Holt-Oram Syndrome

Alternative Names
HOS
HOS1
Heart-Hand syndrome
Atriodigital Dysplasia

WHO International Classification of Diseases
Congenital malformations, deformations and chromosomal abnormalities

OMIM Number
142900

Mode of Inheritance
Autosomal Dominant

Gene Map Locus
12q24.1

Description
Holt-Oram syndrome is a developmental disorder characterized by distinctive malformations of the bones of the thumbs and upper limbs and abnormalities of the heart. The syndrome shows a marked variability in phenotype, with radial ray defects ranging from minor thumb abnormality through to severe reduction defect or phocomelia. The cardiac manifestations of Holt-Oram syndrome are similarly varied, and patients can present with a variety of structural heart abnormalities, atrial septal defects and ventricular septal defects being the most common, or conduction defects evident on ECG profiles. The syndrome is estimated to occur in about 1 out of every 100,000 births. 60% of affected individuals have an affected parent. In about 40 percent of cases, the disorder is the result of a spontaneous genetic change.

Molecular Genetics
The gene for Holt-Oram syndrome has been identified as TBX5 on chromosome 12q24. The TBX5 gene encodes a protein of 518 amino acids that belongs to the family of the T box transcriptional factors, and is expressed in embryonic heart and limb tissues, consistent with its involvement in development of the heart and skeletal structures. TBX5 contains a highly conserved DNA binding domain, the T box domain. TBX5 can bind to DNA and activate transcription of its target genes.

Epidemiology in the Arab World

Jordan
Boehme and Shotar (1989) described a Jordanian family of normal intelligence in which members of three generations had complex malformations of the arms combined with variably expressed congenital heart disease. Because of the pedigree pattern, which included one instance of male-to-male transmission, they suggested autosomal dominant inheritance, but concluded that the disorder was distinct from Holt-Oram syndrome.

Lebanon
Elias and Karouny (1991) reported two subjects of the same family (a father and his daughter) with Holt-Oram syndrome. The two years’ old child presented bilateral upper limb abnormalities with a large patent ductus arteriosus, rarely associated with this syndrome. She was operated for a ligation and resection of the patent ductus arteriosus. The girl had two (twin) brothers, 6-months-old, who were completely normal. The father presented bilateral upper limb abnormalities without congenital heart disease.

Saudi Arabia
Najjar et al. (1988) studied three families in which patients with the Holt-Oram syndrome had various skeletal abnormalities and congenital heart defects. Patient 1 was a 1-month-old Saudi boy born to first cousin parents and admitted for cyanosis, congenital absence.
of both thumbs, and congestive heart failure. Examination showed absence of the thumbs and of the first metacarpals, and hypoplastic radii. Patient 2 was a 9-year-old Saudi girl born to first cousin parents and referred for evaluation of heart murmur and easy fatigability. Patient 2 had pulmonary stenosis, an atrial septal defect, and triphalangeal thumbs. A sister had atrial septal defect and abnormalities of the thumbs; two brothers had abnormalities of the thumbs. The mother had unilateral defect of the thumb with a normal heart. Patient 3 was an 18-year-old Saudi girl with deformed left arm, tetralogy of Fallot, and hypoplastic pulmonary artery. In two families the Holt-Oram syndrome appeared to be the result of new mutations; in one it was transmitted as an autosomal dominant trait.

**United Arab Emirates**

Megahed (1988) described a small-for-date female neonate of Emirati nationality with Holt-Oram syndrome showing complete phocomelia of the left upper limb with absent thumb and index finger. Right thumb was also absent. Examination of the heart revealed normal heart sounds and the presence of a soft pansystolic murmur of fourth degree. The femoral pulses were adequately palpated. X-ray showed absence of the left humerus, radius and ulna, left first and second metacarpals and phalangeal bones and right first metacarpals and phalangeal bones. Echocardiography showed ventricular septal defect. Family history revealed consanguinity of third degree. The father was normal but the mother had a fingerized left thumb and an atrial septal defect. Four of their children were normal, and two abnormal – a girl with absent left thumb and a boy with bilateral long thumbs. In addition one boy died on day 7 of birth from undiagnosed congenital heart disease. He also showed complete bilateral phocomelia.

**References**


**Contributors**

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Ghazi O. Tadmouri: 22.2.2005