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Review Article

Decoding synpolydactyly the genetic landscape of hoxd13 and the hox gene family" A comprehensive review."

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ABSTRACT

Congenital limb malformations are among the most prevalent developmental abnormalities, occurring in approximately one in every 500 live births. These defects are frequently linked to genetic disruptions within the *HOX* gene family, which plays a pivotal role in embryonic limb patterning. This review comprehensively examines the genetic and molecular basis of synpolydactyly (SPD), a hereditary limb deformity characterized by fusion and duplication of digits, focusing on the HOXD13 gene and its association with other *HOX* genes. Mutations in *HOXD13*, including polyalanine tract expansions, missense, nonsense, and frameshift mutations, have been identified as major contributors to SPD and related limb malformations. Furthermore, the functional interplay between *HOXD13* and other *HOX* genes (*HOXA1, HOXA2, HOXA11, HOXA13, HOXB1,* and *HOXB13*) underlies a spectrum of genetic syndromes affecting limb and organ development. The review highlights the genotype–phenotype correlations, molecular mechanisms of *HOXD13* mutations, and their broader implications in developmental and pathological contexts, including genitourinary and oncogenic disorders. Understanding the complex regulation of *HOXD13* and its paralogues provides critical insight into congenital limb anomalies and offers a framework for genetic counseling, diagnosis, and potential therapeutic strategies.

Keywords: Synpolydactyly; Hox gene; mutation; polyalanine; duplication.

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INTRODUCTION

Malformation of fingers and toes is most common abnormalities present in infants, with an occurrence of about 1 out of every 500 births (Pickering & Towers, 2014). Limb abnormalities are initiated at the very early stages of embryonic development on days 26th and 28th of pregnancy in the upper and lower limbs (Al-Qattan et al., 2009; Barham & Clarke, 2008). The limb, after developing from mesenchymal cells in the lateral plate of mesoderm, expands along the three main axes depending on how the several centers work (Barham & Clarke, 2008). Of these sites, the apical ectodermal ridge (AER), through the use of FGFs (fibroblast growth factors), controls the development of the limb with proximal-distal axis (Al-Qattan et al., 2009).

The anterior-posterior organization of limbs is stimulated by the zonal polarizing activity (ZPA) and signaling centers, and is triggered by the Sonic Hedgehog (Shh) activity. The non-apical ectodermal ridge, the third signaling center, is ultimately in charge of limb development along the dorso-ventral axis (Al-Qattan et al., 2009; Barham & Clarke, 2008). Along the signaling centers, different factors are also involved in the formation of limbs. The most common factors are encoded by the HOX gene clusters (Zuniga et al., 2012). A total of 39 HOX genes are present in

