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MINIREVIEWS

Polydactyly: Clinical and molecular manifestations

Zisis Kyriazis, Panagoula Kollia, Ioanna Grivea, Nikolaos Stefanou, Sotirios Sotiriou, Zoe H Dailiana

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Abstract

Polydactyly is a malformation during the development of the human limb, which is characterized by the presence of more than the normal number of fingers or toes. It is considered to be one of the most common inherited hand disorders. It can be divided into two major groups: Non-syndromic polydactyly or syndromic polydactyly. According to the anatomical location of the duplicated digits, polydactyly can be generally subdivided into pre-, post-axial, and mesoaxial forms. Non-syndromic polydactyly is often inherited with an autosomal dominant trait and defects during the procedure of anterior-posterior patterning of limb development are incriminated for the final phenotype of the malformation. There are several forms of polydactyly, including hand and foot extra digit manifestations. The deformity affects upper limbs with a higher frequency than the lower, and the left foot is more often involved than the right. The treatment is always surgical. Since the clinical presentation is highly diverse, the treatment combines single or multiple surgical operations, depending on the type of polydactyly. The research attention that congenital limb deformities have recently attracted has resulted in broadening the list of isolated gene mutations associated with the disorders. Next generation sequencing technologies have contributed to the correlation of phenotype and genetic profile of the multiple polydactyly manifestations and have helped in early diagnosis and screening of most non-syndromic and syndromic disorders.

Key Words: Polydactyly; Gene; Syndromic; Non-syndromic; Preaxial; Postaxial

Core Tip: The molecular basis of hand and foot polydactyly, syndromic or non- syndromic, is diverse. There are several phenotypes of the disorder which are correlated to a specific molecular profile and other whose molecular basis is still unclear. We summarize and provide an overview of gene mutations that cause hand and foot polydactyly as an isolated disorder or as part of a syndrome and present the clinical manifestations that they cause.

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INTRODUCTION

Non-syndromic (Table 1) or syndromic polydactyly (Table 2) is often inherited with an autosomal dominant trait with variable penetrance[1]. It is related with a disturbance of the anterior–posterior axial development procedure of the limb[2] and is classified into preaxial, axial (central), and postaxial polydactyly[3]. Preaxial polydactyly is defined as an extra digit affecting the radial/tibial digits while postaxial involves the ulnar/peroneal digits. The rare type of axial (central) polydactyly refers to the duplication of three central hand or foot digits. Mirror-image polydactyly and Haas-type polysyndactyly are rare and distinct types, not fitting to the three categories[4].

Many specific phenotypes, including all types of hand and foot polydactyly, have been identified and correlated to gene mutations[5].

Since polydactyly is often a part of a syndrome, the ability to identify the potential syndromes associated with this anomaly is very important for the clinician. Additionally, it is important to distinguish between syndromic and non-syndromic cases for reasons of genetic counselling. In this paper, we review the recent progress in the molecular genetics, including clinical and molecular manifestations of disorders, and present some representative syndromes including polydactyly as a phenotype.

CLINICAL AND MOLECULAR MANIFESTATIONS OF NON-SYNDROMIC HAND AND FOOT POLYDACTYLY

Preaxial polydactyly

The preaxial form of polydactyly is the second most common phenotype behind the postaxial with a reported prevalence of approximately 0.8 to 2.3 in 10000 live births. It is characterized by an extra digit on the tibial/radial side of limb (Figure 1). The following classification has been suggested:

Preaxial polydactyly type I, which is thumb polydactyly (*OMIM 174400*)[6]—characterized by duplication of one or more skeletal elements of a biphalangeal thumb.

Preaxial polydactyly type II, which is polydactyly of a triphalangeal thumb (*OMIM 174500*).

Preaxial polydactyly type III, which is polydactyly of the index finger, characterized by the presence of one or two triphalangeal digits (*OMIM 174600*).

Preaxial polydactyly type IV and syndactyly of various degrees involving the middle and ring finger/second and third toe (*OMIM 174700*) or hallux polydactyly (*OMIM 601759*)[7].

