REVIEW ARTICLE

Syndactyly genes and classification: a mini review

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ABSTRACT

Syndactyly (Syn = together; Dactylos = digits) is the most common limb defect mostly characterized by webbing of digits. It may be webbing with or without bony fusion and inherited mostly in autosomal dominant manner, although also reported as autosomal recessive, X-linked or isolated entity. It also shows diverse clinical and phenotypic heterogeneity and mostly observed as unilateral or bilateral and symmetrical or asymmetrical forms. Syndactyly mostly occurs either as an isolated anomaly or as a part of a complex syndrome (+150 syndromes). Here, non-syndromic syndactyly has been classified according to genetic and molecular basis. The non-syndromic syndactyly has been classified into nine different types. Up till now, the major genes identified to cause hereditary syndactyly are mainly involved in the sonic hedgehog pathway and zone of polarizing activity. The present review mostly focuses on summarizing the recent advances in molecular genetics, including known genes and loci responsible for non-syndromic syndactyly. The present review will contribute to the understanding of the pathogenesis underlying non-syndromic and syndromic syndactyly, improving clinical and molecular diagnosis; thus, making genetic counseling and prenatal testing easier in future.

Keywords: Limb malformation, syndactyly, digit webbing, molecular genetics.

Introduction

The term syndactyly originated from the Greek word "Syn" meaning together and "Dactylos" meaning digits. Syndactyly is a limb abnormality more specifically a digital abnormality where contiguous phalanges and/or toes are webbed due to the embryological failure of phalanges to separate during limbs development. It is common in several species, including kangaroos and birds. The incidence of syndactyly is 3–10/10,000 births, depending on the form of syndactyly either syndromic or non-syndromic, though much higher assessments (10–40/10,000) have also been reported (1,2). Clinically, syndactyly is classified as a heterogeneous group of a genetic disorder of hands and feet, it may be symmetrical or asymmetrical, unilateral or bilateral. Syndactyly can be described as cutaneous or boney, partial or complete, involving the phalanges and can be extending up to carpal/tarsal or metacarpal/metatarsal levels (3). Syndactyly is expressed in autosomal dominant, autosomal recessive, and isolated forms. The recent classification scheme describes nine types of syndactyly with subdivisions, showing its affinity with other digit abnormalities, such as oligodactyly, polydactyly, and brachydactyly (4,5). In the present review, signaling pathways, molecular epidemiology, and clinical genetics have been focused on non-syndromic syndactyly.

Developmental Pathways and Genes Involved

The limb formation in the vertebrate is linked with many genes that encode specific proteins, which play a very important role in development and differentiation. Numerous signaling pathways have been reported to play a very important part in various developmental processes, tissue-specific gene activation, cis-regulatory regions in-activation, and animal mouse models which are commonly generated for severe human syndromes. During the 4th and 8th weeks of development, the limb buds arise from the main body (trunk). Many different players such as fibroblast growth factor (FGF), retinoic acid, T-boxe (TBX) transcription factors, and Wingless/Integrated (WNT) signaling pathways help in the initiation of limb bud development (6).

Initially, along with the three asymmetrical axes, the limb bud is directed by mesodermal cells growth. These axes include the anterior-posterior axis (thumb to little finger), dorsal-ventral axis (back to the palm of the hand), and the proximal-distal axis (shoulder to finger). The anterior-posterior axis appears most important in

digit formation. The final limb architecture fallouts as a result of cell fate determination, cell differentiation, proliferation, and also apoptosis (7).

The human limb structure is controlled by two main signaling centers including the zone of polarizing activity (ZPA), which controls the overall patterning in relation to the anterior-posterior axis and the apical ectodermal ridge (AER) that plays a very important part in limb growth. Different pathways reported having a substantial role in the development of limbs including cartilage-derived morphogenetic proteins, FGFs, hedgehog pathways, bone morphogenetic proteins (BMPs), and WNTs (8).

Sonic hedgehog (SHH) and Indian hedgehog (IHH)

The Sonic hedgehog (SHH) pathways expressed in the ZPA (controlling anterior-posterior limb patterning) have been mostly associated with both syndactyly and polydactyly phenotypes. In the posterior mesenchyme, the activation of SHH expression is controlled by interactions of HAND2 and HOX transcription factors with the GLI3. Different transcription factors (such as Gli3, Alx4, several BMP antagonists, and dHand) have been reported to be involved in the ZPA and SHH interactions. Pathogenic mutations in any of these transcription factors cause severe limb malformations including syndromic types of syndactylies (9). In particular, chondrocytes, regulation, and differentiation Indian hedgehog (IHH) that is biologically similar to SHH and mostly expressed in the FGF 3 (9). IHH has been reported to cause several congenital anomalies and also involved in the later development of syndactyly (10). Cilia function in the SHH signal transduction is vital. Different proteins and GLI that are essential for SHH signal transductions are localized and processed in the cilium. Thus, mutations in the genes involved in the development of cilium cause severe disorders known as ciliopathies by either gain or loss of SHH pathway. These ciliopathies include phenotypes such as polydactyly, syndactyly, and other severe anomalies, e.g., Ellis-van Creveld syndrome (MIM 225500), Bardet Biedl syndrome (MIM 20900), and Postaxial polydactyly (IQCE) (11,12).