vertebrates, which are organized in 4 clusters as follows: HOXA to HOXD (Nunes et al., 2003). The 3' end genes of these clusters are expressed at their early stages, while the 5' end genes are expressed in later stages of their development. The 3' end genes are effective in the anterior part, while the 5' end genes are effective in the posterior part (Duboule & Morata, 1994). The 1365 bp *HOXD13* gene is located on chromosome 2q31 at the 5' end of its cluster. The triple repeat sequence found in the two exons of 343 amino acids that make up the *HOXD13* gene forms a polyalanine chain (Akarsu et al., 1996; Malik, 2012). Synpolydactyly, also referred to as digit fusion, is a common genetic deformity that demonstrates clinical heterogeneity and is typically brought on by webbing. It can be syndromic, with nearly 300 distinct defects, or it can only have one of nine non-syndromic types (Teebi & Druker, 2001). A connection between the fingers from first to last is known as synpolydactyly, which combines the terms syno and poly. It can be arranged as central (ring, middle, and index fingers), preaxial (thumb), or postaxial (little finger). (Ali et al., 2025; Dorshorst et al., 2010; Sharma et al., 2015; Teebi & Druker, 2001). Mostly it affects 2/3, 3/4 fingers and 4/5 toes. Mostly, the non-syndromic SPD (Synpolydactyly) is linked with a mutation in the *HOXD13* gene on chromosome 2q31 and is classified as synpolydactyly type 1(SPD1), also termed as syndactyly type II. Synpolydactyly caused by the *FBLN1* gene and its mutation on chromosome 22q13.31 and *SPD3* is visualized on 14q11.2-q12 chromosome (Dai et al., 2014; Malik & Grzeschik, 2008; Temtamy & McKusick, 1978). Three primary mutations have been found in the *HOXD13* gene: expansion of the polyalanine tract, loss of function (LOF), which additionally comprises missense, nonsense, and frame shift mutations (Dai et al., 2014; Ibrahim et al., 2016). Synpolydactyly is a clinical autosomal dominant condition that bilaterally affects the third and fourth fingers in the middle axis of hands and 5th of toes in the distal part of feet (Sayli et al., 1995; Winter & Tickle, 1993). In a study reported and mapped synpolydactyly localized to a region 2q31 of the chromosome and revealed a compact linkage with an intragenic marker at a locus of the *HOXD8* gene in affected individuals and implicated other genes at the 5' end, such as *HOXD9* to *HOXD13*, *EVX2,* and *DLX1*/*DLX2,* are also show capability for this condition (Sarfarazi et al., 1995). *HOXD13* and *HOXA13* are both located at the 5' end of their clusters and have a role in the transformation of the distal /postaxial part of the limb, the urogenital tract, and the genital tubercle (Duboc & Logan, 2009; Zuniga et al., 2012). It has been found that the *HOXD13* is associated with defects in patterning and causes synpolydactyly, while the *HOXA13* causes the HFGSs (Mortlock & Innis, 1997; Muragaki et al., 1996). Synpolydactyly is known to be designated as such as *SPD1* to *SPD3* (Malik & Grzeschik, 2008). These are the mutations caused by the HOXD13 gene. The gene responsible for SPD type is the FBLN1 gene, localized on 22q13.31 chromosome region (Debeer et al., 2002). A total of ten genes are known to cause malformations and abnormalities in humans. These genes are *HOXA1, HOXA2, HOXA11, HOXA13, HOXB1, HOXB13, HOXC13, HOXD4, HOXD10*, and *HOXD13* (Akarsu et al., 1996; Muragaki et al., 1996).

ASSOCIATION OF *HOXD13* WITH OTHER GENES

HOXD13 functions as a central regulator of distal limb patterning and exerts its effects through coordinated interactions with multiple members of the *HOXA* and *HOXB* clusters (Figure 1). These interactions collectively influence limb morphogenesis, craniofacial and hindbrain development, genitourinary formation, and disease susceptibility (Table 1).

HOXA1

HOXA1 is linked to the organization of various tissues and organs, including the hindbrain, spinal and cranial nerves, inner ear, parathyroid and thymus glands. It helps in the anterior-posterior axis. This gene is located on chromosome 2q15. The Bossley-Salih-Alorainy Syndrome (BSAS) and Athabaskan brainstem dysgenesis syndrome (ABDS) are the two most severe conditions associated with *HOXA1*. There is a proper overlap between the two syndromes (BSAS and ABDS). The patients with Athabaskan BDS can be identified on the basis of the presence of bulbar paresis and central hypoventilation, and the lack of facial dysmorphisms and limb abnormalities (Bosley et al., 2008; Holve et al., 2003). *HOXA1* is like all *HOX* genes, consisting of 2 exons, and most mutations have been found in exon 1 of the *HOXA1* gene. There are a total of 4 mutations that have been revealed in this gene. In BSAS syndrome on position c.185delG, C.175-176insG, these two mutations have also been reported in Saudi Arabian infected individuals, while the c.84C>G is documented in the Turkish lineage. ABDS syndrome is caused by a c.76C>T Mutation in patients of Athabaskan descent. Both conditions occur as a result of truncated proteins that defect the homeodomain for binding of DNA (Bosley et al., 2008). Functional interaction between *HOXA1* and *HOXD13* reflects shared regulatory roles within early developmental patterning pathways (Table 1; Figure 1).

