The split hand/split foot malformation (SHFM), which is also known as ectodactyly, is a limb malformation syndrome involving the central rays of the hand or foot. The typical SHFM may present with syndactyly; median clefts of the hands and feet; and aplasia or hypoplasia (or both) of the phalanges, metacarpals, and metatarsals.

Numerous human gene defects can cause SHFM. For example, the SHFM1 gene is associated with deletions of varying extent on chromosome 7q21–q22 [1], whereas SHFM2 is associated with genes localized at Xq26–q26.16 [2]. Previous research has reported multiple types of syndromic or nonsyndromic ectodactyly [3]. The most common mode of inheritance is autosomal dominant with reduced penetrance. These cases can occur in families or in isolation. Interfamilial variability appears to be significantly greater than intrafamilial variability, which indicates genetic heterogeneity. The syndrome is characterized by various clinical manifestations that vary significantly among affected individuals and generate various combinations.

We present a case of "lobster claw hand" observed during a prenatal ultrasound examination. A 21-week pregnant 39-year-old woman (gravida 4, para 1) was referred to our hospital after the detection of SHFM during fetal ultrasound screening (Fig. 1). Ultrasonography at referral confirmed a fetus with SHFM but without any facial or genitourinary anomaly. A review of her birth history showed that her first son had syndactyly of his left hallux and second toe, but no other detectable anomaly. The child’s intelligence was also of normal development.

She sought genetic counseling for this pregnancy. The pregnancy was terminated because of the possible deletion of chromosomes. The abortus exhibited a specific characteristic of deficiency of the second and third toes (Fig. 2). Both hands were claw-like (Fig. 3). The placental tissue was examined using oligonucleotide-based array comparative genomic hybridization (aCGH) analysis with a CytoChip Oligo array (BlueGenome, Cambridge, UK). The genomic version of the chip is the CytoChip ISCA+ version 2.0 x860K (BlueGenome, Cambridge, UK). We employed the protocol presented in the reference manual (www.cytochip.com).

The results revealed three microdeletions: 1.9 Mb deletions at 7p22.1–p22.1 (4,583,819–6,498,129), 3.9 Mb deletions at 7q11.23–q11.23 (72,119,820–75,977,247), and 4.1 Mb deletions at 7q21.3–q22.1 (97,723,732–101,812,625). Two other larger deletions were 24 Mb deletions at 19p13.3–p12 (210,424–24,170,303) and 26.2 Mb deletions at 19q11.31–q13.43 (37,601,047–63,787,200) (Fig. 4).

Split hand/split foot malformation has been identified by numerous terms such as "ectodactyly", "cleft hand", "partial terminal aphaflagia", "oligodactyly", "central oligodactyly", "central ray deficiency", "crab claw malformation", and "lobster claw anomaly/malformation". Elliott et al [4] summarized previously reported SHFM patients. Our patient was diagnosed prenatally, which differs from numerous reported cases that are typically observed after birth. In 1995, the first case was diagnosed during pregnancy [5]. Detailed ultrasonography revealed multiple anomalies, which included oligodactyly. Split hand/split foot malformation is genetically heterogeneous with mutations identified at five loci: SHFM1 at 7q21.3, SHFM2 at Xq26, SHFM3 at 1q42, SHFM4 at 3q27, and SHFM5 at 2q31 [3]. The location heterogeneity complicated the identification and genetic counseling.

Array comparative genomic hybridization is a technique that enables high-resolution, genome-wide screening of segmental genomic copy number variations. It is becoming an essential and routine clinical diagnostic tool, and it is gradually replacing traditional cytogenetic methods [6].
A shortcomer of classical karyotype analysis is that it lacks sensitivity in detecting subtle chromosome rearrangements (i.e., <4 Mb). Fluorescent in situ hybridization has improved the diagnostic resolution, but it is a time-consuming targeted method that requires previous knowledge of the chromosomal region. However, comparative genomic hybridization platforms can cover approximately one clone per megabase to one clone per 100 kb. Commercial whole-genome oligonucleotide arrays range from one probe per 6–70 kb. Shaikh [7] reported a detailed review and comparison of various commercial oligonucleotide array platforms.

Five genomic loci have been implicated, based on cases and family studies. These loci are SHFM1 (chromosome region, 7q21–q22), SHFM2 (Xq26), SHFM3 (10q24), SHFM4 (3q27), and SHFM5 (2q31). In the past, molecular tests such as fluorescence in situ hybridization or polymerase chain reaction were used to detect the mutated loci in people with SHFM. Because of improvements in the resolution of aCGH, it detected SHFM type 1 in our patient. The deletions at chromosome 7q21–q22 in patients with SHFM type 1 cause the deletion of several candidate genes including DLX5, DLX6, or DSS1. A knockout mouse model showed the concurrent loss of DLX5 and DLX6, and resulted in the failure of apical epidermal ridge development; this was finally expressed as the phenotype of ectrodactyly [3].

In addition to microdeletions of 7q, our patient had two other microdeletions at chromosome 19p. In the literature, there has been only one SHFM case report with genomic loci studies at 19p [8]. Aten et al. [8] identified a de novo deletion of chromosome 19p13.11 in a male patient with SHFM, but no candidate genes in other SHFM loci (e.g., DSS1, FGF13, FBXW4, TP73L, and DLX2). Subsequent screening of 21 syndromic and nonsyndromic SHFM patients with no TP73L mutation failed to detect any deletion or duplication in chromosome 19, which indicated that SHFM is genetically more heterogeneous than previously reported. Chromosome 19p contained two genes (EPS15L1 and CALR3) that may be associated with limb malformations [9]. EPS15L1 functions as a substrate for tyrosine kinase activity of the epidermal growth factor receptor [10]. The signal pathway of the epidermal growth factor receptor is associated with the apical epidermal ridge, thereby affecting limb formation.

We observed EPS15L1 gene deletion in our patient. However, because of the concurrent loss of SHFM type 1 gene at chromosome 7, it was difficult to identify the relationship between phenotype and genotype when both deletions are present.

If a couple with fetal anomalies accepts fetal chromosome studies, aCGH could expand the ability to detect microdeletions in genetic diseases. During genetic counseling, physicians should...
recommend an aCGH test for patients with a family history of fetal anomalies.

**Conflicts of interest**

The authors have no conflicts of interest relevant to this article.

**References**