Preaxial polydactyly type I: Thumb polydactyly is usually observed in unilateral form. In bilateral cases, hands are more often affected and the left hand is also more often affected than the right. It follows an autosomal dominant inheritance model[7]. However, a recent study in a Pakistani family has revealed a rare autosomal recessive form of preaxial polydactyly, linked to a novel variant (c.1517T>A; p. Leu506Gln) in the *GLI1* gene on chromosome 12q13.3[8].

The most commonly used classification is Wassel classification which divides thumb duplication into six subtypes according to the level and the extent of duplication (partial or complete)[9]. Hallux polydactyly is known to exist as a predominant presentation or an isolated disorder. The incidence of hallux duplication is 2.4/100000 as compared to thumb polydactyly incidence in South America, which is 1.65/10000.

Preaxial type I polydactyly is caused by sequence variants in the sonic hedgehog (*SHH*) enhancer, called zone of polarizing activity (*ZPA*) regulatory sequence (*ZRS*), which is regulated by *LMBR1* gene.

Table 1 Mutated genes isolated in non-syndromic polydactyly

Preaxial	Central	Postaxial	Complex
CEP290	*CPLANE1*	*GLI3*	*MIPOL1*
RPGRIP1		*ZNF141*	*PITX1*
TMEM216		*DACH1*	*LMBR1*
FBN1		*GLI1*	
CEP164			
MEGF8			
LMBR1			
ZRS			
GLI3			
ZNF141			
STKLD1			
GLI1			
KIAA0586			
EVC			
HES1			

Table 2 Mutated genes isolated in syndromic polydactyly

Syndrome	Mutated gene(s)
Bardet-Biedl	*CCDC28B, ARL6, MKS1, BBS8, SDCCAG8, LZTFL1, WDPCP, BBS4, BBS12, TMEM67, BBS1, BBS2, BBS6, BBS10, BBS9, BBS7, BBS5, CEP290, TRIM32, BBIP1, ALMS1, MKKS*
McKusick-Kaufman	*MKKS*
Carpenter	*P4HB, RAB23*
Saethre-Chotzen	*TWIST1, FGFR2*
Poland syndrome	-
Greig cephalopolysyndactyly	*GLI3*
Short-rib polydactyly	*ATD1, LBN, DYNC2H1, IFT81*
Pallister-Hall	*GLI3*
Triphalangeal thumb-polydactyly	*LMBR1*
Smith-Lemli-Opitz	*DHCR7*

Mutations in *CEP290, RPGRIP1, TMEM216, FBN1, CEP1*, and *MEGF8* genes have been isolated and suspected to play a role in Wassel III and Wassel IV manifestations[10]. Recently, a mutation in *STKLD1* gene, located on chromosome 9q34.2, was found and correlated with the disease phenotype in all members of the studied family[11]. Another molecular study of the *SHH/GLI* signaling axis, identified *HES1* gene as a downstream modifier which can cause preaxial polydactyly[12].

Next generation sequence analysis in a large four-generation family with isolated preaxial polydactyly revealed a new *ZRS* mutation (g.101779T>A) which can cause the disease phenotype[13]. Another recent genetic analysis of 20 Chinese patients with preaxial polydactyly identified two novel mutations in *GLI3* gene (c.G2844A) and in *EVC* gene (c.1409_1410del). Mutations in *KIAA0586* gene, which are related with ciliopathies (*OMIM 610178*), were also detected[14].