WNT signaling pathways and fibroblast growth factors (FGF)

The WNT6 and WNT10B (Wingless-type MMTV integration site family) have been involved in the development of somites, limb bud, reproductive system, and apoptosis in the mouse. Mutations in the WNT10B (MIM 601906) have been reported to cause split hand foot malformation mapped on chromosome 12q13.12, having severe syndactyly phenotypes while the human WNT6 (MIM 604663) has been mapped to 2q35 (13–15). The FGF have been reported to be involved in the mesenchymal ossification and expressed along the WNTs. The Fgf8 expression during AER formation is activation and conditional in-activation reduce the limb bud size in the mouse embryos; thus, resulting in the reduced femur, hypodactyly, and stylopod hypoplasia (16).

Bone morphogenetic proteins (BMPs)

Similarly, the BMPs and growth and differentiation factors (GDFs) are cytosine knot proteins that help in inducing the eptopic bones and belong to the superfamily of transforming growth factor β blocking the BMPs has been reported to cause syndactyly, having a possible role in apoptosis and influence the digit number, respectively (17). The role of interdigital mesenchyme is also important and its removal resulted in the loss of digit integrity in chickens (18). In chick limb, the BMP and FGF signaling occurs downstream of SHH signaling (7). Furthermore, the involvement of the transcription factors such as zinc finger (ZNF) and N-Myc cannot be ignored and cause syndactyly in mice (10).

The HOX clusters

The transcription factors that originate from HOX clusters (HOXA-D) have a key role during mouse limb development. The 39 known HOX genes are organized into four clusters, which control the development of limbs, central nervous system, axial skeleton, and gastrointestinal tract. Mutations or deletions in one or more HOX genes (A–D clusters) have been reported to cause limb abnormalities (19–22).

Sal-like Zinc finger transcriptional repressors

The Sal-like ZNF transcriptional repressors genes such as (Sall1, Sall3, and Sall4) are expressed in distal limb buds. The SALL4 protein interacts with the TBX and the WNT signaling pathways, thus presenting several phenotypes. SALL4 gene mutations in humans cause Okihiro/Duane-radial ray deficiency syndrome having features such as radial ray defects, facial asymmetry, strabismus, as well as malformations of the anus, kidney, heart, hearing loss, and feet. Mouse lacking Sal1 and Sal3 suffer from severe limbs defects such as syndactyly, digit loss, and hypodactyly (23).

The DLX homeodomain

The DLX homeodomain transcriptional factors include six members including DLX1/2, DLX3/7, and DLX5/6 that mostly regulate Runx2 expression during osteoblast differentiation and BMP pathways. The DLX5/6 are expressed in the AER while pathogenic mutations in these genes have been reported to cause ectrodactyly limbs phenotypes (SHFM1; 24).

As syndactyly types are mostly inherited dominantly while the autosomal recessive inherited types show more severe features. To date, 11 loci and 8 disease-causing genes have been identified for non-syndromic syndactyly including HOXD13, FBLN1, GJA1, LMBR1, LRP4, GREM1, FMN1, and FGF16 while disease-causing genes for other syndactyly types have not been identified yet.

Current Classification

The Temtamy-McKusick classification has been an adopted scheme of syndactyly classification. The current review is an adaptation and extension of Malik and Temtamy-McKusick system of classification by highlighting the genetic, clinical, and molecular developments and pathways involved in the pathogenesis of syndactyly (3,4; Figure 1, Table 1, Supplementary Table 1).
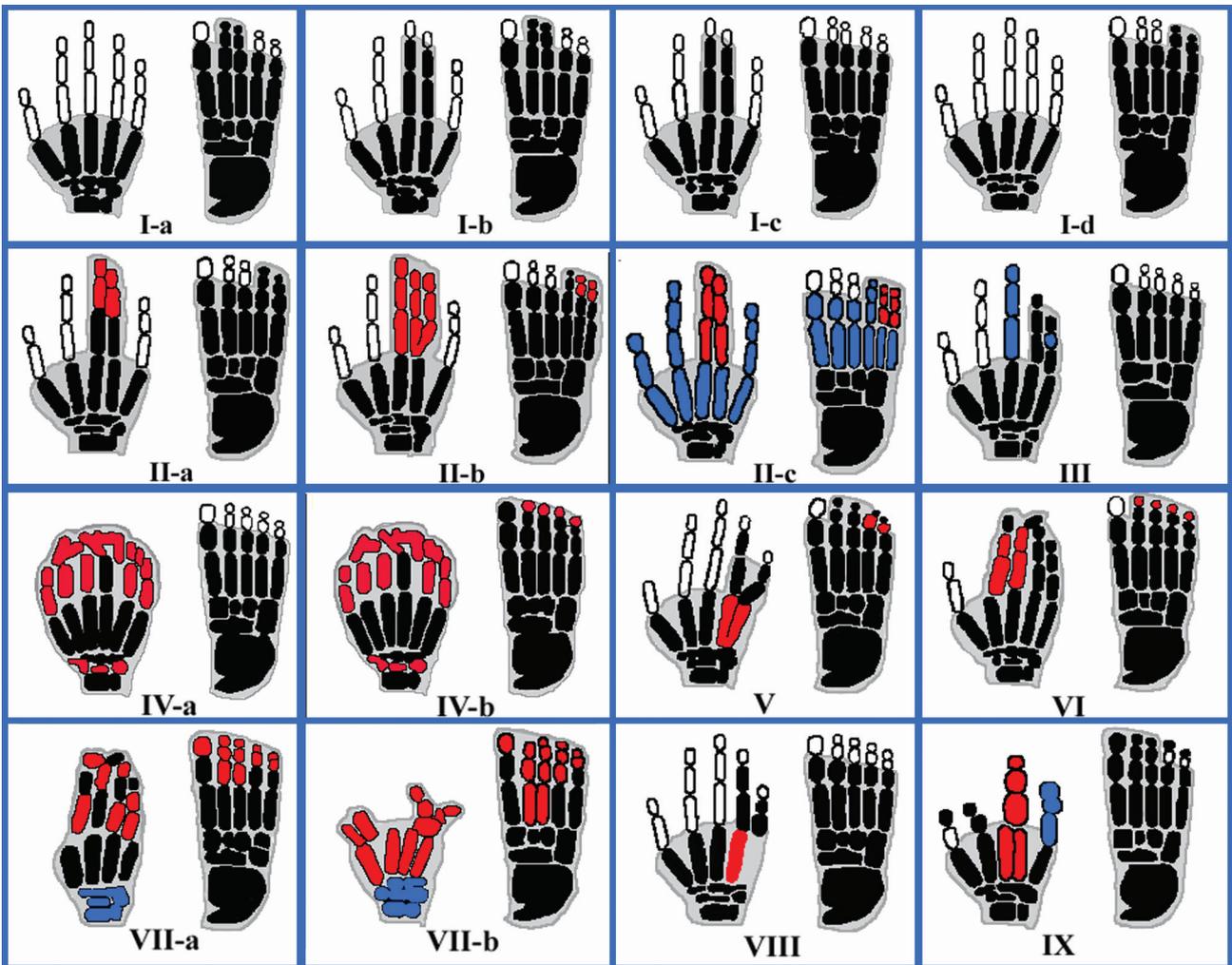
Syndactyly type I (SD1)

