Split Hand and Foot Malformation, Prenatal Diagnosis using Single Nuceotide Polymorphism

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Abstract— Short Hand and Foot Malformation is a rare medical condition of ectrodactyly with hand and foot having lobster claw-like appearance. It varies in severity in phenotypes depending on the mutation in genes responsible for Short Hand and Foot Malformation. It can be diagnosed in clinic on inspection and then confirmed by molecular testing methods including Single Nucleotide Polymorphism. Single Nucleotide Polymorphism can further be used in prenatal screening and diagnosis of SHFM in fetus very early in pregnancy using amniotic fluid. We shall here consider briefly a pregnant patient with phenotype of SHFM whose fetus was diagnosed with SHFM3 after undergoing Single Nucleotide Polymorphism testing. In so doing we point out the importance of Single Nucleotide Polymorphism in prenatal genetic testing.

Index Terms— Short Hand and Foot Malformation, ectrodactyly,Single Nucleotide Polymorphism

1 Introduction

Split Hand Foot Malformation (SHFM) is a congenital birth defect characterized by the partial or complete absence of fingers/ toes, which can be of variable severity. The remaining fingers/ toes may fuse together giving a lobster-claw like appearance. SHFM may occur by itself (isolated) or it may be part of a syndrome with abnormalities in other parts of the body. At least six different forms of isolated SHFM have been reported and each type is associated with a different underlying genetic cause. SHFM may be inherited in an autosomal dominant, autosomal recessive, or X-linked manner [1]. In clinic it can be diagnosed on inspection of the individual hands and feet and then confirmed by molecular testing for the causative gene mutations. In this case review, we consider the use of Single Nucleotide Polymorphism for the prenatal diagnosis of SHFM in a fetus whom after her mother was previously diagnosed with SHFM.

2 Case Review

2.1 Review

In this review we shall briefly consider one of our patient with SHFM. A 21y old pregnant female presenting with a history of malformation of all four limbs since birth, presented to our Genetic department for prenatal counseling. She was otherwise healthy with no abnormal medical, surgical and drug history. Physical examination revealed an otherwise active female with malformation of the upper and lower limbs. She was worried that her fetus might also have similar deformities and opted for molecular testing. After we proposed her the different molecular testing methods available, she opted for SNP. Venous blood sample was obtained from mother and amniotic fluid for fetus was collected. SNP technic, under standard protocol, was use for detection of the causative genes from a array of genes known for SHFM including *BTRC, DPCD, FBXW4, LBX1* and *POLL* and to check whether the fetus had any such mutations too [2].

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3 Results

3.1 Clinical Examination

The patient hands were clearly lacking the middle fingers and the remaining fingers appeared to be fused together resulting in a lobster-claw like hand. Similarly the feet, lacking middle toes with resulting toes fused together, had the same lobster claw like appearance. Despite of her deformities in all four limbs (Figure 1), the patient was able to perform her daily activities without much difficulty.

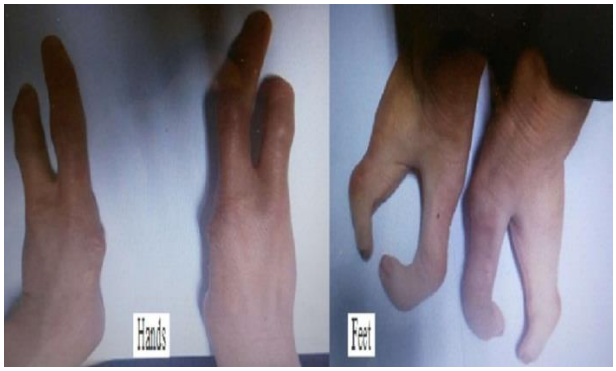

Figure 1 Lobster-Claw like appearance of hand and feet

3.2 Single Nucleotide Polymorphism

SNP performed for the array of genes responsible for SHFM revealed mutation in the *BTRC* genes at chromosome 10 and 4 of varying length. There were repeats mutation within the chromosome 10 and chromosome 4 for mother and similar repeats mutation within chromosome 10 for the fetus. The results are briefly tabulated (Table 1) and SNP results also shown (Figure 2).

Table 1 Mother and Fetus mutations in the *BTRC* genes and chromosome locations

	CNV type	CNV nature	start	end	length (bp)	chromosome zone
MOTHER	3	repeat	102873339	103333271	459932	10q24.31q24.32
	2	UPD	114332705	128921442	14588737	4q26q28.1
FETUS	3	repeat	102903286	103392503	489217	10q24.31q24.32

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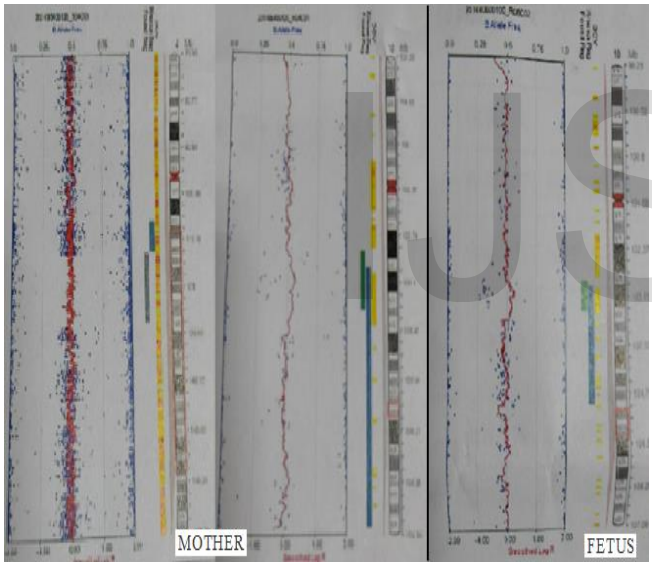

Figure 2 SNP result showing mutation for mother and fetus respectively

4 Discussion

SHFM is a rare condition of distal limbs malformation and its severity may vary in phenotypes among members of a given family. It is usually diagnosed in clinic by careful physical examinations followed by molecular testing confirmation. Nowadays it is also possible to extend our screening in the prenatal period. SNP proved to be a proper tool in helping to map some mutations responsible for SHFM within fetus DNA. In our case reiew we detected a common repeat mutation within mother and fetus DNA at chromosome 10 location. The most likely diagnosis was SHFM 3.

SHFM3 is clinically characterized by the typical clinical features including dysplastic ears with hearing loss, cleft palate, face with maxillary hypoplasia and micrognathia, renal anomalies, ectrodactyly, clinodactyly, triphalangeal thumbs and preaxial polydactyly. It is transmitted as an autosomal dominant trait accounting for classical SHFM phenotypes[1]. About 20% of the SHFM3 cases are caused by duplications mapped to chromosome 10q24 as confirmed in our case review. Several genes may account for SHFM phenotypes namely *FGF8*, *LBX1* , *BTRC* , and *DACTYLIN* [2]. As for our patient and fetus, we did note the repeated mutations involving the *BTRC* genes as the responsible genetic cause for the SHFM3 phenotypes.

In conclusion, clinical and genetic heterogeneity of SHFM make precise clinical diagnosis challenging thereby necessiting the use of molecular testing. SNP has helped for pinpoint diagnosis which not only helps families and physicians to understand the exact genetic nature of disorder but also helps to set up appropriate management strategies. SNP will help in the setting of proper family planning, preconceptual and prenatal screening. Furthermore SNP not only allow screening for known genetic mutations but also novel mutation within the whole geneome sequencing. In short, SNP proved a proper tool for genes mutation identification in the prenatal period.

Conflict of Interest

The author has no conflict of interest.

References

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