ranges as follows: broadness of the distal phalanx (duckbill appearance) or the duplication of distal phalanx; rudimentary extra thumb receiving no tendinous attachment and depicting hypoplasia of the thumb musculature; distinct bifurcation of the distal two third of phalanx but with common base; rudimentary thumb with two supernumerary phalanges which attach near the base of the proximal phalanx, sometimes articulating with the metacarpal head; duplication of whole thumb, comprising a metacarpal and two phalanges (3). This type may also be presented as triplicated thumb resulting in a total of seven digits (heptadactyly or septodactyly) (20).

Familial pre-axial type I segregates autosomal dominantly with reduced penetrance (5, 15). It is a genetically a heterogeneous condition. Mutations in ZRS/SHH are known to cause one subtype of pre-axial I polydactyly (21, 22).

Hallucal polydactyly (OMIM-601759)

The thumb polydactyly may accompany duplication of hallux, however, hallux polydactyly is also known to exist as an isolated entity or a predominant presentation in families (Fig. 1a) (5). Hallux duplication israrer as compared with thumb polydactyly (0.024/1000 vs 0.165/1000 in South America, respectively). Similar to thumb polydactyly, hallux duplication depicted a significant excess in males, involved predominantly the right foot, and was mainly unilateral (81.5%) (15). The molecular bases of isolated hallucal polydactyly remains unknown. A possible causal relationship between maternal diabetes and hallucal polydactyly with a very unusual proximal placement of the extra digit, has been suggested (23). Duplication of halluc

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Pre-axial type II: triphalangeal thumb polydactyly (OMIM-174500)

The biphalangeal thumb is replaced by a TPT (Fig. 1b). There is an extra middle phalanx in the thumb and the first metacarpal is abnormally long and gracile containing epiphyses at both ends (3). Alternatively, a TPT phenotype with normal first metacarpal is usually associated with polydactyly of the thumb. The TPT is usually opposable. In the feet there may be duplication of great toe (3). TPT is frequently bilateral and symmetrical (25). It segregates autosomal dominantly with incomplete penetrance (3). There is a decreased expression in females.

TPT is a rather rare type. It is also presented as a part of a broader phenotypic spectrum. For instance, triphalangeal thumb-PPD, triphalangeal thumb-poly-syndactyly syndrome (TPT-PS), and tibial hemimelia-poly-syndactyly-triphalangeal thumb syndrome (TH-TPTPS) (9). Isolated TPT and several of the TPT-associated limb anomalies have been observed to be caused by the mutations in ZRS/SHH locus at chromosome 7q36 (22). However, ZRS/SHH mutations account for neither all isolated TPT families nor different types of TPT phenotypes, considering that alternative mechanisms could still be responsible for PPD.

Pre-axial type III: polydactyly of index fingers (OMIM-174600)

In this very rare autosomal dominant polydactyly type, there is duplication of index finger (Fig. 1c). The thumb is replaced by one or two triphalangeal digits. There is a distal epiphysis for the metacarpal of the accessory digit, by which this entity is separated from type II polydactyly or TPT (3, 25). There is sometimes PPD of first or second toes.

‘Index polydactyly’ is often lumped together with ‘central polydactyly’, but has also been considered as a variant of thumb duplication (26). The radialis duplicated typically is smaller and the level of duplication may be at the metacarpal or more distal. The additional digit typically is in significant radial deviation or angulations, and the normal digit may be forced into a varying degree of ulnar deviation (27).

Pre-axial type IV: polysyndactyly, CP (OMIM-174700)

In this polydactyly type, the thumb shows mildest degree of duplication, being broad, bifid or with radially deviated distal phalanx (Fig. 1d). Syndactyly of various degrees of third-and-fourth fingers is occasionally present (3). In the feet, there is polydactyly of first toe and the first metacarpal is short and tibially deviated. Syndactyly of second and third toe (or all toes) is present. It is of note that this entity is distinct from synpolydactyly (OMIM-186000), in which syndactyly is associated with additional digit within the web (28, 29).
Table 1. Well-characterized polydactyly types: cardinal features, inheritance and mapped loci/genes