Syndactyly type I (MIM 185900) is responsible for the majority of isolated syndactyly cases and inherited in an autosomal dominant form (2). SD1 is phenotypically characterized by partial or complete webbing of the 2nd and 3rd toes and the 3rd and 4th fingers while bony fusion is also associated with SD1. Based on current classification and clinical observations, SD1 can be subdivided into four types (SDI-a, SDI-b, SDI-c, and SDI-d).

Syndactyly type I-a

SDI-a (MIM 609815) also known as Weidenreich type (MIM 609815) involves bilateral fusion of the 2nd and 3rd toes, not including hand abnormalities. Malik et al. (5) designated and proposed ZD1 locus for zygodactyly and mapped this subtype to chromosome 3p21.31 in a large Pakistani family. It mostly involves cutaneous webbing of the 2nd and 3rd toes without hand involvement affecting fewer females than males.

Syndactyly type I-b

SD1-b (MIM 185900), known as the Lueken type (MIM 185900), and the second most frequent type of syndactyly type I. Clinical features include bilateral cutaneous 3rd and 4th fingers and fusion of the 2nd and 3rd toes. A large German syndactyly type 1b family was mapped by Bosse et al. (25) on chromosome 2q34-q36. This locus was known as SD1 locus. The disease-causing gene has not been identified while the locus was later confirmed in an Irani family (25,26).

Figure 1. *Cartoonic representation of non-syndromic syndactyly types. Red portion represents synostosis and blue region represents clinodactyly and other abnormalities. (Figure was composed following Malik [4] design.)*

Table 1. Genetic loci and disease-causing genes for non-syndromic syndactyly.

ID	Type	OMIM	Inheritance	Locus	Gene	Gene/Locus OMIM Number	References
I-a	ZD1	609815	AD	3p21.31	–	–	[5]
I-b	SD1	185900	AD	2q34-q36	–	–	[5,25]
I-c	Montagu type	–	AD	2q31-q32	*HOXD13*	142989	[5,28]
I-d	Castilla type	–	AD?	–	–	–	[4,5]
II-a	SPD1	186000	AD	2q31	*HOXD13*	142989	[18,19]
II-b	SPD2	608180	AD	22q13.3	*FBLN1*	135820	[30]
II-c	SPD3	610234	AD	14q11.2-q13	–		[13]
III	SDTY3	186100	AD	6q21-q23	*GJA1*	121014	[35,36]
IV-a	SDTY4	186200	AD	7q36	*ZRS (LMBR1)*	605522	[39–43]
V	SDTY5	186300	AD	2q31	*HOXD13*	142989	[44,45]
VI	Mitten type	–	AD	–	–		[3]
VII-a	Cenani-Lenz type	212780	AR	11p12-p11.2	*LRP4*	604270	[15,19]
VII-b	Oligodactyly type	–	AD	15q13.3	*FMN1- GREM1*	136535	[51]
VIII-a	Metacarpal 4–5 fusion	309630	XLR	Xq21.1	*FGF16*	300827	[54,55]
VIII-b	Lerch type	–	AD	–	–		[56]
IX	MSSD	609432	AR	17p13.3	*BHLHA9*	615416	[59]

Abbreviations: AR = autosomal recessive, AD = autosomal dominant, XLR = X-Linked recessive.

Syndactyly type I-c

SD1-c is also known as the Montagu type or 3rd and 4th fingers syndactyly. SD1-c is characterized by phenotypes such as bilateral or unilateral cutaneous or bony webbing of the 3rd and 4th fingers and occasionally of the 4th and 5th fingers, with no involvement of feet (27). The locus for the SD1-c was mapped to chromosome 2q31-2q32, and two mutations (p.R306G and p.R306Q) were identified in the homeodomain of the *HOXD13* gene in two Chinese families (28).

