Split-hand/feet malformation in three tamilian families and review of the reports from India

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Brief Report

Introduction

Split-hand/foot malformation (SHFM) also known as ectrodactyly or Lobster hand foot malformation, is defined as longitudinal deficiency of a digital ray of the hand or foot except the first or fifth digits\(^1\) (Biesecker, 2009).

SHFM can be a part of a syndrome or can manifest as an isolated malformation. Nearly 50 syndromes have been described with SHFM, the most common being the ectrodactyly-ectodermal dysplasia-cleft syndrome (EEC). Nonsyndromic SHFM can be autosomal dominant (AD), recessive (AR), or X-linked recessive (XLR).\(^2\) We report three unrelated families with nonsyndromic SHFM.

Case Report

Pedigree 1

A 40-year-old man was admitted for poisoning. His son was incidentally noted to have SHFM. He was born of nonconsanguineous marriage. Similar deformities were present in his mother and brother [Figure 1]. This was present over four generations of the mother’s family (seven more members) suggesting AD pattern of inheritance. None of the observed members had any features of ectodermal dyplasia. Despite the deformities, both the brothers were employed, while the mother could knit clothes in her free time.

Pedigree 2

A 12-year-old girl who had come to visit a patient was found to have SHFM without any skin or teeth anomalies. Similar deformities were present in her sister [Figure 2], but not in the parents; suggestive of AR pattern.

Pedigree 3

A 19-year-old boy was on follow-up for diabetes. He had developmental delay with deaf mutism. He had SHFM of the left upper limb [Figure 3]. Skin and teeth were normal. He was born of consanguineous marriage and his father said that the boy’s elder sibling died after birth and it had similar shaped hands and feet. The parents were normal suggesting AR inheritance.

Discussion

The basis for SHFM is related to the defects in

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the patterning of the limb development. The three major tissues responsible for limb patterning are: Apical ectodermal ridge (AER), zone of polarizing activity (ZPA), and progress zone (PZ). The AER determines the proximodistal axis by directing the PZ. The ZPA determines the anteroposterior axis of the limb.\footnote{2}

Three mechanisms have been proposed for the limb defects in SHFM. Experimental evidence suggests a defect in the AER or ZPA. Second, involvement of late limb patterning genes like Ho × 13 could produce similar defects. A third explanation involves viewing the defect as a branching rather than a patterning defect.\footnote{2}

SHFM can be nonsyndromic or as a part of other syndromes like EEC. Nonsyndromic form can have associated long bone defects like tibial aplasia, known as SHFM with long bone deficiency (SHFLD).

The EEC syndrome is the most common form of syndromic SHFM, with cleft lip/palate and teeth and skin anomalies. Mutations in the p63 locus (SHFM 4) are often associated with EEC and SHFM.

So far six genetic loci have been described for SHFM\footnote{2} [Table 1]. These include AD (most common), AR (SHFM 6) and XLR inheritances (SHFM 2) have been described. Of these, only p63\footnote{3} and Wnt10B\footnote{4} have been identified conclusively as the disease causing genes.

**Review of reports from India**

We searched PubMed, Google, and IndMed with the keywords: SHFM, ectrodactyly, India, EEC syndrome. One report was not included due to the nonavailability of any details. A total of 30 prior published reports were included.
for analysis. Adding our 14 persons to the previously published 66 people, a total of 80 were analyzed [Table 2].

Two-thirds of the 80 individuals were familial (AD 65% and AR 12%), with the rest being sporadic (23%). Maternal valproate use was implicated in one case.

The EEC syndrome was present in 50% of the patients with AD inheritance in 32 and sporadic occurrence in 10 patients. There were no AR cases with EEC syndrome.

Of the 18 sporadic cases, EEC syndrome was present in 10, tibial aplasia in two, and fibular aplasia in one with only five having SHFM. Only one of the nine AD families had isolated SHFM; whereas, all the AR cases had isolated SHFM.

Overall, other associated anomalies included tibial aplasia (four), deafness (two), enlarged cisterna magna (one), fibular aplasia (one), and nystagmus (Karsch-Neugebauer syndrome - one).

### References

9. Thakkar S, Marfatia Y. EEC syndrome sans clefting:

### Table 1: Split-hand/foot malformation types and associated conditions with genes responsible

<table>
<thead>
<tr>
<th>Type</th>
<th>Inheritance</th>
<th>Locus</th>
<th>Gene</th>
<th>Associated conditions</th>
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<tr>
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<td>XLR</td>
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<td>HOX1D13</td>
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<td>WNT10B</td>
<td>EEC</td>
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</tbody>
</table>

**AD**: Autosomal dominant, **AR**: Autosomal recessive, **EEC**: Ectrodactyly-ectodermal dysplasia-cleft syndrome, **SHFM**: Split-hand/foot malformation, **XLR**: X-linked recessive.

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