Split-Hand/Foot Malformation with Long Bone Deficiency 1

Alternative Names
Aplasia of Tibia with Ectrodactyly
Cleft Hand and Absent Tibia
Ectrodactyly with Aplasia of Long Bones
SHFLD
SHFLD1
Split-Hand/Foot Malformation with Long Bone Deficiency
Tibial Aplasia with Split-Hand/Split-Foot Deformity

Record Category
Disease phenotype

WHO-ICD
Congenital malformations, deformations and chromosomal abnormalities > Congenital malformations and deformations of the musculoskeletal system

Incidence per 100,000 Live Births
0-1

OMIM Number
119100

Mode of Inheritance
Autosomal dominant

Gene Map Locus
1q42.2-q43

Description
Limb deficiency disorders are etiologically heterogeneous, occur as an isolated anomaly or as a part of a syndrome, and may be acquired or congenital. The term “limb deficiency” incorporates both absence and size reduction of 120 human limb bones, with 205 identified limb deficiency disorders.

Congenital deficiency of the tibia (tibial hemimelia, aplasia, or dysplasia) also known as long bone deficiency is a rare and severe lower limb malformation, with an incidence of approximately 1:1,000,000 live births. It is characterized by lack of part or the entire tibia, with relatively intact fibula. Usually the affected leg is rotated externally and the ventral surface of the foot faces the opposite leg. The majority of the reports are sporadic cases; however apparent autosomal dominant and autosomal recessive families with or without ectrodactyly and other associated limb anomalies also have been reported. The phenotype has been classified into four types: type-I (entire tibia absent), type-II (distal tibia not seen), type-III (proximal tibia not seen), and type-IV (tibia-fibular diastases).

Bilateral and/or unilateral tibial aplasia associated with various other skeletal and extraskeletal malformations, such as congenital diplopodia, triphalangeal thumbs and polydactyly, cleft lip/palate, congenital cardiac defect, vaginal agenesis, cardiovascular defects, imperforate anus radioulnar synostosis, and the most common phenotype, ectrodactyly (split hand /foot) have been seen. Treatment of tibial aplasia traditionally consists of amputating the affected limb to facilitate use of artificial limbs. However, treatment varies with individual cases.

Absence of tibia combined with ectrodactyly is a rare malformation with highly variable manifestations. The full-blown syndrome consists of aplasia of tibia and split-hand/split-foot deformity. Distal hypoplasia or bifurcation of femora, hypo- or aplasia of ulna, and minor anomalies such as patellar aplasia, hypoplastic big toes, postaxial and intermediate polydactyly in connection with split-hand deformity, and cup-shaped ears may be additional malformations. The mildest visible manifestation may be hypoplastic big toes; the severest is tetramonodactyly or transverse hemimelia.

Molecular Genetics
The exact molecular etiology of the cleft hand and absent tibia disorder is not determined yet. However,
ongoing molecular studies focus on a number of candidate genes including: GLI-Kruppel Family Member 3 (GLI3) on 7p13, Sonic Hedgehog (SHH) on 7q36, Langer-Giedion syndrome on 8q24.1, and split-hand/foot malformation 3 on 10q24.

Epidemiology in the Arab World

Algeria
In 1996, Majewski and colleagues studied a recessive form of ectrodactyly and absence (hypoplasia) of the tibia in a kindred of brother, sister, and one maternal nephew. The parents of the sibs originated from the same small Algerian village and the parents of the cousin were consanguineous. The mother’s seven sibs and their 39 children were unaffected. Case one, a 2-month-old boy, presented with malformations of his lower limbs and capillary hemangioma of the forehead and neck. Radiological examination revealed a moderately hypoplastic and shortened tibia. The first metatarsal was hypoplastic in the left foot, bearing one very small phalanx. The second toe was absent; however, the second metatarsal was present. There were only two lateral rays with hypoplastic phalanges. In the right foot, there were four metatarsals, the two medial ones being hypoplastic and the second bearing no toe. The phalanges of toes 3-5 are hypoplastic. Case two, an 11-year-old girl with congenital deafness, presented with both hands and left foot normal. The right foot showed the same malformation as the left foot of the younger brother with talipes equinus and two lateral rays; the malformed and proximally displaced hallux was removed. Case three, their cousin, had split hands lacking ray three on the right and rays two and three on the left. The left forefoot shows the same malformations as the left foot of case one. Majewski et al. (1996) noted that until the gene(s) are identified, the question remains open whether a dominant and recessive form of SHSF with a (hypo)plasia of tibia exist and therefore genetic counseling in healthy sibs of affected is difficult in isolated SHSF and in aplasia of tibia with SHSF. Furthermore, there may be a recurrence risk to offspring of up to 25%.