Syndactyly type I-d

SD1-d also known as the Castilla type syndactyly, only reported in an epidemiological study. It is characterized by webbing of the 4th and 5th toes. This fourth subtype is very rare and little is known about it. No locus/gene has been identified for the rare SD1-d subtypes (2).

Syndactyly type 2 (SD2)

SD2 (MIM 185900), also called synpolydactyly or Vordingborg type. It is genetically and clinically one of the most heterogeneous groups, involving bilateral synpolydactyly of the 4th web spaces of the feet and the 3rd web spaces of the hands with complete or partial digit duplication within the web. SD2 is the only type with a mesoaxial extra finger, thus, synpolydactyly is classified into three different types (SPD1-3). It is the second most frequent syndactyly type associated with additional features such as camptodactyly, or clinodactyly of the 5th finger, brachydactyly, and variable syndactyly with middle phalanx hypoplasia.

SPD1 (MIM 186000) is caused by pathogenic mutations in the *HOXD13*, located on 2q31 (19–22), and having an autosomal dominant inheritance. HOX gene family includes the *HOXD13* gene (MIM 186000) and several other genes. The HOX genes encode many different regulatory transcription factors containing homeodomain proteins, play a very important role in the regional identities and might control cell fates during limb axes development. HOX genes assemble in a cluster form, located on four different genomic loci (HOXA-D) while the *HOXD13* gene encoding 343 amino acids protein is located in the 5′ region. The *HOXD13* protein regulates the expression of genes involved in skeletal patterning and early limb development (29). SPD2 (MIM 608180) is caused by pathogenic sequence variants in the *FBLN1* gene (MIM 608180) (30), located on chromosome 22q13.31. The SPD3 (MIM 610234), was mapped by Malik et al. (31) on chromosome 14q11.2-q12 in a five-generation Pakistani kindred using linkage analysis, however, no candidate gene has been reported so far. The family presented additional variable features such as cutaneous webbing, abnormal metacarpals, symphalangism, camptodactyly, and clinodactyly (31).

The FBLN1 protein expresses in most tissues, including calcifying regions of developing bones, the perichondrium, epithelial region of the skin, early human embryo, and in the gut sub-epithelium (32). The *Fbln1* knockout mice cause endothelial cell abnormalities and perinatal lethality in several vessel compartments (33).

Syndactyly type 3 (SD3)

SD3 (MIM 186100), also named as a small ring syndactyly or a Johnston-Kirby type, having phenotypes such as bilateral and/or distal phalangeal fusion, or having an undeveloped middle phalanx in the 5th digit (34). The fourth finger usually shows valgus deviation when the fusion is complete (3). The feet are usually unaffected, and the nails are medially fused of the syndactylous fingers. Oculo-dento-digital-dysplasia (ODDD) was mapped on human chromosome 6q22-q23 (35), with characteristic phenotypes of SD3, with connexin 43 (*GJA1*; MIM 121014) identified as the candidate gene for SD3 (36). Pathogenic mutations in the *GJA1* gene have also been reported to cause atrioventricular septal defect 3 (MIM 600309), hypoplastic left heart syndrome 1 (MIM 241550), and craniometaphyseal dysplasia (MIM 218400). GJA1 has been reported to play an important role in normal limb and facial development and several pathogenic mutations have been associated with limb and craniofacial abnormalities through modifying BMP2 and SHH (37,38).

Syndactyly type 4 (SD4)

SD4 (MIM 186200), known as the Haas-type synpolydactyly, was described for the first time by Haas in 1940 as complete syndactyly, having an incidence of 1/300,000 live births and inherited in an autosomal dominant fashion (2). In this type, all the digits of the hands are affected, with associated polydactyly, usually involving six digits and six metacarpals, with completely fused nails. SD4 is extremely rare and characterized into two subtypes: (SD4a) Typical Haas type without the involvement of feet. (SD4b) Complete fingers fusion (hand) with a variable fusion of all digits in feet. SD4 with tibial hypoplasia was mapped on chromosome 7q36 (39) and duplication in regulator (ZRS) of SHH, have been associated with SD4 (40–42). Wang et al. (43) identified a mutation in intron 5 of the *LMBR1* gene (MIM 605522) in a Chinese family being the causative agent for SD4 development (43).

Syndactyly type 5 (SD5)

SD5 (MIM 186300) is a rare limb anomaly, also known as the Dowd type syndactyly, and inherited in an autosomal dominant manner. This type is mainly characterized by webbing of the ring and middle fingers, along with webbing of the 2nd and 3rd toes with a fusion of the 4th and 5th metacarpals (44).

HOXD13 (MIM 142989) was identified as the causative gene for SD5 in two large Chinese families (45). Pathogenic sequence mutations in the *HOXD13* gene also causes different limb phenotypes such as SPD1, syndactyly type I-c, BDA4 (MIM 112800), BDD (MIM 113200), VACTERL association (MIM 192350), and BDE1 (MIM 113300). *Hoxd13*$^{-/-}$ knockout mice showed extensive limb defects, and intriguingly.

Trans-heterozygotes mice for the *Hoxd13*$^{+/-}$ showed more severe phenotypes as compared to heterozygotes, thus demonstrating a possible genetic interaction (13).

Syndactyly type 6 (SD6)

SD6 (MIM 609432) is a unilateral syndactyly, also known as Mitten type. Typical feature includes all fingers in a hand are webbed except the thumb along with fused 2nd and 3rd toes (3). In most cases, the terminal and distal phalanges are merged in a knot-like structure. SD6 is mostly inherited dominantly, with variable expressivity and incomplete penetrance. So far, no disease-causing locus/gene has been associated with SD6 and no additional cases have been reported.