HOXA2

HOXA2 is associated with autosomal recessive microtia, hearing loss, cranial abnormalities, and developmental delay. The gene is located on chromosome 7q15. The *HOXA2* gene controls the growth and development of many tissues

and organs, including the skull and facial organs, inner ear, brain, spinal cord, and limbs. All the reported individuals are from an Iranian family having grade II microtia. Those individuals have normal external ear anatomy and absent inner-ear structures. A narrow, short auditory canal, cleft palate. In these individuals, a homozygous mutation was identified on position (c.556C>A). The evolutionary conserved glutamine at position 186 affects the 44th position of the homeodomain (Alasti et al., 2008; Mallo & Gridley, 1996; Monks et al., 2010). Although *HOXA2* does not directly cause limb malformations, its developmental overlap with *HOXD13* underscores the broader role of *HOX* gene coordination during embryogenesis (Table 1; Figure 1).

HOXA11

The HOXA11 gene is a member of the Homeobox (HOX) family that plays a role in the development of forelimbs, hindlimbs, skeletal patterning, radius and ulna, tibia and fibula, Gonadal development, Ovarian development, and testicular development. This gene is associated with thrombocytopenia and radioulnar synostosis. Thompson and Nguyen identified two unrelated affected. Father and all of their children had both the radioulnar synostosis, and 3/4 were also affected by thrombocytopenia. There was a deletion of 1 base pair of *HOXA11* (C. 872delA). The homeodomain of axon 2 is affected by the deletion, which causes a frameshift mutation and truncates the proteins by 22 amino acids (Small & Potter, 1993; Thompson & Nguyen, 2000). The combined loss of *HOXA11* and *HOXD11* is crucially disrupted the transformation of zeugopod, while the non-activation of these two genes resulted in the complete loss of fingers. Regulated *HOXA11* leading to *HOXA11* repression in the *HOXA13* domain must have developed the emergence of pentadactyly in the deceased tetrapod (Xie et al., 2021). These findings highlight the cooperative role of *HOXA11* and *HOXD13* in limb segmentation (Table 1; Figure 1).

HOXA13

Hand-foot-genital syndrome and Guttmacher syndrome are both caused by genetically heterogeneous mutations in *HOXA13*. Hand Foot Genital Syndromes are caused by an autosomal dominant mode of inheritance characterized by both limbs and genitourinary abnormalities. Polyalanine expansions and point mutations in *HOXA13* cause HFGS (Dunø et al., 2004; Zuniga et al., 2012).

Guttmacher syndrome is also similar to limbs and urinogenital defects, but also with an additional limb malformation, including distal-axis polydactyly of hands and shortening of unappealingly 2nd toes with an absence of nails. In these types of syndromes, a specific missense mutation, on this region (c.1112A>T), was identified. In the promoter region, a 2 bp deletion was also identified at a point (79-79delGC) that analyzes both the loss and gain of function mutations (Goodman, 2002; Innis et al., 2002; Mortlock & Innis, 1997). Both the *HOXA11* and *HOXD13* Genes perform their role in these disorders, such as Holt-Oram syndrome, Alagille and Andersen syndromes, CHARGE syndrome, Vacterl and Mullerian duct defects have been reported (Jaouadi et al., 2023). The shared phenotypic spectrum and overlapping expression domains of *HOXA13* and *HOXD13* emphasize their cooperative regulation of distal limb identity (Table 1; Figure 1).

HOXB1

A homozygous *HOXB1* mutation has been identified in 4 patients. In review, the characteristic features include hearing loss, congenital facial palsy, upturned nose, speech delay, and feeding difficulties. Autosomal recessive inheritance was found on region c.619C>T. A loss-of-function mutation is suggested in this data. These phenotypes are closely similar to *Hoxb* mice in which the reduction in size of the facial motor nerve explains the loss of hearing (Guthrie, 2007; Webb et al., 2012).