Palestine
Der Kaloustian and Mnaymneh (1973) reported bilateral tibial aplasia with lobster-claw hands in the offspring of parents related as first cousins once removed. Another member of the family related as a first cousin to the proband’s mother and as a first cousin once removed to the proband’s father was identically affected. Der Kaloustian and Mnaymneh (1973) suggested autosomal dominant inheritance with reduced penetrance, despite the consanguinity in these families.

Kohn et al. (1989) described two Arab unrelated healthy consanguineous families, each with two affected offspring presenting with tibial agenesis with bifurcation of the femora and ectrodactyly. Case one, a female, presented with bifid femur, tibial agenesis, ulna hypoplasia, and split hand, all on the right side. Case two, sister of case one, had bifurcation of the femora on the right side, bilateral tibial agenesis, and ectrodactyly on the left. Case three, a girl, presented only with bifid femur on the right side and bilateral tibial agenesis. Case four, the sister of case three, had also only bifid femur on the right side and bilateral tibial agenesis with no ectrodactyly. Kohn et al. (1989) postulated that this combination of malformations is causally heterogeneous with both autosomal dominant and autosomal recessive modes of inheritance; hence, it is established as a developmental field defect.

Saudi Arabia
Mufti and Wood (1987) described an extended family from Saudi Arabia in which the unaffected father had four affected girls presenting with ectrodactyly from two unaffected wives; he was consanguineous with one wife, but not with the second. Two of the sisters had associated agenesis of the tibia. Mufti and Wood (1987) invoked autosomal recessive inheritance to explain the occurrence in the four half sisters.

Syria
Majewski et al. (1985) reported six families with a total of 34 affected persons with the syndrome of tibial aplasia and ectrodactyly. One of the families was a healthy, consanguineous couple of Syrian origin who had three affected children presenting with tibial aplasia and ectrodactyly. Majewski et al. (1985) concluded that the disorder is autosomal dominant with markedly reduced penetrance.

United Arab Emirates
Naveed et al. (2006) described an eight-generation consanguineous Arab family originating from the United Arab Emirates with multiple severe defects of the extremities. The pedigree consisted of 145 individuals with 23 affected (14 males and 9 females) and 10 consanguineous marriages. All members of the family were analyzed by a dysmorphologist and clinical geneticist, and evaluation of previous medical records, radiographs, dysmorphological examinations and skeletal surveys of the affected parts was also conducted. The expression of the phenotype was
variable within the family and ranged from unilateral to bilateral. Tibial aplasia was seen in 18 affected persons with other associated limb anomalies. The majority of unilateral tibial aplasia was found only on the right side. Other anomalies observed in this family with or without tibial aplasia included ectrodactyly (n=20), syndactyly (n=5), camptodactyly (n=5), short femur (n=1), and club foot (n=14). Linkage analysis with 18 microsatellite markers previously used for genetic analysis of the candidate genomic regions of GLI3 morphopathies on 7p13, sonic hedgehog on 7q36, Langer-Giedion syndrome on 8q24.1 and split-hand/foot malformation-3 on 10q24 was carried out to see if the phenotype of the family was allelic these known loci. Two-point linkage and haplotype analyses did not segregate with the phenotype in the family. Chromosome analysis of all affected individuals, their parents and sibs was also preformed, however, no cytogenetic abnormalities were detected and FISH studies using subtelomeric probes were also negative. Naveed et al. (2006) hypothesized that the phenotype in this pedigree is caused by mutations in a gene at another locus, or by mutations in long-range regulators of the above candidate loci.

References

Related CTGA Records
Split-Hand/Foot Malformation with Long Bone Deficiency 2

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http://www.ggc.org/shfm.htm

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