Syndactyly type 7 (SD7)

Syndactyly type VII-a

SD7a (MIM 212780) is also named as Cenani-Lenz type syndactyly (CLS) and segregates in an autosomal recessive manner. Clinical features manifest severe abnormalities of hands and all the digital elements. The phalanges, carpals, and metacarpals show asymmetrical synostosis giving the appearance of a cup-shaped hand (3). CLS also has two grossly different types including an oligodactyly type and a spoon hand type (14). It was also reported that both oligodactyly and spoon-hand types, with limb and kidney malformations, are caused by multiple mutations in the *LRP4* gene (MIM 604270), and mapped on chromosome 11p11.2 (15).

LRP4 is crucial for different developmental processes and a member of the low-density lipoprotein receptors gene family. During development, the LRP4 protein acts as a modulator of extracellular cell signaling pathways (46). LRP5 antagonized by LRP4 and LRP6 is involved in the activation of Wnt/β-catenin signaling pathway, which plays a very vital role in the developmental process during tissue regeneration and organogenesis (46–48). *Lrp4*$^{-/-}$ knockout mice show features of growth-retardation including polysyndactyly, mild, and partially craniofacial abnormalities (49). Features such as bilateral kidney agenesis and delay in ureteric bud formation have also been observed in *Lrp4*$^{-/-}$ mice (50).

Syndactyly type VII-b

This class of syndactyly named as Cenani–Lenz phenotype, inherited in an autosomal dominant fashion with features such as hearing impairment and renal defects. Cenani-Lenz-like non-syndromic oligosyndactyly is caused by genomic rearrangements of the *GREM1-FMN1* locus on chromosome 15q13.3 (51). Pathogenic variants in the mouse *Fmn1* gene are associated with recessively limb deformities or aplasia (52).

Syndactyly type 8 (SD8)

SD8 commonly known as Orel-Holmes type, in which fusion of the 4th and 5th metacarpals is observed with

a clear ulnar deviation of the 5th finger having no other abnormality. The 4th and 5th metacarpals are shortened with significant separation between their distal ends (53). Entered as metacarpal 4–5 fusion (MF4), (309630) in OMIM and the candidate gene reported is *FGF16* (MIM 300827) on chromosome Xq21 (54,55). There has been an autosomal dominant type reported in the literature known as Lerch type classified as syndactyly type 8b. The genetic cause has not been identified yet (56).

In humans and mice, the FGF gene family consists of a total of 22 proteins including the FGF16 protein. FGF16 belongs to the *FGF* gene subfamily E, having 624 bp open reading frame encoding a 207 amino acids protein (57). During embryogenesis, FGF16 helps in the patterning of the established limb bud and also functions intercellular signaling molecule in the limb formation. As FGF16 is required for embryonic development of the heart, the $Fgf16^{-/-}$ mice exhibited features such as severe craniofacial, cardiac defects, thus causes embryonic death (58).

Syndactyly type 9 (SD9)

SD9 (MIM 609432), also named as Mesoaxial synostotic syndactyly (MSSD; MIM 609432), was reported in two consanguineous pedigrees from Turkish and Pakistani families (59). MSSD is mostly characterized by a mesoaxial reduction of the fingers, clinodactyly, synostoses of metacarpals, hypoplasia of the thumbs, and complete or partial soft tissue syndactyly of the toes (59).

SD9 was mapped to chromosome 17p13.3 and inherited in an autosomal recessive manner (59). Malik et al. (59) identified mutations in *BHLHA9* (MIM 615416) gene, having a single exon and coding a 235 amino acid protein, as the candidate gene for MSSD.

Syndromic Syndactyly

Syndromic syndactyly involves other congenital phenotypes and may be a part of some other syndrome (severe abnormality). Due to severe associated organ dysfunction or malformation, 18% of the affected children having different congenital limb malformation die before 6 years of age. Using the mesh syndactyly in the OMIM, we identified 447 entries involving both syndromic and non-syndromic syndactylies (Table 1, Supplementary Tables 1 and 2). Syndromic syndactylies involve many different disorders, and the present review only focused on the classification of the non-syndromic syndactyly types. The list of genes and syndactyly syndromes would help the clinicians and researchers in proper diagnoses of syndromic and non-syndromic syndactyly cases.

Treatment

Accurate and proper diagnosis of genetic disorders such as syndactyly using different molecular genetic tools with the combination of family history, clinical features, radiological analysis, and ultrasound may help in surgery and future rehabilitation. The optimal surgical time for simple syndactyly range from 6 to 18 months of age, before 6 months for complex syndactyly and should be corrected in the early stages. The open treatment as the patchwork-like scar is not observed while the commonly used technique is the surgical techniques (skin grafts). "Z"-method incision along with skin grafts is used in combination as well and such methods can reduce scar formation. Furthermore, after the syndactyly division, methotrexate medication is mostly applied. As syndactyly can be very complex, the predicted outcome of the treatment is difficult and such surgical treatments should be applied with much care (60).