The *HOXB1* gene accelerates Mowat-Wilson syndrome and Duane's retraction syndrome. There is a proper interaction between *HOXA1* and *HOXB1* (Ingram et al., 2000). The functions of HOX genes are not only in individual genes but on entire clusters. The combination of clusters or entire clusters has its role to expose functional requirements in patterning to be deleted and alter their expression (Lebert-Ghali et al., 2016; Qian et al., 2018). These interactions indirectly intersect with *HOXD13*-mediated developmental pathways (Table 1; Figure 1).

HOXB13

In *HOXB13,* missense mutations have been identified that are commonly associated with prostate cancer, breast cancer and colorectal cancer. The majority of Missense mutations (G84E) are initially reported in the *HOXB13* gene. This G84E mutation changes a glycine of exon 1. Rare mutation at a position c.404G>A; p. G135E also causes an increased risk of prostatic cancer (Ewing et al., 2012). Loss of function in Hoxb13 shows overgrowth of tail bud structures due to increased cell proliferation (Economides & Capecchi, 2003). The HOXB13 gene plays a functional role in the organization of the dermis and posterior regions. The role of the *HOXB13* gene has been associated mostly with breast cancer due to the overexpression of this gene. The 2 Novel mutations align with the concept of different

HOXB13 mutations, about 60% of colorectal cancer (CRC), abnormal expression of *HOXB13* was detected in Urogenital cancer, and overexpression of *HOXB13* is associated with Ovarian, endometrial, and Cervical cancers (Botti et al., 2019). Although distinct from HOXD13-related limb malformations, HOXB13 highlights the broader pathological consequences of HOX gene dysregulation (Table 1; Figure 1).

HOXD13

The autosomal dominant phenomenon of polyalanine expansions in SPD type II was found to be caused by mutations in *HOXD13*. SPD is a soft tissue that is found between the third and fourth fingers and between the fourth and fifth toes. The *HOXD13* at position (c.916C>T, R306W; c.683G>T. G228V) has been found to have both intragenic deletion and missense mutation in SPD (Merlob & Grunebaum, 1986; Sayli et al., 1995). Positioned at the center of the HOX interaction network, *HOXD13* integrates signals from multiple HOX paralogues to coordinate distal limb identity (Table 1; Figure 1).

