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Congenital Ectrodactyly and Its Genetic Linkage

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Abstract

Congenital ectrodactyly is usually clinically characterized with phalangeal dysplasia. Severe cases may be manifested with median split of hand and foot and/or combined with fusion of the rest fingers and toes, named a syndrome of split hand/foot malformation (SHFM). Some severe patients may be accompanied by ectodermal and craniofacial dysplasia, mental retardation and orofacial fissure. Till now there were seven types of SHFM reported. Among them, *SHFM1, SHFM3, SHFM4*, and *SHFM5* are autosomal dominant, *SHFM6* is autosomal recessive, *SHFM2* is X-linked inheritance, and *SHFLD* manifested as autosomal incomplete dominant inheritance. The related genes are *DSSI, DLX5,* and *DLX6* at 7q21.3-q22.1 (SHFM1), *FGF3* and *TDU* at Xq26 (*SHFM2*), *HUG1*、*TLX1*、*LBX1*、*BTRC*、*POLL*、*FBXW4* at 10q24 (SHFM3), *TP63* at 3q27 (SHFM4), *DLX1, DLX2* at 2q31 (*SHFM5*), *WNT10B* at 12q13.11-q13 (*SHFM6*), and *BHLHA9* at 17p13.3 or l19p13.11. Gene diagnosis is the key to locate the mutation and the effective methods for healthy reproduction. Genetic diagnostic steps should be based on genetic frequency and the healthy reproductive strategy may be based on pre-implantation genetic diagnosis (PGD) and prenatal genetic diagnosis.

Keywords: Congenital ectrodactyly; Genetic linkage; Genetic consulting; Gene diagnosis

Introduction

Congenital ectrodactyly refers to the absence of fingers and/or toes recognizable before birth, mostly due to genetic factors. It can be abnormality of missing fingers/toes, missing + synpolydactyly, palm/foot splitting, or a variety of coexistence. One serious case is that the median axis hypoplasia and the remaining end bones are fused in varying degrees, showing central dividing of the hand and foot, phalangeal hypoplasia and syndactyly deformity, called Split hand / foot malformation syndrome (SHFM). Some patients may be associated with ectodermal and craniofacial dysplasia, mental retardation and orofacial fissure [1,2]. Its incidence is about 1/18000 [3]. It seriously affects the patient's fine work, dynamic activity and mental health. This article reviews the characteristics of abnormal abnormalities and the genetic factors associated with this syndrome, summarizes the research progress of related genes, and discusses the methods of gene diagnosis.

Literature Review

Clinical types and related genes

The genetic linkage of SHFM can be autosomal dominant inheritance; it may also be expressed as autosomal recessive, or as X-linked inheritance [4-6]. There were seven congenital types reported. Among them, type 1, 3, 4 and 5 are autosomal dominant, [5,7-9] type 6 is autosomal recessive [10], type 2 is X-linked [11] and *SHFLD* is manifested incomplete dominant inheritance.

SHFM-type 1: It is caused by a misalignment of genes in the 7q21.3-q22.1 region. It is often due to genetic variation, but can also be expressed as autosomal dominant inheritance with weakened phenotype. Gene mutations can be expressed as translocations, inversions, and repeats, but the most common mutations are gene deletions [5,12]. The deletion or insufficient expression of DSS1, *DLX5* and *DLX6* genes in this region is currently reported leading to SHFM. It may present as a reduced penetrance of phenotype or a syndromic limb malformation [13]. Sensorineural deafness is noted in 35% of patients while ectrodactyly-ectodermal dysplasia-cleft lip/palate are much less frequent [14,15]. Linkage analysis, using microsatellite markers may exclude this region from containing the gene responsible for *SHFLD* [16]. Polymerase chain reaction (PCR) may show deletion of the microsatellite markers [17]. Mutant codes for these genes can be found by gene sequencing analysis or array comparative genomic hybridization (aCGH) [18,19]. Exome sequencing may identify critical region for SHFM [20]. Gene analysis for split hand/foot with sensorineural hearing loss was found linked to markers in 7q21 for locus D7S527 [21]. In addition, it appears to be associated with deletions of a more telomeric region encompassing the brain enhancer element hs1642. Thus, SHFM1 as well as hearing loss at the same locus are caused by deletion of regulatory elements. Deletions of the exons with regulatory potential of DYNC1I1 are an example of the emerging role of exonic enhancer elements [22].