Conclusion and Perspectives

During the process of organogenesis, failure in the separation of the digits results in syndactyly. It may occur, in association with over 125 different syndromic types or as an isolated entity. Digit specification mechanisms and limb patterning can only be properly elucidating after the identification of novel syndactyly genes. The clinical phenotype of syndactyly is very diverse, with novel gene identification; many other players such as epigenetics, coding genes variants, and many unknown factors might be responsible for the occurrence of syndactyly. Next-generation sequencing technologies such as whole-genome sequencing, whole exome sequencing, and RNA sequencing are best choices to identify novel candidate genes for both syndromic and non-syndromic syndactyly. Moreover, animal models and the latest technology such as CRISPER-Cas9 could add significantly to the understanding of limb developmental pathways. The unveiling of the pathways involved in the development of complex syndactyly will ultimately help to explain strong genetic heterogeneity, diverse clinical phenotypes, and may contribute to the targeted therapy of severe syndactyly types.

Declaration of conflicting interests
The authors declare that there is no conflict of interests.

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References

1. Hay S. Incidence of selected congenital malformations in Iowa. Am J Epidemiol 1971; 94:572–84.

2. Castilla EE, Paz JE, Orioli-Parreiras IM. Syndactyly: frequency of specific types. Am J Med Genet 1980; 5:357–64. https://doi.10.1002/ajmg.1320050406

3. Temtamy SA, McKusick VA. Syndactyly. In: The genetics of hand malformations. Alan R Liss (ed.), New York; 1978. pp 301–22.

4. Malik S. Syndactyly: phenotypes, genetics and current classification. Eur J Hum Genet 2012; 20:817–24. https://doi.10.1038/ejhg.2012.14

5. Malik S, Schott J, Ali SW, Oeffner F, Amin-ud-Din M, Ahmad W, et al. Evidence for clinical and genetic heterogeneity of syndactyly type I: the phenotype of second and third toe syndactyly maps to chromosome 3p21.31. Eur J Hum Genet 2005; 13(12):1268–74. https://doi.10.1038/sj.ejhg.5201492

6. Duboc V, Logan MP. Regulation of limb bud initiation and limb-type morphology. Dev Dyn 2011; 240:1017–27. https://doi.10.1002/dvdy.22582

7. Zuniga A, Zeller R, Probst S. The molecular basis of human congenital limb malformations. Wiley Interdiscip Rev Dev Biol 2012; 1(6):803–22. https://doi.10.1002/wdev.59

8. Albuisson J, Isidor B, Giraud M, Pichon O, Marsaud T, David A, et al. Identification of two novel mutations in SHH long-range regulator associated with familial pre-axial polydactyly. Clin Genet 2011; 79:371–7. https://doi.10.1111/j.1399-0004.2010.01465.x

9. Vokes SA, Ji H, Wong WH, McMahon AP. A genome-scale analysis of the cis-regulatory circuitry underlying sonic hedgehog-mediated patterning of the mammalian limb. Genes Dev 2008; 22(19):2651–63. https://doi.10.1101/gad.1693008

10. Chiang C, Litingtung Y, Lee E, Young KE, Corden JL, Westphal H, et al. Cyclopia and defective axial patterning in mice lacking Sonic hedgehog gene function. Nature 1996; 383(6599):407–13. https://doi.10.1038/383407a0

11. Hildebrandt F, Benzing T, Katsanis N. Ciliopathies. N Engl J Med 2011; 364(16): 1533–43. https://doi.10.1056/NEJMra1010172

12. Umair M, Shah K, Alhaddad B, Haack TB, Graf E, Strom TM, et al. Exome sequencing revealed a splice site variant in the IQCE gene underlying post-axial polydactyly type A restricted to lower limb. Eur J Hum Genet 2017; 25(8):960–5. https://doi.10.1038/ejhg.2017.83

13. Davis AP, Capecchi MR. A mutational analysis of the 5′ HoxD genes: dissection of genetic interactions during limb development in the mouse. Development 1996; 122(4):1175–85.

14. Harpf C, Pavelka M, Hussl H. A variant of Cenani-Lenz syndactyly [CLS]: review of the literature and attempt of classification. Br J Plast Surg 2005; 58(2):251–7. https://doi.10.1016/j.bjps.2004.10.024

15. Li Y, Pawlik B, Elcioglu N, Aglan M, Kayserili H, Yigit G, et al. LRP4 mutations alter Wnt/beta-catenin signaling and cause limb and kidney malformations in Cenani-Lenz syndrome. Am J Hum Genet 2010; 86(5):696–706. https://doi.10.1016/j.ajhg.2010.03.004

16. Mariani FV, Ahn CP, Martin GR. Genetic evidence that FGFs have an instructive role in limb proximaldistal patterning. Nature 2008; 453(7193):401–5. https://doi.10.1038/nature06876

17. Jain AP, Pundir S, Sharma A. Bone morphogenetic proteins: The anomalous molecules. J Indian Soc Periodontol 2013; 17(5):583–6. https://doi.10.4103/0972-124X.119275

18. Sarfarazi M, Akarsu AN, Sayli BS. Localization of the syndactyly type II (synpolydactyly) locus to 2q31 region and identification of tight linkage to HOXD8 intragenic marker. Hum Mol Genet 1995; 4(8):1453–58. https://doi.10.1093/hmg/4.8.1453

19. Muragaki Y, Mundlos S, Upton J, Olsen BR. Altered growth and branching patterns in synpolydactyly caused by mutations in HOXD13. Science 1996; 272(5261):548–51. https://doi.10.1126/science.272.5261.548

20. Kurban M, Wajid M, Petukhova L, Shimomura Y, Christiano AM. A nonsense mutation in the HOXD13 gene underlies synpolydactyly with incomplete penetrance. J Hum Genet 2011; 56(10):701–16. https://doi.10.1038/jhg.2011.84