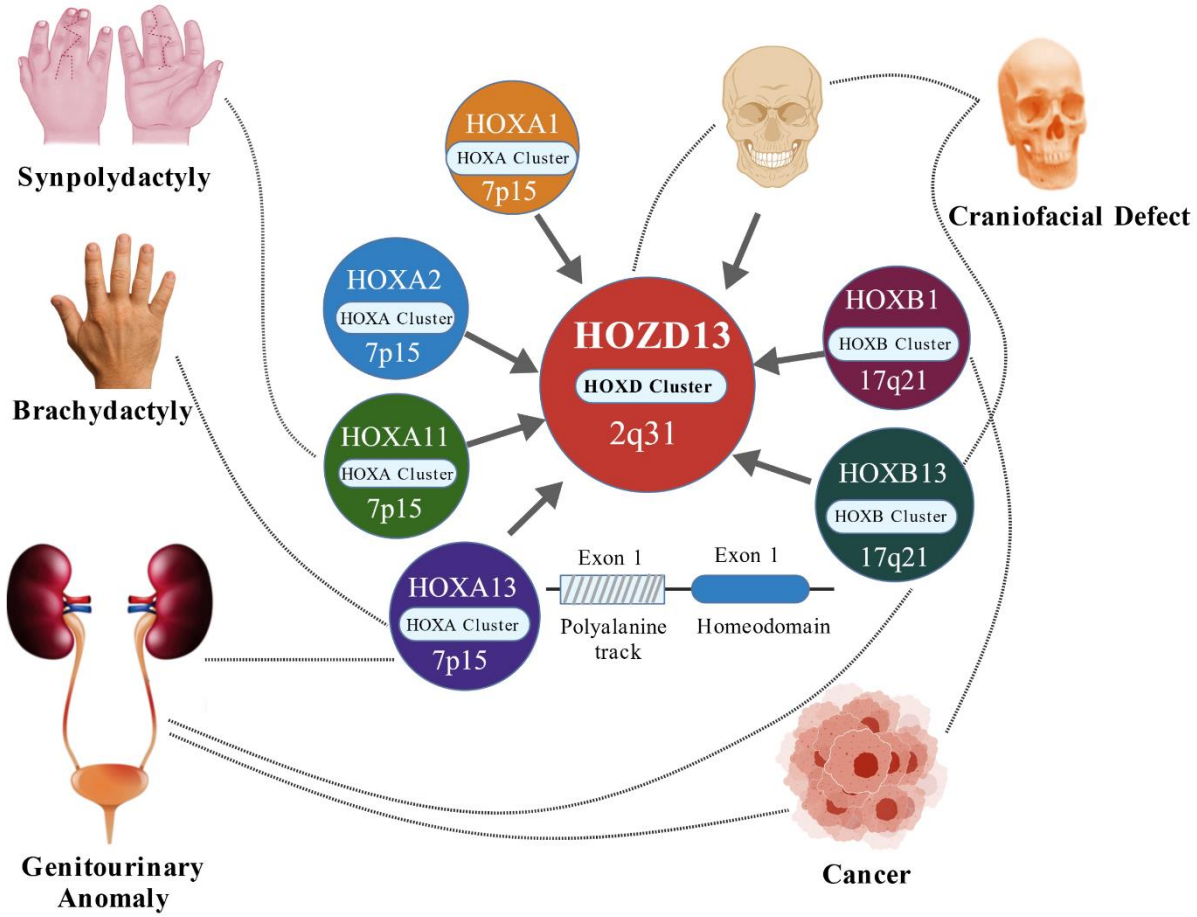

Figure 1. Functional and genetic interactions between HOXD13 and other HOX genes.

HOXD13 is a key posterior HOX gene regulating distal limb development and digit patterning. This schematic illustrates the genomic organization, functional interactions, and disease associations of *HOXD13* with selected *HOXA* and *HOXB* genes. *HOXA1* and *HOXB1* contribute to anterior–posterior axis formation and cranial nerve development; *HOXA2* regulates craniofacial and inner ear development; HOXA11 participates in zeugopod formation and gonadal development; *HOXA13* and *HOXD13* cooperatively regulate distal limb and genitourinary patterning; and *HOXB13* is involved in posterior tissue organization and cancer susceptibility. Distinct *HOXD13* mutation types, including polyalanine tract expansions, missense mutations, and truncating variants, are associated with a spectrum of limb phenotypes such as synpolydactyly, brachydactyly, and syndactyly. Solid lines indicate developmental interactions, while dashed lines denote pathological associations.

BRACHYDACTYLY TYPE D & E

Generalized brachydactyly, the responsible gene is *HOXD13,* which causes hypoplasia or aplasia of the 5th finger, phalangeal
duplications, syndactyly of fingers 3rd and 4th, and shortening of the metacarpal and metatarsal. The c.947C>G; S316C is responsible for the abnormalities (Johnson et al., 2003).

SYNDACTYLY TYPE V

Metacarpal synostosis caused by mutations in *HOXD13.* Fusion of metacarpal and metatarsal in synpolydactyly type V. Other abnormalities include clinodactyly of the 5th finger, cutaneous syndactyly of the 3rd and 4th digits, and syndactyly of the mild cutaneous toe (Zhao et al., 2007).

Table 1. *HOXD13* and associated HOX genes: functions, mutations and human disorders.