Preaxial polydactyly type II: Preaxial polydactyly type II is characterized by the presence of a usually opposable triphalangeal thumb with or without additional duplication of one or more skeletal components of the thumb. The thumb appearance can differ widely in shape or it can be deviated in the radio-ulnar plane. It can also be associated with Holt-Oram syndrome and Fanconi anemia. *LMBR1* and its related pathways *Wnt/Notch* and *Hedgehog* play a significant role in the development of the disorder. The disease gene locus was mapped to chromosome 7q36[15]. Mutations in the *SHH* regulatory factor

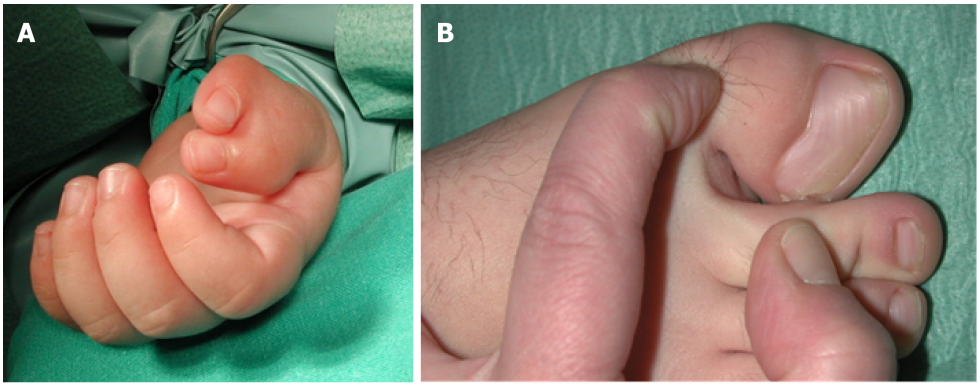

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Figure 1 Preaxial polydactyly. A: Preaxial/radial hand polydactyly phenotype; B: Preaxial/tibial foot polydactyly phenotype.

were also reported[16]. Two mutations, a 739A>G transition near the 5- end of the *ZRS* and a 621C>G mutation in the *ZRS* of the *LMBR1* gene, were identified[17]. Triphalangeal thumb-polysyndactyly can manifest as a syndrome. It is an isolated limb deformity characterized by pre- and postaxial polysyndactyly of hands and feet. Mutations in *ZRS* have been identified[18,19].

Preaxial polydactyly type III: Preaxial polydactyly type III is an autosomal dominant disorder which is characterized by a malformation of fingers, where the thumb is replaced by one or two triphalangeal digits with dermatoglyphic pattern specific for the index finger. It can occur unilaterally and bilaterally. No responsible gene has been identified[20].

Preaxial polydactyly type IV: Preaxial polydactyly type IV is an autosomal dominant disorder which can be described as mild duplication of the thumb, syndactyly that affects the third and fourth hand/foot fingers/toes, duplication of the first or second toes, and toes syndactyly. There are patients who have only foot malformations. *GLI3* gene mutations are associated with the disorder. Genetic analysis in two families with the phenotype were found heterozygous for p.L1216PfsX31 and p.R290X mutations in the *GLI3* gene[21].

Postaxial polydactyly

Postaxial polydactyly is a frequent congenital hand malformation characterized by fifth digit duplications in hands and/or feet (Figure 2). Its prevalence is estimated between 1/630 and 1/3300 in Caucasian race and between 1/100 and 1/300 in Black race. Two phenotypic categories have been described: Type A, the extra digit is well formed and articulates with the fifth or an extra metacarpal; Type B, there is a rudimentary extra fifth digit which is usually represented by an extra skin tag. Both types can be inherited by autosomal dominant or recessive trait[22]. There are six subcategories of type A postaxial polydactyly.

Postaxial polydactyly type A1: In postaxial polydactyly type A1, the extra digit is well-formed and articulates with the fifth or a sixth metacarpal/metatarsal. Genetic analysis in an Indian family resulted in the identification of association of *GLI3* gene mutations with the phenotype[23]. It was mapped to 7pl5-q11.23. Mutation in the C- and the N-terminal or the zinc finger domain of the *GLI3* gene causes isolated postaxial polydactyly type A1 and is also linked to Greig cephalopolysyndactyly syndrome, while a mutation in the post-zinc finger region is incriminated for Pallister–Hall syndrome[24]. A recent genetic study in a Chinese family with isolated postaxial polydactyly revealed a new mutation of *GLI3* (c.1180C>TT, p.P394fs18x)[25]. A *DACH1* gene mutation was identified in a patient with bilateral postaxial polydactyly who was subjected to whole exome sequencing[26]. New mutations of the *GLI1* gene have been incriminated for postaxial polydactyly according to a novel study which aims to help in prevention of the disorder[27].