<table>
<thead>
<tr>
<th>OMIM</th>
<th>Type; Symbol</th>
<th>Description</th>
<th>Inheritance</th>
<th>Locus; Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>174400</td>
<td>Pre-axial I; PPD1</td>
<td>Polydactyly of biphalangeal thumb/hallux; hypoplasia of thumb musculature, radial deviation of thumb terminal phalanx</td>
<td>AD, reduced penetrance</td>
<td>7q36; ZRS/SHH</td>
</tr>
<tr>
<td>601759</td>
<td>Pre-axial hallucal polydactyly</td>
<td>Pre-axial hallucal polydactyly, proximal placement of extra digit</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>174500</td>
<td>Pre-axial II; PPD2; TPT-PS</td>
<td>TPT; duplication of distal thumb phalanx, opposable/non-opposable TPT, duplication of great toes. Other phenotypes: TPT-polysyndactyly syndrome (TPT-PS; webbing of 3–4–5; pre-, post-axial polysyndactyly of toes); tibial hemimelia-TPTPS; complex polysyndactyly (TPT-pre-, post-axial polydactyly, syndactyly)</td>
<td>AD, nearly complete penetrance</td>
<td>7q36; ZRS/SHH</td>
</tr>
<tr>
<td>174600</td>
<td>Pre-axial III; PPD3</td>
<td>Duplication of index fingers; thumb replaced by one or two triphalangeal digits, distal epiphyses present for metacarpals of accessory digits; occasional polydactyly of first or second toes</td>
<td>AD</td>
<td></td>
</tr>
<tr>
<td>174700</td>
<td>Pre-axial IV; PPD4; Crossed polydactyly</td>
<td>Polysyndactyly; mild thumb duplication, dysplastic distal thumb phalanges with a central hole; syndactyly of three to four fingers; first or second toe duplication, syndactyly of all toes, crossed type I (post-axial polydactyly in hands and pre-axial in feet); crossed type II (pre-axial polydactyly in hands and post-axial in feet)</td>
<td>AD</td>
<td>7p14.1; GLI3; 7q36; ZRS/SHH</td>
</tr>
<tr>
<td>174200</td>
<td>Post-axial A1 (types A/B); PAPA1</td>
<td>Polydactyly of fifth finger/toe; type A: well-formed articulating extra digit containing one to three phalanges; type B: minor protuberance, a knob like pedunculated postminimi</td>
<td>AD</td>
<td>7p14.1; GLI3; 7q36; ZRS/SHH</td>
</tr>
<tr>
<td>602085</td>
<td>Post-axial A2; PAPA2</td>
<td>Phenotypes A, extra digit is well-formed</td>
<td>AD</td>
<td>13q21-32</td>
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<tr>
<td>607324</td>
<td>Post-axial A3; PAPA3</td>
<td>Phenotypes A/B in hands and feet</td>
<td>AD</td>
<td>19p13.1-13.2</td>
</tr>
<tr>
<td>608652</td>
<td>Post-axial A4; PAPA4</td>
<td>Phenotypes A/B in hands and feet; two to three syndactyly</td>
<td>AD</td>
<td>7q21-q34</td>
</tr>
<tr>
<td>263450</td>
<td>Post-axial A</td>
<td>In hands and feet; minor syndactyly, five to six metacarpal synostosis</td>
<td>AR</td>
<td>13q13.3-q21.2</td>
</tr>
<tr>
<td></td>
<td>Post-axial A</td>
<td>Functionally developed digit in hands and/or feet</td>
<td>AR</td>
<td>4p16.3; ZNF141</td>
</tr>
<tr>
<td>135750</td>
<td>Mirror image polydactyly</td>
<td>Mirror duplication of posterior digits, the supernumerary digits are arranged in descending order or size from a single central digit, absence of a thumb/hallux</td>
<td>AD</td>
<td>14q13; MIPOL; 5q31.1; PITX1</td>
</tr>
<tr>
<td>186200</td>
<td>Haas type</td>
<td>Complete cutaneous fusion of all fingers with additional digit ray in the web</td>
<td>AD</td>
<td>7p14.1; GLI3; 7q36; ZRS/SHH</td>
</tr>
</tbody>
</table>

AD, autosomal dominant; AR, autosomal recessive; PPD, pre-axial polydactyly; TPT, triphalangeal thumb.