SHFM-type 2: By gene mapping analysis, the genetic association of SHFM2 is found located in Xq26. It is a X-linked dominant inheritance [11]. Experimental cytogenetic examination of this type excludes X-chromosome and autosomal translocations [11,23,24]. The investigation found that the possible pathogenic genes of SHFM2 being associated with abnormal FGF13 and TONDU genes in Xq26 [11]. Fine gene mapping defines a 5.1 Mb region with a new centromeric boundary at DXS1114 and a telomeric boundary at DXS1192 in the reported family [11]. The complete expression can be the split hand/foot with fusion of fingers/toes. There are more male patients than female patients in the affected family, and female patients can be partially expressed.

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SHFM-type 3: The genetic association of SHFM3 is located at 10q24-q25, which is autosomal dominant and has a large phenotypic variation [7,25,26]. It can be a typical finger/deficient deformity to partial finger/toe loss and finger/toe insufficient development. Studies have found that repeated DNA mutations in the 10q24.3 region are associated with the occurrence of SHFM type 3 [27,28]. The repeat regions may include the HUG1, TLX1, LBX1, BTRC, POLL, and FBXW4 genes, as well as partial duplication of these genes [7,29,30]. Based on clinical association analysis, abnormal expression of FNXW4 and BTRC genes may be closely related to abnormal limb development [31,32]. Submicroscopic analysis could find the gragments of chromosome 10q24 [26,33]. A 514 kb gain at 10q24.31-q24.32 (chr10:102,962,134-103,476,346, hg19) was identified using 6.0 single nucleotide polymorphism (SNP) microarray, resulting in the duplication of nine genes, including BTRC and FBXW4 [28]. By using array comparative genomic hybridization techniques, a 10q24 microduplication was detected the individuals with distal limb deficiencies associated with micrognathia, hearing problems and renal hypoplasia [33]. Linkage analysis using informative microsatellite markers may indicate a linkage to D10S577, which can be identified two novel alleles (191 and 211 pb) [34]. Single-nucleotide polymorphism (SNP) microarray analysis may detect copy-number variants (CNVs) in SHFM cases without other birth defects and validated these CNVs using quantitative real-time polymerase chain reaction (qPCR) [35].

SHFM-type 4: The genetic association of SHFM4 was localized to 3q27, which was autosomal dominant, and the clinical manifestations varied greatly [36,37]. The abnormalities of the patients were mostly affected of the extremities [38]. The causative gene of SHFM4 is *TP63* mutation [39]. Gene mapping analysis found that about a quarter of the SHFM pathogenic genes are located in 3q27, and directly related to *TP63* gene mutation, which is the only single gene dominant genetic locus in the SHFM pathogenic gene [40]. *TP63* plays a crucial role in the development of ectodermal thorn. It plays a key role in regulation of ectoderm cell proliferation and differentiation. Its abnormal expression can cause dysplasia of ectodermal origin, including finger/toe loss [41]. *TP63* mutation may be associated with 10-16% of SHFM, and is associated with 93% of ectrodactyly ectrodermal dyspasia cleftlip/palate (EEC) [42,43].

SHFM type 5: The genetic association of *SHFM5* is located in 2q24.3-q31, which is autosomal dominant. Its clinical manifestations vary greatly compared with other SHFM types [9]. Genetic variants in key regions include the DLX1 and DLX2 genes [44], but mutations in the *HOXD*13 gene in this region may appear as synthetic finger/toe or multi-finger/multi-toe deformity [45,46]. The deletion of chromosome 2q31 encompasses the deletion of the *HOXD* gene cluster, leading to SHFM syndrome [9,47]. Goodman et al. believe that the gene deletion of *SHFM5* is related to the *EVX2* gene located about 5-Mb apart from the centromere upstream of the *HOXD* cluster. The authors report that two families are associated with limb malformations, the first family has affected father and daughter. Family genetic analysis involves the upstream 85 kb *EVX2* gene in the *HOXD* gene cluster (*HOXD*-*HOXD*13) located at the 5' end. The second family proband showed foot division and the gene analysis was chromosome 2q31-q33 deletion, including the *HOXD*1-*HOXD*13 gene cluster. *HOXD*1, *HOXD*3, *HOXD*4 and *HOXD*8 located at the 3' end of this gene cluster were not expressed [46]. In summary, the deletion of the *HOXD* gene cluster at the 5' end causes a foot division malformation rather than a hand-foot division malformation, while the gene locus of the split hand-foot malformation is 2q31 close to telomere. Another report using cytogenetic studies and haplotype analysis of a fetus and both parents showed that the fetus carried a *de novo* deletion encompassing a region of about 30 Mb on the paternal chromosome 2q (karyotype 46, XX, del (2) (q24.2-q32.2) [48].