Postaxial polydactyly type A2: It consists of Type A polydactyly phenotypes with an extra digit well-formed. A genetic study of an Indian kindred revealed disease gene locus of postaxial polydactyly type A2 (*OMIM 602085*) which was mapped to 13q21-q32[28]. The underlying gene for the disorder has not been identified.

Postaxial polydactyly type A3: It manifests with polydactyly phenotypes Type A/B in hands and feet. Genetic analysis of a Chinese family discovered incomplete penetrance of the phenotype and identified the disease gene locus which was mapped to 19p13.2-p13.1[29]. There is not an identified gene responsible for the disorder.

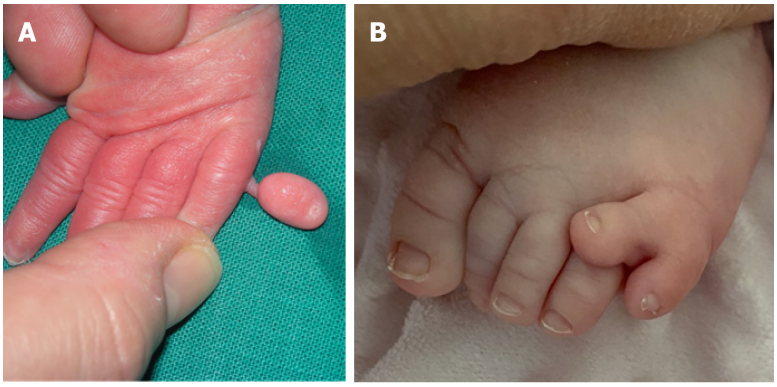

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Figure 2 Postaxial polydactyly. A: Postaxial/ulnar hand polydactyly phenotype; B: Postaxial/fibular foot polydactyly phenotype.

Postaxial polydactyly type A4: It is characterized by polydactyly phenotypes Type A/B in hands and feet and two to three finger/toe syndactyly. The disease locus (*OMIM 608562*) was mapped to 7q21-q34 by genetic analysis in a Dutch family with an autosomal dominant inheritance of the phenotype[30]. Until now there is no candidate gene for this manifestation.

Postaxial polydactyly type A5: It is characterized by polydactyly of hands and feet, minor syndactyly, and five to six metacarpal synostoses. Two Indian families and a Sicilian family were identified to have this type of autosomal recessive postaxial polydactyly[31]. Postaxial polydactyly type A5 (*OMIM 263450*) was mapped to 13q13.3- 13q21.2 region. The underlying gene for this phenotype has not yet been identified.

Postaxial polydactyly type A6: The phenotype is characterized by an extra functionally developed digit in hands and/or feet. Mutations in the *ZNF141* gene are considered to cause postaxial polydactyly type A6 (*OMIM 615226*). Exome sequencing in a Pakistani family resulted in showing autosomal recessive inheritance of A6 phenotype. The *ZNF141* gene consists of four exons[32]. The final protein is expressed in many different tissues and it is still unclear whether it plays a role in embryogenesis[33].

Postaxial polydactyly type B: It is the most common type of polydactyly. There is a vestigial nonfunctional, partially formed, ulnar (or fibular) digit with no bony attachments, attached by a narrow neurovascular pedicle to the lateral aspect of the hand or foot[25]. *GLI3* gene mutations are associated with this often manifestation.

Central polydactyly

Central polydactyly (*OMIM 174200*) is a very rare phenotype which is characterized by duplication of one of the three middle digits of the hand and foot. It can be an isolated defect or can be accompanied with other anomalies. The most often manifestation of hand central polydactyly is duplication of the fourth digit[3]. Foot central polydactyly is very rare and the second toe is most commonly duplicated [34]. Central polydactyly is related to split-foot malformation with mesoaxial polydactyly and Holzgreve syndrome. *CPLANE1* is the only known gene which is associated with central polydactyly.