A term ‘crossed polydactyly’ is usually employed for the presence of pre-axial and post-axial polydactyly with a difference in axis of the additional digits between the hands and feet. CP type I depicts polydactyly which is post-axial in hands and pre-axial in feet. In CP type II, PPD of hands is combined with post-axial polydactyly of feet (Fig. 1d) (3). Molecular studies have demonstrated that CP type I is allelic to post-axial polydactyly A/B, and mutations in GLI3 as well as ZRS/SHH are known to cause the phenotype (30).

Post-axial polydactyly (OMIM-174200)

There is an occurrence of one or more extra-ulnar or fibular digits or part of it. Specifically for the ulnar polydactyly, two distinct entities have
been recognized, i.e. types A and B, which differ in severity, inheritance pattern and penetrance estimates (3).

Post-axial type A
In type A, the extra digit is rather well-formed and articulates with the fifth or an extra metacarpal/metatarsal (Fig. 2a) (3). Depending upon its size, the extra digit may harbor one to three bony elements, corresponding flexion creases and a well-developed nail. The angle-of-articulation of post-axial digit along the fifth ray is highly variable (i.e. $<30^\circ$–$180^\circ$). In majority of the cases, the additional digit remains non-functional and may pose difficulty in daily-life activities. This type is inherited as an autosomal dominant trait with marked penetrance ($\sim68\%$) (14, 31).
Malik

There is an evidence of autosomal recessive type of post-axial type A (OMIM-263450) (32). In a case–control clinical epidemiological study, Castilla et al. (33) recruited 6586 individuals exhibiting post-axial polydactyly (types A and B as single entity). Through complex segregation analysis, the authors obtained very high heritability value for this trait and a major recessive gene effect (33). Two post-axial recessive types have been mapped to chromosomes 13q13.3-q21.2 and 4p16.3 (ZNF141), respectively (34, 35).

Post-axial type B
In post-axial type B, the most abundant type of polydactyly in various populations, the extra digit is rudimentary ranging from a minor sign of small protuberance on the ulnar aspect of fifth finger to spine-like outgrowth, to a 2–3 cm long nubbin-like ‘pedunculated postminimus’ which usually contains an osseous element and a nail (Fig. 2b) (5). The articulation site of this nubbin along the fifth digit is variable and is usually through a small cutaneous bridge. The upper limbs and the left hand are preferentially affected (6). The genetics of this type has been suggested to be more complicated, and the penetrance estimates are ~43% (5).

Post-axial types A and B have been considered as two distinct and genetically heterogeneous entities due to their independent occurrences and different segregation patterns (5, 3). Contrastingly, however, several other reports witnessed both types in the same kindred and/or individual (31). Mapping studies have revealed that there are at least four distinct autosomal dominant entities (PAPA1–4), all of which exhibit phenotypes A and B, simultaneously (Table 1). PAPA1 is known to be caused by mutations in GLI3 and ZRS/SHH (30, 21). Thus, there is so far no molecular clue that dominantly segregating phenotypes A and B are genetically heterogeneous.

Complex and other polydactylies
This category includes polydactylies which do not fit into the familiar phenotypes of pre-axial or post-axial.

Mirror-image polydactyly of hands/feet: seven fingered hand without thumb (OMIM-135750)
There is mirror duplication of posterior digits and the anterior digits are replaced by the posterior but in reverse order, i.e. the supernumerary digits are arranged in descending order from a single central digit (e.g. 5-4-3-2-3-4-5), with the absence of a thumb/hallux (Fig. 3a) (3). Martin et al. (36) described a family in which the affected subjects had a complete duplication of all fingers with 9 digits on the right and 10 digits on the left, forming a rosebud type configuration, bilaterally. Mirror-image polydactyly (MIP) segregates as an autosomal dominant entity.

Isolated MIP is very rare, while it is normally observed as a part of Laurin-Sandrow syndrome.

