

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

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Split-hand/foot malformation (SHFM) is a rare condition which can be either syndromic or nonsyndromic. We report three unrelated pedigrees, one with autosomal dominant (AD) inheritance and the other two with autosomal recessive (AR) pattern. We also briefly review the published reports from India.

Key words: Autosomal dominant, autosomal recessive, ectrodactyly, Indian, split-hand/foot malformation

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 dysplasia. 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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Figure 1: Mother and two siblings with split-hand/foot malformation (SHFM)



Figure 2: Two sisters with SHFM

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.^[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 *Hox 13* could produce similar defects. A third explanation involves viewing the defect as a branching rather than a patterning defect.^[2]

SHFM can be nonsyndromic or as a part of other syndromes like EEC. Nonsyndromic form can have

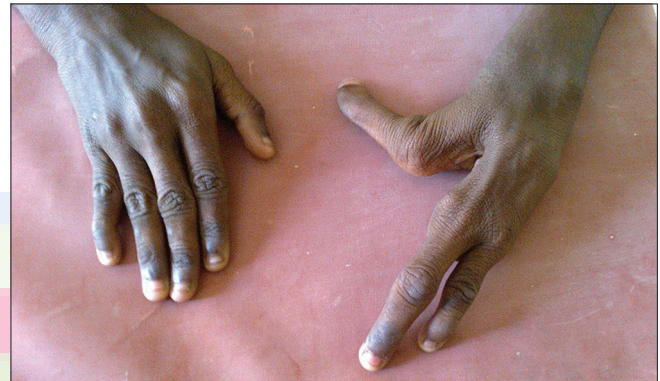


Figure 3: SHFM in one limb

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^[2] [Table 1]. These include AD (most common), AR (SHFM 6) and XLR inheritances (SHFM 2) have been described. Of these, only *p63*^[3] and *Wnt10B*^[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

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

Type	Inheritance	Locus	Gene	Associated conditions
SHFM1	AD	7q21	DLX6, DLX5, DSS1	Sensorineural hearing loss
SHFM2	XLR	Xq26	FGF13	-
SHFM3	AD	10q24	HOX11, FGF8	-
SHFM4	AD	3q27	TP63	EEC syndrome
SHFM5	AD	2q31	HOXD13	Mental retardation micrognathia low set ears
SHFM6	AR	12p11	WNT10B	Syndactyly/polydactyly

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

Table 2: Summary of the reported Indian cases

Authors	Inheritance	No. of families	No. of patients	Associated features
Joseph <i>et al.</i> , ^[5]	AD	1	3	EEC
Nadkarni <i>et al.</i> , ^[6]	AD	1	4	EEC
Sett <i>et al.</i> , ^[7]	AD	2	18	EEC
Singh <i>et al.</i> , ^[8]	AD	1	4	EEC
Thakkar <i>et al.</i> , ^[9]	AD	1	3	EEC
Mishra <i>et al.</i> , ^[10]	AD	1	2	Deafness
Choonia and Salgar ^[11]	AD	1	2	Deafness
Shenoy and Kamath ^[12]	AD	1	2	Tibial aplasia
Sharma <i>et al.</i> , ^[13]	AD	1	4	
Our patients	AD	1	10	
Jindal <i>et al.</i> , ^[14]	AR	1	2	
Verma <i>et al.</i> , ^[15]	AR	1	2	
Smith ^[16]	AR	1	2	
Our patients	AR	2	4	
Malvankar <i>et al.</i> , ^[17]	S		1	EEC
Shivaprakash <i>et al.</i> , ^[18]	S		1	EEC
Marwaha <i>et al.</i> , ^[19]	S		1	EEC
Koley <i>et al.</i> , ^[20]	S		1	EEC
Cyriac and Lashpa ^[21]	S		1	EEC
Kumar <i>et al.</i> , ^[22]	S		1	EEC
Batra <i>et al.</i> , ^[23]	S		1	EEC
Parkash <i>et al.</i> , ^[24]	S		1	EEC
Thapa <i>et al.</i> , ^[25]	S		1	EEC, cisterna magna
Mathian <i>et al.</i> , ^[26]	S		1	EEC, nystagmus
Sarkar ^[27]	S		1	
Lodha <i>et al.</i> , ^[28]	S		1	Fibular aplasia
Thami and Kaur ^[29]	S		1	
Kalla and Garg ^[30]	S		1	
Pandey <i>et al.</i> , ^[31]	S		1	Tibial aplasia
Managoli and Chaturvedi ^[32]	S		1	Tibial aplasia
Riyaz <i>et al.</i> , ^[33]	S		1	
Sukumaran <i>et al.</i> , ^[34]	S		1	Maternal valproate

AD: Autosomal dominant, AR: Autosomal recessive, EEC: Ectrodactyly-ectodermal dysplasia-cleft syndrome, S: Sporadic

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 cistern magna (one), fibular aplasia (one), and nystagmus (Karsch-Neugebauer syndrome - one).

Conclusion

This report highlights the varied presentation and inheritance of SHFM in India, with a significant number of reports with a negative family history. These patients may have recessive inheritance or new mutations. Further analysis of these persons could help in understanding this unique condition.

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