Complex types

Mirror image polydactyly: This rare non-syndromic limb malformation (*OMIM 135750*) presents with mirror-image hand or foot polydactyly. The malformation can be unilateral, bilateral, and very rarely tetramelic. It can be associated with other congenital anomalies or can present isolated. *MIPOL1* and *PITX1* gene mutations have been identified and incriminated for this disorder. A recent German study in a patient with the phenotype showed a heterozygous deletion of 4.9 Mb on 5q31 including *PITX1*[35].

Haas-type polysyndactyly: Haas-type polysyndactyly (*OMIM 186200*) is characterized by complete cutaneous syndactyly of all hand fingers and occasionally foot toes are affected. It frequently presents with polydactyly with six digits and six metacarpals. It is inherited with an autosomal dominant trait. It is usually classified as syndactyly type IV. The locus for Haas-type polysyndactyly was mapped on 7q36 by linkage and haplotype analysis of a Chinese family[36]. Mutations of the *ZRS* region of *LMBR1* gene and other *ZRS* point mutations were found in families presenting with the clinical sings of Haas-type polysyndactyly according to two recent studies[37,38].

CLINICAL AND MOLECULAR MANIFESTATIONS OF SYNDROMIC HAND AND FOOT POLYDACTYLY

Bardet-Biedl syndrome

Bardet-Biedl syndrome (*OMIM 209900*) is an autosomal or digenic recessive disorder which can present with vision loss, obesity, hand and/or foot polydactyly, intellectual disabilities, and hypogonadism. Mutations in at least 20 genes have been identified and associated with the syndrome[39]: *CCDC28B*, *ARL6*, *MKS1*, *BBS8*, *SDCCAG8*, *LZTFL1*, *WDPCP*, *BBS4*, *BBS12*, *TMEM67*, *BBS1*, *BBS2*, *BBS6*, *BBS10*, *BBS9*, *BBS4*, *BBS7*, *CEP290*, *TRIM32*, *BBIP1*, *IFT27,* and *IFT172*genes are examples of them. A recent study in four Iranian children with a clinical diagnosis of Bardet-Biedl syndrome identified in three children one previously reported mutation in *BBS12* gene (c.265-266delTT, p.L89fs) and two newly detected mutations in *MKKS* (c.1196T>G, p.L399X) and *BBS7* gene (c.1636C>T, p.Q546X). A new mutation in *ALMS1* gene was isolated in the other child[40].

McKusick-Kaufman syndrome

McKusick-Kaufman syndrome's phenotype (*OMIM 236700*) consists of the following features: Genitourinary malformations (hydrometrocolpos, glanular hypospadias, and prominent scrotal raphe), postaxial hand and/or foot polydactyly, and rarely cardiac defects. *MKKS* gene mutations are associated with McKusick-Kaufman syndrome and they are inherited with an autosomal recessive trait [41].

Carpenter syndrome

Carpenter syndrome (*OMIM 201000*) is characterized by craniosynostosis, involving a pointed head (acrocephaly), syndactyly of certain fingers or toes, and polydactyly. It appears most commonly with foot polydactyly, rarely hand polydactyly and hand or toe cutaneous syndactyly. *RAB23* gene mutations are associated with the syndrome, which appears with autosomal recessive inheritance[42]. Recent molecular studies have identified two new mutations in *RAB23* gene (NM_001278668:c.T416C:p.Leu139-Pro and NM_016277.5:c.398+1G>A)[43] and a new mutation in *P4HB* gene [44].

Saethre-Chotzen syndrome

Saethre-Chotzen syndrome's phenotype (*OMIM 101400*) is characterized by premature closure of cranial sutures, hand syndactyly, and foot polydactyly. Foot polydactyly most often involves the first toe. *TWIST1* and *FGFR2* gene mutations are usually incriminated and inherited with an autosomal dominant trait[45].