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Fig. 2. Schematic diagrams of autopods depicting post-axial polydactylies. Black filled elements depict the affected/polydactylous digits. Digital elements with amorphous borders symbolize dysplastic/hypoplastic bones.
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Fig. 3. Schematic diagrams of autopods showing complex and other polydactylies. Black filled elements depict the affected/polydactylous digits. Digital elements with amorphous borders symbolize dysplastic/hypoplastic bones. Shaded digits represent syndactyly.

OMIM-135750), which is characterized by the duplication of ulna and/or fibula, agenesis of radius and/or tibia, duplication of middle, ring and little fingers, and absence of thumbs. The recurrent involvement of tubular bones of upper and lower limbs has lead to a suggestion of three heritable types of MIP: (i) tibial defect with PPD is a rare, autosomal dominant trait with variable penetrance and expressivity; (ii) agenesis of the tibia and mirror foot; and (iii) ulnar and fibular dimelia (3).

One type of MIP phenotype is caused by mutations in MIPOL1 localized at chromosome 14q13 (37). Additionally, MIP with lower-limb malformations are caused by mutations in PITX1 (38).

Central polydactyly
Central polydactyly, also referred as ‘hidden’ duplications may present as a mass of tissue in the mid part of the hand, with obvious syndactyly and even synonychia. However, not all central types are hidden (Fig. 3c). Central polydactyly like duplications of index finger, usually is inherited autosomal dominantly (27). The anomaly is often bilateral, although contralateral hand deformities of different types (central cleft or complex syndactyly) also can manifest. The ring digit is duplicated most frequently, followed by the long ray, both of which are more common than index digit duplications (3).

Haas type: extra digital ray with extensive syndactyly (OMIM-186200)
Haas type polysyndactyly manifests itself as complete cutaneous fusion of all fingers accompanied by the presence of extra pre- or post-axial ray(s) in the web (Fig. 3b) (39). Owing to an extensive syndactyly the flexion of fingers is limited and the union of contiguous fingers gives the hand a cup-shaped appearance.

Haas type anomaly is usually classified as type IV syndactyly (29). Genetic heterogeneity has been witnessed in Haas polysyndactyly and mutations in GLI3 and ZRS/SHH are known to cause this anomaly (30, 21).

Palmer/ventral and dorsal polydactyly
A very rare and unusual presentation of polydactyly is a supernumerary digit arising from the dorsum (or ventrum) of the autopod. It may be presented as a minor skin appendage or a partially developed digit ray, or a fully developed digit with/without nail and inserted into the autopod/palm as a peg (Fig. 3d). Depending upon the extent of growth, articulation and musculature, the accessory digit could be mobile and active. In the hand, a palmer/ventral origin of a mobile accessory digit is reported (40). Likewise, an accessory digit originating from the dorsum of foot has been described (41). Embryologically, this accessory digit appears to deviate from the antero-posterior axis of digital alignment in
six distinct polydactyly types

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in two different factors, i.e. polydactylies have common genetic bases. Mutations in GLI3, a protein that antagonizes Shh, are common in mirror-image polydactyly. Complete syndactyly resulting in a cup-shaped hand is particularly accompanying recessive type A. Polydactylies with combined pre-axial and post-axial types may also be presented with syndactyly, and there is usually a fusion of fourth to fifth fingers and toes. In post-axial type A, partial cutaneous syndactyly involving digits fourth to fifth (or fifth to sixth) fingers and second to third (or fifth to sixth) toes is a frequent finding. Syndactyly is particularly accompanying a post-axial type A.

On the basis of their etiologies, several researchers have appreciated two main pre-axial polydactylies. In the first type, the additional digit results from the duplication of a thumb, while in the second type the superfluous thumb materializes from variable splitting of the single thumb. In the case of post-axial polydactyly, there may also be two different underlying mechanisms: first, the additional digit may arise from the mass of superfluous cells in the limb field, and second, environmental/stochastic factors trigger the formation of additional digit.