SHFM type 6: The genetic association of SHFM6 is located at 12q13.11-q13, which is autosomal recessive with the clinical manifestation of split hand-foot malformation [10,49]. Seven locus variants of three genes (*TP63*, *WNT10B*, *DLX5*) in this region were found to be involved in the pathogenesis of SHFM type 6 by means of gene sequence analysis [50,51]. Ugar and Tulon first found homozygous *WNT10B* in Turkey to cause SHFM pedigrees. They found that the variant of this gene (R332W) is the key cause to SHFM because there is no disease in members of the same family without this mutation. In addition, they also found that homozygous duplicated fragmentation of the *WNT10B* gene can also cause the disease [49]. Later, Khan also reported in Pakistan that the *WNT10B* gene screening found a mutation (T329R) causing the same syndrome [52].

***SHFLD* (Split hand/foot malformation with long bone deficiency):** SHFM may be associated with long bone dysplasia. Its genetic association is located in the repetition of 17p13.3 [53]. It is autosomal dominant and manifested as split hand and foot malformation combined with shortness of tibia and fibula, but has a tendency to weakened phenotype [6,54-56]. Lezirovitz et al. found that the repetition of 17p13.3 caused SHFM with tibia/fibia dysplasia [57]. They use segregation analysis and multipoint Lod scores calculations by using all potentially informative family members, both affected and unaffected, identified the chromosomal region 17p13.1-17p13.3 as the best and only candidate for harboring a novel mutated gene responsible for the syndrome in the affected family. It was confirmed to be BHLHA9 gene duplication. They confirmed the role of this gene in tibia development through animal experiments [53]. However, the genetic discovery of this gene is only 50% of the penetrance, and about 50% of the gene repeaters are not clinically manifested. In addition, other authors reported that the 19p13.11 deletion caused SHFM, and that the *EPS15L1* gene is the root cause of this disease [58- 60].

Gene diagnosis and genetic counseling

There are often many patients in the family since congenital ectrodactily is a hereditary disease and most of them are dominant inheritance. It is not difficult to make the clinical diagnosis with the clinical features of congenital hand and foot deformity. Nevertheless, it is difficult to find its pathogenic genes and to establish the laboratory diagnostic methods. Specifically, for those with fertility needs, it is necessary to find the pathogenic gene and establish a genetic diagnosis method to create a solid clinical preventive foundation for blocking the inheritance of the disease at the reproductive stage.

The diagnosis of SHFM should be based on clinical manifestation and genetic diagnosis. The clinical manifestations of each type of SHFM are described in Table 1, and the steps of genetic diagnosis can be determined according to the SHFM classification corresponding to the clinical manifestation. The most common genetic type in clinical practice is autosomal dominant inheritance, followed by autosomal recessive inheritance and X-linked inheritance, and sporadic cases may be new genetic variants [3]. The genetic manifestations of SHFM can be weakened expressed, non-Mendelian, and gender differences [61]. Most cases of SHFM can be derived from complex genes and chromosome multiple and combined mutations. Therefore, the clinical genetic counseling of SHFM is relatively difficult. It is necessary to judge the genetic variation by genetic laboratory diagnosis.

