SPLIT-HAND AND FOOT MALFORMATION-3 (SHFM3)

Chandra Bhan Singh¹, Rashmi Patel¹, Anjali Rani², Subodh Kumar Singh³, and Akhtar Ali¹*

¹Centre for Genetic Disorders, Institute of Science, Banaras Hindu University, Varanasi-221005, India
²Department of Obstetrics & Gynaecology, Institute of Medical Sciences, Banaras Hindu University
³Department of Plastic Surgery, Institute of Medical Sciences, Banaras Hindu University

*Corresponding author

Abstract

Split-hand/foot malformation (SHFM) is a genetically heterogeneous group of limb malformations and is clinically variable. It is also known as ectrodactyly. SHFM is a rare congenital anomaly that is characterized by absence of central ray and fusion of the remaining bones to variable degrees. Both syndromic and non-syndromic as well as sporadic and familial SHFM cases have been reported. So far six loci have been identified for SHFM; SHFM1 (7q21-q22), SHFM2 (Xq26), SHFM3 (10q24-q25), SHFM4 (3q27), SHFM5 (2q31) and SHFM6 (12q13.11). Genes for only 2 out of these six loci have been identified; TP63 (SHFM4) and WNT10B (SHFM6). No correlation have been found between clinical phenotypes and six loci of SHFM.

Key words: Split-hand/split-foot malformation, duplication, limb malformation, BTRC, 10q24

Abbreviations: SHFM, Split-hand/split-foot malformation; WHO, World Health Organization; UTR, Untranslated Region

1. Introduction

According to World Health Organization (WHO), an average of 303000 newborns die within 4 weeks of birth every year due to congenital defects, worldwide. The congenital anomalies affect lifelong disability and cause significant economic, psychological and physical burden to the families in specific and to the society and government in general. Congenital abnormalities affect between 1 and 2% of live births, of these, around 10% have upper-limb deformities.

Split-hand/split-foot malformation (SHFM) is a congenital limb malformation commonly known as ectrodactyly. SHFM involves the central rays of the autopod which shows variable degree of phenotypes ranging from mild syndactyly to severe median clefts of the hands and feet, oligodactyly, or monodactyly and aplasia and/or hypoplasia of the phalanges, metacarpals and metatarsals (fig. 1) [1, 17]. SHFM is heterogeneous disorders in the perspectives of both clinically and genetically. Both sporadic and familial cases are found in SHFM. This disorder may occur as a separate entity (nonsyndromic) or associated with other anomalies (syndromic). Estimated incidence of SHFM is 1/8,500 ~1/25,000 [2].
Six loci for SHFM have been mapped in human genome; SHFM1 (7q21-q22), SHFM2 (Xq26), SHFM3 (10q24-q25), SHFM4 (3q27), SHFM5 (2q31) and SHFM6 (12q13.11). Genes for only 2 out of these six loci have been identified; TP63 (SHFM4) and WNT10B (SHFM6) whereas rest have still to be identified. No correlation have been found between clinical phenotypes and six loci of SHFM.

2. Genomic rearrangements in SHFM3 patients

The locus of SHFM3 has been mapped on chromosome 10q24-q25 of 2cM region by linkage analysis [6, 7, 11, 12]. In the SHFM3 patients, 0.5 Mb tandem duplications of the genome on chromosome 10q24 has been identified [13] and is considered as the cause of SHFM3 phenotypes. It has been reported that the smallest duplicated region contained a disrupted extra copy of the dactylin (FBXW4) gene and the complete ladybird homeobox 1 (LHX1), beta-transducin repeat containing (BTRC), DNA polymerase lambda (POLL), and deleted in primary ciliary Dyskinesia homolog (mouse) (DPCD) genes.