The current molecular data including mapping and mutation studies suggest that several clinically discrete polydactylies have common genetic bases. Mutations in two different factors, i.e. GLI3 and SHH enhancer ZRS/SHH, cause at least six polydactylies, i.e. PPD1, PPD2, TPT-PS, PPD4, PAPA1, and Haas type. This finding demonstrates not only the vital role of these genetic factors in the control of digit number but also the intimate functional crosstalk between GLI3 and SHH during limb development.

In order to understand the etiology of polydactyly, it is imperative to understand the key events taking place during limb development and digit morphogenesis and the role of Shh and Gli3 elucidated by studies on animal models. In humans, embryogenesis of limb occurs between 4 and 8 weeks of gestation. The limb bud grows as a bulge of cells from lateral plate mesoderm covered by a sheath of cells of ectodermal origin. Specific signal centers develop in the growing limb field which guide patterning and anterior/posterior identity, i.e. digit morphogenesis and determination of digit number and identity.

Sonic hedgehog (Shh) is one of three signal centers in the growing limb and it operates from the posterior end (Shh-end or zone of polarizing activity) of the limb bud (Fig. 4a). Shh signaling is pivotal in determining digit number and identity. In a mouse limb, a specific gradient of Shh patterns anterior digits and the length of time that proliferating region cells are exposed to direct Shh signaling patterns the posterior digits. Gli3 protein is an antagonist of Shh, expresses at the anterior end (i.e. opposite to Shh-end, Fig. 4b). The Gli3 itself is a downstream mediator of the Shh pathway and this pathway includes several genes that cause abnormal human phenotypes when mutated (e.g. PTC1, CBP, Smo, Twist, GLI1, and dHand). Gli3 has a dual function: the full-length GLI3 acts as an activator (GLI3A) of Shh pathway while its truncated version GLI3R, acts as Shh repressor. A proper balance between the GLI3A and the GLI3R specifies limb digit number and identity (Fig. 4b,c).

The formation of correct number of digital rays correlates with the size of the digital plate in the autopodium which depends on the amount of tissue available. SHH, by influencing the rate of proliferation of cells in the limb plate, influences the amount of tissue available in the autopodium. Furthermore, ectopic origin of extra digit in the growing limb plate is also possible by minor disturbances by external or stochastic factors during digit morphogenesis. During digit morphogenesis, the digits become demarcated and form the digital rays that are separated by the flattened interdigital tissue. The digits will form in the digital rays and the interdigital tissue will disappear through apoptosis. The simple generation of a wound or minor physical disturbance in the interdigital tissue is sufficient to activate the chondrogenic phenotype resulting in an extra digit. This may at least partly explain why the majority of polydactyly cases are sporadic, isolated and with no evidence of further transmission in family.

The variety of limb phenotypes caused by the mutations in GLI3 or ZRS/SHH reflects the complexity of their interaction as well as the extraordinary importance of the pathway in controlling the number of digits. However, among the intricacies of polydactyly lies genetic heterogeneity. There are many polydactyly phenotypes both pre-axial and post-axial, which are not associated to mutations in GLI3 or ZRS/SHH. Owing to the broad phenotypic variability witnessed particularly in pre-axial type I and post-axial A and/or B, a substantial underlying genetic heterogeneity is expected across different populations and ethnic groups. The clue that many genetic factors involved in the etiology of polydactyly/limb malformations still remain to be identified is also gleaned from the enormous number of anomalies/syndromes in which polydactyly accompanies. The development of innovative methods should allow the dissection of stochastic factors responsible for a copious number of sporadic polydactylies.
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Fig. 4. Schematic depiction of the growing limb bud (a) with five digits precursor zones materializing through the SHH-GLI3 antagonism along the antero-posterior developmental axis. Shh is turned on in the posterior through the early expression of Hoxd genes and dHAND (shown in the pathway) (b). Expression domains of SHH at the posterior axis and GLI3 at the anterior axis, shown as gradients. (c). Schematics of limb depicting various polydactylies which could be identified as pre-axial, meso-axial or post-axial types. Mutations in GLI3 and ZRS/SHH cause both pre-axial and post-axial polydactylies.

Supporting Information
The following Supporting information is available for this article:
Table S1. Summary of contributions in polydactyly classification (selected publications)
Additional Supporting information may be found in the online version of this article.

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