21. Gong L, Wang B, Wang J, Yu H, Ma X, Yang J. Polyalaninerepeat expansion mutation of the HOXD13 gene in a Chinese family with unusual clinical manifestations of synpolydactyly. Eur J Med Genet 2011; 54(2):108–11. https://doi.10.1016/j.ejmg.2010.10.007

22. Montero JA, Lorda-Diez CI, Gañan Y, Macias D, Hurle JM. Activin/TGFbeta and BMP crosstalk determines digit chondrogenesis. Dev Biol 2008; 321(2):343–56. https://doi.10.1016/j.ydbio.2008.06.022

23. Al-Qattan MM. WNT pathways and upper limb anomalies. J Hand Surg Eur 2011; 36(1):9–22. https://doi.10.1177/1753193410380502

24. Ullah A, Hammid A, Umair M, Ahmad W. A novel heterozygous intragenic sequence variant in DLX6 probably underlies first case of autosomal dominant split-hand/foot malformation type 1. Mol Syndromol 2017; 8(2):79–84. https://doi.10.1159/000453350

25. Bosse K, Betz RC, Lee YA, Wienker TF, Reis A, Kleen H, et al. Localization of a gene for syndactyly type 1 to chromosome 2q34-q36. Am J Hum Genet 2000; 67:492–7. https://doi.10.1086/303028

26. Ghadami M, Majidzadeh-A K, Haerian BS, Damavandi E, Yamada K, Pasallar P. Confirmation of genetic homogeneity of syndactyly type 1 in an Iranian family. Am J Med Genet 2001; 104(2):147–51. https://doi.org/10.1002/ajmg.10061

27. Hsu CK. Hereditary syndactylia in a Chinese family. Chinese Med J 1965; 84:482–5.

28. Dai L, Liu D, Song M, Xu X, Xiong G, Yang K, et al. Mutations in the homeodomain of HOXD13 cause syndactyly type 1-c in two Chinese families. PLoS One 2014; 9(5):e96192. https://doi.10.1371/journal.pone.0096192

29. Salsi V, Vigano MA, Cocchiarella F, Mantovani R, ZappavignaV. Hoxd13 binds in vivo and regulates the expression of genes acting in key pathways for early limb and skeletal patterning. Dev Biol 2008; 317(2):497–507. https://doi.10.1016/j.ydbio.2008.02.048

30. Debeer P, Schoenmakers EF, Twal WO, Argraves WS, De Smet L, Fryns JP, et al. The fibulin-1 gene (FBLN1) is disrupted in at (12;22) associated with a complex type of synpolydactyly. J Med Genet 2002; 39(2):98–104. https://dx.doi.org/10.1136/jmg.39.2.98

31. Malik S, Abbasi AA, Ansar M, Ahmad W, Koch MC, Grzeschik KH. Genetic heterogeneity of synpolydactyly: a novel locus SPD3 maps to chromosome 14q11.2-q12. Clin Genet 2006; 69:518–24. https://doi.10.1111/j.1399-0004.2006.00620.x

32. Miosge N, Götz W, Sasaki T, Chu ML, Timpl R, Herken R. The extracellular matrix proteins fibulin-1 and fibulin-2 in the early human embryo. Histochem J 1996; 28(2):109–16. https://doi.org/10.1007/BF02331415

33. Kostka G, Giltay R, Bloch W, Addicks K, Timpl R, Fässler R, et al. Perinatal lethality and endothelial cell abnormalities in several vessel compartments of fibulin-1-deficient mice. Mol Cell Biol 2001; 21(20):7025–34. https://doi.10.1128/MCB.21.20.7025-7034.2001

34. Johnston O, Kirby VV Jr. Syndactyly of the ring and little finger. Am J Hum Genet 1995; 7:80–2.

35. Gladwin A, Donnai D, Metcalfe K, Schrander-Stumpel C, Brueton L, Verloes A, et al. Localization of a gene foroculodento digital syndrome to human chromosome 6q22-q24. Hum Mol Genet 1997; 6:123–7. https://doi.org/10.1093/hmg/6.1.123

36. Paznekas WA, Boyadjiev SA, Shapiro RE, Daniels O, Wollnik B, Keegan CE, et al. Connexin 43 (GJA1) mutations cause the pleiotropic phenotype of oculodentodigital dysplasia. Am J Hum Genet 2003; 72:408–18. https://doi.10.1086/346090

37. Richardson R, Donnai D, Meire F, Dixon MJ. Expression of Gja1 correlates with the phenotype observed in oculodento digital syndrome/type III syndactyly. J Med Genet 2004; 41(1):60–7. https://dx.doi.org/10.1136/jmg.2003.012005

38. Dobrowolski R, Hertig G, Lechner H, Wörsdörfer P, Wulf V, Dicke N, et al. Loss of connexin43-mediated gap junctional coupling in the mesenchyme of limb buds leads to altered expression of morphogens in mice. Hum Mol Genet 2009; 18(15):2899–911. https://doi.10.1093/hmg/ddp227

39. Sato D, Liang D, Wu L, Pan Q, Xia K, Dai H, et al. A syndactyly type IV locus maps to 7q36. J Hum Genet 2007; 52:561–4. https://doi.10.1007/s10038-007-0150-5

40. Sun M, Ma F, Zeng X, Liu Q, Zhao XL, Wu FX, et al. Triphalangeal thumb-polysyndactyly syndrome and syndactyly type IV are caused by genomic duplications involving the long-range, limb-specific SHH enhancer. J Med Genet 2008; 45(9):589–95. https://doi.10.1136/jmg.2008.057646