Gene	Chromosomal Location	Major Function	Mutation Type	Associated Disorders	Key References
HOXA1	2q15	Hindbrain, cranial nerves	Truncating (LOF)	BSAS, ABDS	Bosley et al., 2008; Holve et al., 2003
HOXA2	7q15	Craniofacial & ear development	Missense (LOF)	Microtia, hearing loss	Alasti et al., 2008
HOXA11	7p15	Zeugopod & gonadal development	Frameshift (LOF)	Radioulnar synostosis, thrombocytopenia	Thompson & Nguyen, 2000
HOXA13	7p15	Distal limb & urogenital patterning	Polyalanine expansion (GOF)	HFGS, Guttmacher syndrome	Goodman, 2002; Innis et al., 2002
HOXB1	17q21	Facial motor neuron development	Nonsense (LOF)	Facial palsy, hearing loss	Webb et al., 2012
HOXB13	17q21	Posterior patterning, oncogenesis	Missense (GOF)	Prostate, colorectal cancer	Ewing et al., 2012; Botti et al., 2019
HOXD13	2q31	Distal limb morphogenesis	Polyalanine, missense, truncation	Synpolydactyly II	Merlob & Grunebaum, 1986; Guo et al., 2021

BRACHYDACTYLY-SYNDACTYLY

Generalized brachy-syndactyly syndrome due to *HOXD13* results in the contraction of the 7-alanine tract in exon 1. Resulting commonly in brachydactyly of upper fingers, broad and short postaxial thumb phalanges, SD of cutaneous toe, with no middle phalanges 2 to 5 of toes, and clinodactyly of 5th finger (Zhao et al., 2007).

Different types of missense mutation associated with limb and toes malformation have been developed in of homeodomain of the *HOXD13* gene in different phenotypes. There are 5 missense mutations in different regions of this Gene on position 892, in which a C-T transition changes arginine to tryptophan, which is associated with synpolydactyly. In this position, R298Q, on position 31 of the homeodomain, in which the arginine changes to glutamine and causes syndactyly. At position 923 transversion of C-G in the second exon of *HOXD13,* which replaces cysteine with serine and causes Brachydactyly (Vural et al., 2020). Our literature findings total 53 families associated with *HOXD13,* but in only 11, polyalanine tract expansion was reported; there were 12 missense mutations, 13 nonsenses mutations, and 5 were insertions. The most common was the polyalanine extension. Missense was the 2nd most common (Guo et al., 2021). Both *HOXC13* and *HOXD13* genes are involved and show great interest in the development of genitourinary structures, and both genes are associated with cervical cancer in women (Juárez-Rendón et al., 2023).

THE *HOXD13* AND SYNPOLYDACTYLY

It is a common hereditary deformity, yet it is clinically heterogeneous, and sometimes digit fusion is referred to as syndactyly, usually caused by webbing (Malik et al., 2005). It may be just one of nine non-syndromic types, yet it may be syndromic, and it occurs with almost 300 different defects. In Phenotype, it varies even within families, and one patient can have a phenotype that is mild or severe, unilateral/bilateral, symmetrical/asymmetrical, full/partial,

skeletal/cutaneous, with several bones involved, and the phenotype may vary even from limb to limb (Zhao et al., 2007). Synpolydactyly means fusion of fingers or toes form webbing, and the synpolydactyly is the correlation of both syno and poly and defines a connection located between the middle and the ring finger, and the fourth and 5th of toes (Malik, 2012).