Types	SHFM1	SHFM2	SHFM3	SHFM4	SHFM5	SHFM6	SHFLD
Inheritance Pattern	AD	X-link	AD	AD	AD	AR	AD
Gene Locus	7q21.2-q21.3	Xq26	10q24-q25	3q27	2q24.3-q31	12q13.11-q13	17p13.3 19p13.11
Gene Mutation	DSS1 DLX5 DLX6	FGF13、TDU	HUG1 TLX1 LBX1 BTRC POLL FBXW4	TP63	DLX1 DLX2	TP63 WNT10B DLX5	BHLHA9
Phenotype	SHFM, EEC, Sensorineural deafness, MR	SHFM, syndactyly, metacarpal or phalangeal hypoplasia	SHFM, triphalangeal and/or duplicated thumbs	SHFM, ectrodactyly, metacarpal or phalangeal hypoplasia, EEC, ADULT, LADD, CHARGE, VATER/MR	SHFM, MR, ectodermal and craniofacial findings, orofacial clefting	SHFM, tibial aplasia or hypoplasia	SHFM, tibial aplasia or hypoplasia

AD: Autosome Dominant; AR: Autosome Recessive; SHFM: Split Hand/Foot Malformation Syndrome; SHFLD: Split Hand/Foot Malformation With Long Bone Deficiency; EEC: Ectrodactyly: Ectoderma Dysplasia: Cleft Lip/Palate; ADULT: Acro: Dermato: Ungual: Lacrimal: Tooth Syndrome; LADD: Lacrimo: Auriculo: Dento: Digital Dyndrome; CHARGE: Coloboma Of The Eye, Heart Defects, Atresia Of The Nasal Choanae, Retardation of Growth And/Or Development, Genital And/Or Urinary Abnormalities, And Ear Abnormalities And Deafness; VATER: Vertebral Anomalies, Anal Atresia, Cardiovascular Anomalies, Tracheoesophageal Fistula, Renal and/or Radial Anomalies, Limb Defects; MR: Mental Retardation

Table 1: SHFM and the associated genes.

Discussion

Genetic diagnostic steps should be based on genetic frequency. The most common genetic variation of SHFM is 10q24.3 repeat (SHFM3, 20%) and 17p13.3 variant (SHFM/*SHFLD*, 16%) [3]. So the number of 10q24 genes should be tested first for SHFM patients. If the number of 10q24 genes is normal, the number of 17p13.3 will continue to be detected. The array comparison genomic hybridization technique can not only obtain the diagnosis results of these two genes, but also diagnose other genes such as 7q21-q22 deletion and 2q31 deletion abnormality [62,63].

Another important diagnosis for SHFM is the *TP63* gene sequencing, because this genetic variation is more common in sporadic cases, which can be new or autosomal dominant, and about 10-16% of cases involve this gene [8,42,43]. Autosomal recessive SHFM cases are currently found in close relatives marriage families. It has been found that *WNT10B* gene and *DLX5* gene abnormalities are related to it [10,50]. Close relatives married patients can have 25% of their children with the disease. It is extremely rare for normal marriage families. So the sequencing of such genes should be followed diagnosis of other genes without finding an abnormality.

For patients of SHFM with long bone dysplasia, the BHLHA9 gene located on 17p13.3 is a diagnostic target gene [53,23]. It should be pointed out that this type of variation is clinically only 50 phenotypic inheritances. It is often derived from unaffected parents. Most of them are male patients while women are often carriers. If they are affected females, the symptoms are often more serious [64-70].

Although the development and application of molecular biology genetic diagnosis technology provides a precise diagnosis method for genetic diagnosis of patients with congenital genetic diseases, including SHFM patients, due to the difference of SHFM types and the genetic variation, the design of the gene diagnostic methods and the clinical consultation for patients with SHFM is still a big challenge, especially for clinical genetic counseling and guidance for families with fertility requirements. It is particularly important to ensure that the next generation in the affected family to be healthy. First, it is necessary to let the patients understand the natural genetic manifestation of the disease and provide them with information of effective methods for prevention and clinical management. Second, it is necessary to provide patients with reliable technical support for healthy births. And finally, it is necessary to rule out the possible other potential genes related to the diseases. Preimplantation genetic diagnosis and prenatal genetic diagnosis and anatomical survey are currently available and reliable methods for clinically assisting SHFM patients or their family members to avoid genetic transmission affected gene [70-73].

Conclusion

Seven types of SHFM have been reported. The genetic linkage to this syndrome is found associated with a serial gene including *DLX5*, *DLX5*/*DLX6*, *TP63*, *WNT10B*, and *BHLHA9*. Gene diagnosis is the key to locate the mutation and the dependable methods for healthy reproductive management. Genetic diagnostic steps should be based on genetic frequency. The healthy reproductive strategy of SHFM should depend on pre-implantation genetic diagnosis (PGD) and prenatal genetic diagnosis and prenatal anatomical survey.

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