41. Klopocki E, Ott CE, Benatar N, Ullmann R, Mundlos S, Lehmann K. A microduplication of the long range SHH limb regulator (ZRS) is associated with triphalangeal thumb-polysyndactyly syndrome. J Med Genet 2008; 45(6):370–5. https://doi.10.1136/jmg.2007.055699

42. Wu L, Liang D, Niikawa N, Ma F, Sun M, Pan Q, et al. A ZRS duplication causes syndactyly type IV with tibial hypoplasia. Am J Med Genet A 2009; 149A(4):816–8. https://doi.10.1002/ajmg.a.32740

43. Wang ZQ, Tian SH, Shi YZ, Zhou PT, Wang ZY, Shu RZ, et al. A single C to T transition in intron 5 of LMBR1 gene is associated with triphalangeal thumb polysyndactyly syndrome in a Chinese family. Biochem Biophys Res Commun 2007; 355:312–7. https://doi.10.1016/j.bbrc.2007.01.129

44. Dowd C. Cleft hand: a report of a case successfully treated with the use of periosteal flaps. Ann Surg 1986; 24:210–6.

45. Zhao X, Sun M, Zhao J, Leyva JA, Zhu H, Yang W, et al. Mutations in HOXD13 underlie syndactyly type V and a novel brachydactyly-syndactyly syndrome. Am J Hum Genet 2007; 80:361–71. https://doi.10.1086/511387

46. Kumar J, Swanberg M, McGuigan F, Callreus M, Gerdhem P, Akesson K. LRP4 association to bone properties and fracture and interaction with genes in the Wnt- and BMP signaling pathways. Bone 2011; 49(3):343–8. https://doi.10.1016/j.bone.2011.05.018

47. Lindy AS, Bupp CP, McGee SJ, Steed E, Stevenson RE, Basehore MJ, et al. Truncating mutations in LRP4 lead to a prenatal lethal form of Cenani-Lenz syndrome. Am J Med Genet A 2014; 164A(9):2391–7. https://doi.10.1002/ajmg.a.36647

48. Johnson EB, Hammer RE, Herz J. Abnormal development of the apical ectodermal ridge and polysyndactyly in Megf7-deficient mice. Hum Mol Genet 2005; 14(22):3523–38. https://doi.10.1093/hmg/ddi381

49. Karner CM, Dietrich MF, Johnson EB, Kappesser N, Tennert C, Percin F, et al. Lrp4 regulates initiation of ureteric budding and is crucial for kidney formation--a mouse model for Cenani-Lenz syndrome. PLoS One. 2010; 5(4):e10418. https://doi.10.1371/journal.pone.0010418

50. Holmes LB, Wolf E, Miettinen OS. Metacarpal 4-5 fusion with X linked recessive inheritance. Am J Hum Genet 1972; 24:562–8.

51. Dimitrov BI, Voet T, De Smet L, Vermeesch JR, Devriendt K, Fryns JP, et al. Genomic rearrangements of the GREM1-FMN1 locus cause oligosyndactyly, radio-ulnar synostosis, hearing loss, renal defects syndrome and Cenani--Lenz-like non-syndromic oligosyndactyly. J Med Genet 2010; 47(8):569–74. https://doi.10.1136/jmg.2009.073833

52. Wang CC, Chan DC, Leder P. The mouse formin (Fmn) gene: genomic structure, novel exons, and genetic mapping. Genomics 1997; 39(3):303–11. https://doi.10.1006/geno.1996.4519

53. Itoh N, Ornitz DM. Evolution of the Fgf and Fgfr gene families. Trends Genet 2004; 20(11):563–9. https://doi.10.1016/j.tig.2004.08.007

54. Jamsheer A, Zemojtel T, Kolanczyk M, Stricker S, Hecht J, Krawitz P, et al. Whole exome sequencing identifies FGF16 nonsense mutations as the cause of X-linked recessive metacarpal 4/5 fusion. J Med Genet 2013; 50(9):579–84. https://doi.10.1136/jmedgenet-2013-101659

55. Jones B, Byers H, Watson JS, Newman WG. Identification of a novel familial FGF16 mutation in metacarpal 4-5 fusion. Clin Dysmorphol 2014; 23(3):95–7. https://doi.10.1097/MCD.0000000000000043

56. Lerch H. Erbliche Synostosen der Ossa metacarpalia IV und V. Z Orthop Unfallchir 1948;78:13–16.

57. Martin GR. The roles of FGFs in the early development of vertebrate limbs. Genes Dev 1998; 12(11):1571–86. https://doi.10.1101/gad.12.11.1571

58. Lu SY, Jin Y, Li X, Sheppard P, Bock ME, Sheikh F, et al. Embryonic survival and severity of cardiac and craniofacial defects are affected by genetic background in fibroblast growth factor-16 null mice. DNA Cell Biol 2010; 29(8):407–15. https://doi.10.1089/dna.2010.1024

59. Malik S, Percin FE, Ahmad W, Percin S, Akarsu NA, Koch MC, et al. Autosomal recessive mesoaxial synostotic syndactyly with phalangeal reduction maps to chromosome 17p13.3. Am J Med Genet. 2005; 134:404–8. https://doi.10.1002/ajmg.a.30656

60. Mandarano-Filho LG, Bezuti MT, Akita R, Mazzer N, Barbieri CH. Congenital syndactyly: case by case analysis of 47 patients. Acta Ortop Bras 2013; 21(6):333–5. https://doi.10.1590/S1413-78522013000600007