The opposite of polydactyly is oligodactyly, which has fewer fingers or toes. Many times, extra fingers are a little piece of soft tissue that may be cut away (Teebi & Druker, 2001). It might consist of a single, functional finger or just a bone without joints. The extra finger is often located on the thumb, incredibly infrequently inside the middle three digits, and most usually on the little finger of the hand. Three kinds of polydactyly are recognized: central (index, middle, and ring fingers), postaxial (little finger), and preaxial (thumb). Though it sometimes begins at the wrist, much like a normal digit, the extra digit is usually an aberrant fork in an already-existing digit (Dorshorst et al., 2010). Duplication is the subject of polydactyly. The extra fingers have abnormal growth and are often smaller than his other fingers. An additional finger or toe may be tiny and non-functional, like skin tags or nubbins, or it may be fully developed with bones and skeletal connections. Although it can happen on just one hand, bilateral polydactyly (on both hands and feet) is the most prevalent occurrence. In a similar vein, an individual may have extra fingers on one or both hands or feet (Dorshorst et al., 2010; Sharma et al., 2015).

It is considered that limb abnormalities are one of the general common congenital abnormalities in babies, which accounts for 1 in every 5 hundred live births. Genetic mutation to the development of the embryo and differentiation of the limbs, as well as some environmental influences such as teratogens, can cause abnormalities to the limbs (Pickering & Towers, 2014). The *HOXD13* gene consists of 1365 bp nucleotides, which contain a 1008 bp coding region. The gene is located at chromosomes 2q31 and it is situated at the 5' end of the gene comprising two exons with the triple repeat sequences that form the polyalanine chain, while the second exon at the 3' end of the gene encodes for a highly conserved homologous box domain (Nowoshilow et al., 2018). Variation in the expression of the *HOXD13* gene mutation has been documented to cause a range of clinical limb abnormalities (Darbellay et al., 2019).

HOXD13 MUTATIONS AND THEIR FUNCTIONAL EFFECTS

Mutations in *HOXD13* can be broadly classified into three major categories: polyalanine tract expansions, missense substitutions, and truncating loss-of-function variants (Figure 2). These mutation classes localize to distinct functional regions of the gene and exert different molecular and phenotypic effects, thereby explaining the marked genotype-phenotype variability observed in synpolydactyly and related limb malformations.

The polyalanine was s45% most common and followed by 32% with a missense mutation. The homeoboxes are mostly connected with LOF mutations (Guo et al., 2021). A study was conducted in which both *HOXD12* and *HOXD13* genes were sequenced and analyzed, in which the affected homozygous individuals and their other family members were screened for potential mutations. This study showed that there were 9 alanine duplications in the affected subjects and 24 total poly (alanine, but in normal individuals, there were 15 polyalanine residues stretched. It was confirmed that this duplication is inserted at position 187 (Akarsu et al., 1996; Goodman et al., 1997; Jin et al., 2011; Xin et al., 2012). There are many differences phenotypically in humans within the *HOXD13* gene. The truncated mutations in human proteins could not bind the specific DNA and cause deleterious functional effects (Copeland et al., 1996; Kjaer et al., 2005; Malik et al., 2007; Zhao et al., 2007).

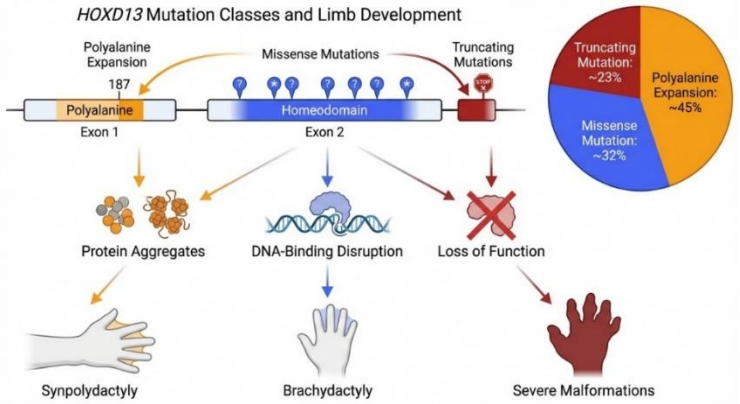

Figure 2. Mutation spectrum of HOXD13 and associated functional effects in limb development.