Dactylaplasia (Dac) in mouse is considered as a SHFM3 model for human since human genomic locus 10q24 is homologous to the Dac locus of mouse on chromosome 19 and Dac mouse is characterized by absence of central digital rays [14,15]. The dactylin gene encodes an F-box/WD40 repeat protein which involved in ubiquitin-dependent proteolytic pathways [16]. According the work done on mouse model, it has been deliberated that dactylin gene is the best candidate gene responsible for SHFM3, while the function of dactylin remains unknown. Since, the mutation analysis of mouse strain Dac2J and Dac1J confirms long range regulatory effects of dactylin that interrupt the normal dosage of genes within the duplicated region of chromosome 10q24, instead of candidate gene for SHFM3.
3. Proximal and distal breakpoints in SHFM3

Southern, pulsed field gel electrophoresis and dosage analysis on samples of SHFM3 patients reported the tandem duplication at 10q24 region. Duplication of genomic region contains complete gene of entire LBX1 and BTRC genes, known to be involved in limb development and disrupted extra copy of the FBXW4 gene [13]. The smallest repeated region of 440 kb size was found in all SHFM3 patients that tappers the number of gene reside within the duplicated region. This region is about 440-570 kb which included genes from LBX1 to a portion of the FBXW4 3 gene. The breakpoints at proximal and distal part of chromosome 10 were within a 130 and 80 kb. Proximal breakpoint is located at the intergenic region which is centromeric to LOC159673 in the two cases, and centromeric to HUG1 (TLX1NB1) in one case. Proximal distal breakpoints is also found telomeric to LOC203696 (centromeric to LBX1) in three cases. Most of the cases, proximal breakpoints are located at the intergenic region centromeric to LBX1. On other hand, the distal breakpoints were located at 5' untranslated region (UTR) in two cases, intron 2 in one case and intron 5 in four cases of FBXW4 gene.

In another report on 28 non-syndromic SHFM familial and sporadic cases, by Southern blot and sequence analysis of the FBXW4 gene, a tandem duplication of 10q24 region was identified [16]. Genomic rearrangement was observed only in two cases amongst all familial cases that display typical SHFM phenotypes in which hand and feet were affected in symmetrical pattern. A duplication of 512 kb region containing genes from LBX1 to FBXW4 was found in one patient. In this study, another cases were sporadic which arise from de novo, 447 kb duplication of maternal origin that includes genes from LBX1 to a portion of exons 9-6 of FBXW4. Thus, proximal breakpoints were located at intergenic region centromeric to LBX1 in both cases, whereas the distal breakpoints were located at intron 5 of FBXW4 gene in the case of small tandem repeat, and at 5'UTR of FBXW4 gene in the case of longer duplication.

Lyle et al., (2006) have shown the duplication of 10q24 in 12 SHFM3 patients having the duplication of the gene FBXW4, KAZALD1, TLX1NB1, LBX1 and BTRC [16]. Furthermore, BTRC and SUFU are known to be involved in beta-catenin signaling and considered as candidate genes for SHFM3 because duplicated region of 10q24 contains three copies of BTRC gene and two copies of SUFU gene which were over expressed in SHFM3 patients compared to control individuals. This suggests that over expression of BTRC and SUFU may be important candidates of SHFM3 [17]. In other SHFM patients, both FBXW4 and BTRC are considered as candidate genes for SHFM phenotype. Duplication and triplication of the genes LBX1 to FBXW4 have been identified in the patients of distal limb deficiency with micrognathia syndrome (DLDMS). Duplication of 539 kb region at 10q24.31–q24.32 containing LINC01514 (exon 6) and FBXW4 has been observed in the SHFM patients [20], whereas duplication of 600 kb genomic region at 10q24.31–q24.32 has been reported that contains TLX1NB and FBXW4 genes in the patients [21-23]. Chen et. al. (2014) has shown a 394 kb duplication at 10q24.31–q24.32 having LBX1 and DPCD genes in the
SHFM3 patients [24]. Recently, it has been reported that duplication in the sequence of exon 1 of BTRC is responsible for SHFM3 phenotype which via cis-acting or trans-acting effects on genes or regulatory sequences that involved in the limb development and related pathway [25].

Conclusions

Split-hand and foot malformation-3 (SHFM3) is congenital limb deformity caused by duplication of genomic region of chromosome 10q24-q25 which involves FBXW4, LBX1, BTRC, POLL, and DPCD genes. Out of these genes, part of exon 1 duplication of BTRC seems to be a strong candidate on the basis of some recent experiments that still needs to be investigated.

Acknowledgement

Indian Council of Medical Research (ICMR) is acknowledged for providing Junior Research Fellowship (JRF) to Mr Chandra Bhan Singh.

REFERENCES


