

## Prenatal Testing for TBX5 Gene Variants: Holt-Oram Syndrome

**Disorder also known as:** Heart-hand disease; HOS; Atrioidigital hypoplasia; cardiac-limb syndrome; upper limb cardiovascular syndrome

### **Clinical Features:**

Holt-Oram syndrome is a malformation syndrome characterized by upper limb abnormalities and heart defects. Affected individuals may present in infancy with obvious limb malformations and/or signs of cardiac failure secondary to cardiac malformations and/or cardiac conduction disease. Although the condition is considered to be fully penetrant, subtle limb involvement may not become clinically apparent without radiographic studies. The spectrum of limb defects ranges from severe (phocomelia) to mild (slight carpal bone abnormalities), the most common limb anomalies being either triphalangeal (finger-like) or absent thumbs. Upper limb deformities are usually bilateral and are frequently asymmetrical. Cardiac abnormalities occur in approximately 75% of patients with HOS (95% of familial cases). The most common cardiac abnormality is an atrial septal defect (ASD) or ventral septal defect (VSD). Strict diagnostic criteria for HOS are met with personal and/or positive family history of cardiac septation and/or conduction defects in combination with preaxial radial ray deformity. Atypical characteristics thought to exclude a diagnosis of HOS include: ulnar or lower limb involvement, renal anomalies, syndactyly involving digits other than the thumb, polydactyly, and craniofacial abnormalities.<sup>1</sup>

Detailed ultrasound examination, usually in the 2nd trimester of pregnancy, may identify characteristic upper-limb malformations and/or congenital heart defects.<sup>7,8</sup> Ultrasound examination may be normal in affected fetuses; therefore, pregnancies at risk to inherit a specific known familial pathogenic variant can be offered targeted molecular testing regardless of ultrasound findings, if desired.

### **Inheritance Pattern/Genetics:**

Autosomal dominant with complete penetrance and variable clinical expression; many cases represent de novo variants.

### **Test Methods:**

Using genomic DNA, analysis is performed by bi-directional sequencing of the coding regions (exons 2-9) and flanking splice sites of the TBX5 gene. For known familial variants, the relevant portion of the gene will be analyzed in duplicate.

Additionally, genotype analysis of maternal and fetal DNA for several polymorphic markers to test for maternal cell contamination will be performed. Therefore, in all prenatal cases a maternal sample should accompany the fetal sample.

## Test Sensitivity:

It has been estimated that 74% of patients who meet strict diagnostic criteria for HOS will have an identifiable variant in the TBX5 gene.<sup>1</sup> Multiple other studies have shown significantly lower sensitivity data (22-35%).<sup>2,3</sup> This discrepancy is explained by the selectivity of patient cohorts; not all study subjects met strict HOS diagnostic criteria and some exhibited additional or atypical anomalies. The sequencing approach used by GeneDx is expected to identify >99% of existing small intragenic variants. The sensitivity of TBX5 analysis in prenatal cases ascertained based on fetal ultrasound abnormalities is currently unknown.

## References:

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