In hypodactyly, mice with limb abnormalities are almost similar to humans with hand-foot genital syndrome (HFGS) and very severe in those mice having mutations with *HOXA13*. In humans, haplo-insufficiency for *HOXA13* are more similar to hypodactyly mice and (GOF) gain–of–function mutation (Brison, Debeer, et al., 2012; Olson et al., 1996). The most common is polyalanine tract expansion in both Homeo and Non-homeodomain. In *HOXA13,* there is only a missense mutation identified in a *HOX* Gene, which replaces the asparagine residue with histidine that affects the resultant protein synthesis (Barham & Clarke, 2008; Gehring et al., 1994; Gordon et al., 2009). The gain-of-function mutations, such as the substitution of the homeodomain and polyalanine tract expansion, can produce phenotypes differently. *HOXD1, HOXD3, and HOXD4* mutations in the coding regions of these genes may cause Mesomelic dysplasia, also accompanied by lumbosacral vertebral and cervical abnormalities. These genes are very important in hindbrain development (Appukuttan et al., 1999; Han, 2009; Petitte et al., 2004; Ventruto et al., 1983).

HOXD13 mutations include polyalanine tract expansions, missense substitutions, and truncating loss-of-function variants. Polyalanine expansions represent the most frequent mutation class and are associated with dominant-negative or gain-of-function effects, whereas missense mutations partially disrupt DNA binding. Truncating mutations abolish homeodomain function, resulting in complete loss of transcriptional activity. These molecular mechanisms contribute to the phenotypic diversity observed in synpolydactyly and related limb malformations.

This study of limb abnormalities enables the identification of mutations by causative gene and facilitates genetic counseling, as well as disease prevention. This review aimed to compile and discuss the numerous experimental findings regarding the fundamental function of the most posterior HOX genes (Cantile et al., 2012; Jeong et al., 2012). Although the whole HOX gene network acts in a coordinated manner in body plan organization during development and in the maintenance of the phenotypic identity in human adult tissues and organs, deregulation of HOX13 paralogues has been strongly related to severe alterations. In this study, there is a reciprocal phenotype-genotype link that works in both directions. This study provides an overview of mutations of the HOXD13 gene that cause limb abnormalities during the developmental stages of an individual (Johnson et al., 2003; Scott et al., 2005). The 10 Hox genes associated with human disorders represent only one-quarter of the 39 human Hox genes. We highlight the importance of the HOXD13 gene for vertebrate limb development and organization. In addition, they also cause different defects when changes or mutations occur in genes. In addition, with genetic heterogeneity of SPD, the genetic analysis may also find implications and affect the development of other organs, which cause many defects (Brison, Tylzanowski, & Debeer, 2012; Mann et al., 2009; Scott et al., 2005). Together, these initiatives will enable it to be possible for future studies to approach the quest to unravel the SPD genotype-phenotype correlation from new angles. Additionally, it will support how new mutations in the HOXD13 protein that result in complicated SPD symptoms are interpreted. It is not surprising that most of the Hox genes impact the skeleton, mainly the vertebral column, with the forelimb and hindlimb bones occurring only marginally less frequently. The association of HOXD13 with other HOX genes from cluster A-D causes many other defects (Akker et al., 2001; Chisaka & Capecchi, 1991; Greer & Capecchi, 2002; Manley & Capecchi, 1995; Ramfrez-Solis et al., 1993).

AUTHOR'S CONTRIBUTION

Principle joint author: Maria Khan and Fazal Akbar, analyzed the data: Muhammad Israr, Asadullah & Samiullah, designed the experiment: Murad Ali Rahat, wrote the paper: Ishaq Khan and Maria Khan.

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AVAILABILITY OF DATA AND MATERIAL

This article presents all of the data that was created or examined for this study as tables and figures.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the relevant forum.

CONSENT FOR PUBLICATION

The publishing was approved by all of the authors.

CONFLICT OF INTERESTS

The authors declare there is no conflict of interest.

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