Poland syndrome

Poland syndrome (*OMIM 173800*) involves underdeveloped pectoralis muscles on one side of chest wall and ipsilateral hand abnormalities, including short fingers and syndactyly (symbrachydactyly); however, there are rare cases of preaxial polydactyly manifestations in the literature[46]. Most cases of Poland syndrome are not related with a family history, and they are sporadic. Rarely it is inherited with an autosomal dominant trait through generations in families. There are no isolated gene mutations correlated with Poland syndrome.

Greig cephalopolysyndactyly syndrome

Greig cephalopolysyndactyly (*OMIM 175700*) syndrome is an autosomal dominant syndrome, which presents with hypertelorism, macrocephaly, and polydactyly. The polydactyly is most commonly preaxial of the feet and postaxial in the hands. Greig cephalopolysyndactyly is associated with *GLI3* mutations[47]. Recently, molecular studies have broadened the spectrum of known *GLI3* mutations correlated with the syndrome[48,49].

Pallister-Hall syndrome

Pallister-Hall syndrome (*OMIM 146510*) is a rare disorder which affects many parts of the body. Very often manifestation of the syndrome is postaxial polydactyly and cutaneous syndactyly of hands and toes. *GLI3* gene mutations are considered responsible for this autosomal dominant disorder[50].

Short-rib polydactyly

Jeune syndrome, Ellis-van Creveld syndrome, Saldino-Noonan syndrome, and Majewski syndrome are called short-rib polydactyly syndromes (*OMIM 613091*). They belong to a group of lethal congenital disorders characterized by shortening of the ribs and long bones, hand and/ or foot polydactyly, and a range of extraskeletal phenotypes. *ATD1* gene is considered to be responsible for Jeune syndrome. *LBN* gene mutations cause Ellis-van Creveld syndrome and individuals carrying *DYNC2H1* gene mutations can present with Saldino-Noonan and Majewski syndromes. Novel exome sequencing studies have isolated two new mutations in *DYNC2H1* gene (c.8077G>T and c.11741_11742delTT) and a new mutation in *IFT81* gene, causing malformation of the cilia[51,52]. Short-rib polydactyly syndromes are

usually inherited with an autosomal recessive trait[53].

Triphalangeal thumb-polydactyly syndrome

Triphalangeal thumb-polydactyly syndrome (*OMIM 173800*) consists of triphalangeal thumbs, pre- or post-axial polydactyly, and syndactyly. *LMBR1* gene is considered to be responsible for this manifestation. It is inherited with an autosomal dominant genetic trait. Typically, the syndrome presents with duplicated triphalangeal thumbs and typical phenotypic findings include duplicated triphalangeal thumbs and syndactyly between middle, ring, or little finger[54].

Smith-Lemli-Opitz syndrome

Smith-Lemli-Opitz syndrome (*OMIM 173800*) is a multi-malformation syndrome. The responsible gene for this syndrome is considered to be *DHCR7* gene and it is inherited with an autosomal recessive pattern[55]. Its phenotype contains foot syndactyly (usually of 2nd and 3rd toes) and postaxial hand polydactyly.

CONCLUSION

Genetic mechanisms which combine epigenetic and environmental factors play a significant role in foot and hand polydactyly manifestations[56]. Proper genotype-phenotype correlations might help in future genetic testing and enhance our knowledge about identified diseases and their associated genes. Recent genetic analysis techniques of extra foot or hand digit formation highlight the existence of nongradual transitions in phenotypes, suggesting a distinction between continuous and discontinuous variation in evolution. Genome sequencing will probably lead to the discovery of a number of new gene mutations responsible for non-syndromic or syndromic polydactyly. Clinical manifestation and genetic profile correlation of polydactyly types will be further established by use of bioinformatics analysis of gene mutations. Progress of prenatal diagnosis, which is still mostly postnatal, prenatal operative treatment planning, and potential future gene modification treatment will be enhanced and unknown molecular background of diseases, which is to date unclear, will be elucidated.

FOOTNOTES

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