Split hand/foot malformation syndrome (SHFM): rare congenital orthopaedic disorder

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DESCRIPTION

A 17-year-old man, the third child of physically normal parents, was diagnosed with a case of cleft hand (lobster hand) in our outpatient department during a routine visit. He was born with deformed hands and feet in the form of syndactyly of thumb with the index finger in the upper limbs. He had a median cleft of the hands (figures 1–3). There was no facial dysmorphism in the patient. He had a history of congenital heart disease (ventricular septal defect with aortic regurgitation) and seronegative hypothyroidism. The two siblings of the index case were physically normal. Our patient most probably had autosomal mode of inheritance. The genetic analysis of the patient showed mutation in *TP63* gene (*R280C* mutation) causing split hand/foot malformation syndrome (SHFM) type 4.

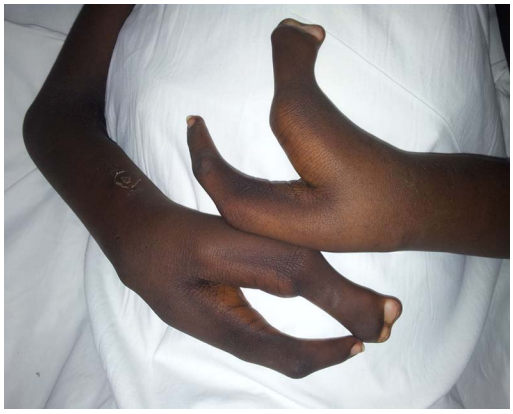

Figure 1 Image showing both claw hands.

DISCUSSION

Ectrodactyly–ectodermal dysplasia–cleft syndrome is a rare orthopaedic malformation with incidence of around 1 in 90 000 live births.[1] It has various names including split hand–split foot–ectodermal dysplasia–cleft syndrome or split hand, cleft hand or lobster claw hand/foot. It is called lobster claw hand/foot as there is a median cleft in upper and lower limbs because of the absence of central digital rays, giving the affected limbs the appearance of lobster claws.[2] It is characterised by the deficiency or absence of one or more central digits of the hand or foot. It is thought to arise because of a wedge-shaped defect of the apical ectoderm of the limb buds.[3] The associated anomalies include tibial aplasia, learning disabilities, ectodermal and craniofacial findings, orofacial clefting, renal abnormalities such as vesicoureteral reflux, recurrent urinary tract infection (UTI), missed or abnormal teeth, enamel hypoplasia and conductive hearing loss.[4 5] There are several classifications for cleft hand but that described by Manske and Halikis is most commonly used.[6] There are five types of SHFM syndrome based on the chromosomal associations and genes thought to be responsible for SHFM. Table 1 shows different types of SHFM with their chromosomal locations and the candidate genes responsible for them. The only proven mutations known to underlie SHFM in humans have been found in the *TP63* gene, which encodes a homologue of the tumour-suppressor *p53* gene.[7] The *p63* gene plays a very important role during embryonic development and does not behave like a tumour suppression gene. The *TP63* gene has at least six different isoforms. Of these different isoforms a few are transcriptional activators similar to *p53*, whereas some other isoforms which have repressive activity towards *p53*-driven and *p63*-driven gene expressions have also been isolated.[8] The first report of mutations in the *TP63* gene was seen in patients with ectrodactyly-ectodermal dysplasia-cleft (EEC) syndrome[9] followed by various case reports of *TP63* mutations in patients with isolated ectrodactyly.[10 11] Various types of *TP63* mutations have been identified in non-syndromic SHFM families and isolated patients.[11]

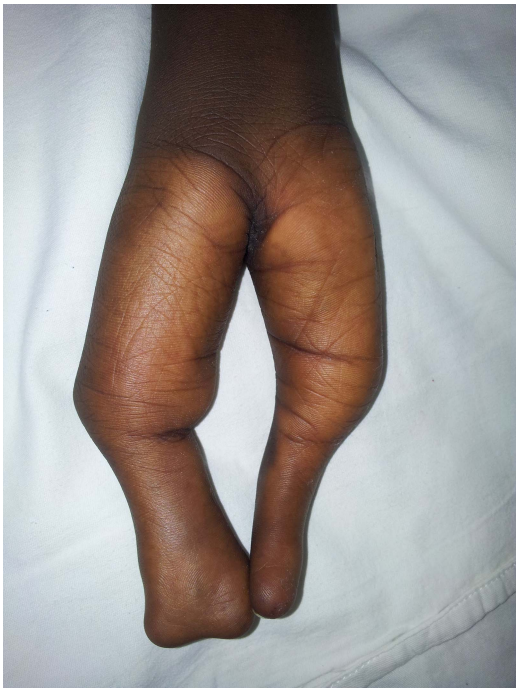

Figure 2 Image of the supine claw hand.

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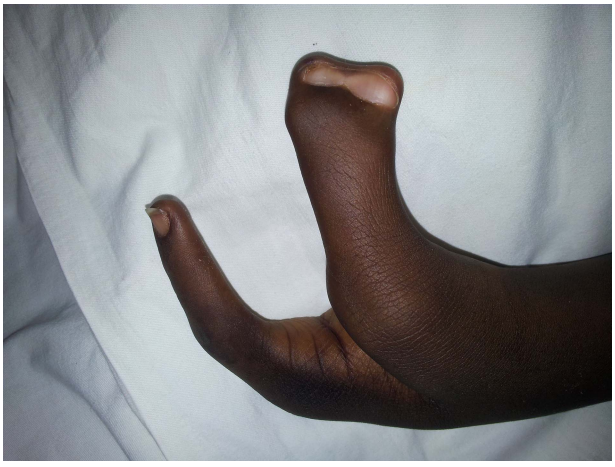

Figure 3 Image showing prone claw hand. Note the fusion of thumb and index finger and two distinct nail beds of the fused fingers.

These include:

1. *K193E*
2. *K194E*
3. *Q634X*
4. *E639X*
5. *R280C*
6. *R280H*
7. *InsP154*

The majority of these mutations lead to amino acid substitutions in the DNA-binding domain that are predicted to abrogate interaction with the DNA and, hence, lead to reduction in transactivation activity. The *R280C* and *R280H* mutations are usually associated with ectrodactyly, ectodermal dysplasia and cleft lip/palate (EEC) syndrome but have also been reported with SHFM syndrome.[11]

Table 1 Different types of Split hand/foot malformation (SHFM) with their chromosomal locations and candidate genes

Disorder	Chromosomal location	Candidate gene(s)
SHFM1	7q21	DLX5, DLX6, DSS1
SHFM2	Xq26	FGF13, TONDU
SHFM3	10q24	Dactylin, SUFU, BTRC
SHFM4	3q27	TP63
SHFM5	2q31	DLX1, DLX2

Learning points

- Patients with claw hand syndrome must be evaluated with ECHO, hearing screening and thyroid screening for early diagnosis and treatment.
- Parents are to be counselled for malformations in the next pregnancy and regular antenatal scans are to be advised for the mother.
- These patients should undergo genetic analysis to identify the mutations involved in the disease.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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