TBX5 Gene Analysis in Holt-Oram Syndrome (HOS)

Disorder also known as: Heart-hand disease; HOS; Atriodigital 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.[1] Prenatal full gene sequence analysis is available when fetal ultrasound abnormalities are suggestive of HOS.

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

Test Methods:
Using genomic DNA from the submitted specimen, the coding regions and splice junctions of the requested gene are PCR amplified and capillary sequencing is performed. Bi-directional sequence is assembled, aligned to reference gene sequences based on NCBI RefSeq transcript and human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Concurrent deletion/duplication testing is performed for most, if not all, of the coding exons using exon-level oligo array CGH (ExonArrayDx), and data analysis is performed using gene-specific filtering. Probe sequences and locations are based on human genome build GRCh37/UCSC hg19. Reported clinically significant variants are confirmed by an appropriate method. If present, apparently homozygous sequence variants are confirmed using alternate primer pairs to significantly reduce the possibility of allele drop-out. Sequence and copy number variants are reported according to the Human Genome Variation Society (HGVS) or

International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

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.[1] Multiple other studies have shown significantly lower sensitivity data (22-35%).[2,3] 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, and ExonArrayDx is expected to detect a complete or partial TBX5 gene deletion/duplication.

Variant Spectrum:

The majority of variants identified to date are frameshift, missense, nonsense, and splice-site variants. Point variants are distributed throughout the TBX5 gene; the majority are located within the T-box DNA-binding domain, essentially exons 3-7. There have been rare cases of large deletions or rearrangements involving TBX5 gene in HOS; Borozdin et al. (2006) report that such deletions represent only 2% of the TBX5 variantal spectrum.[4,5,6] At this time there appears little support for genotype-phenotype correlations in HOS.[3]

References:

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3. Brassington, A. et al., Am J Hum Genet. 73: 74-85, 2003.
4. Akrami, SM. et al. J Med Genet. 38:E44, 2001.
5. Fan, C. et al. J Med Genet. 40:e29, 2003.
6. Borozdin, W. et al. Hum Mutat. 27:975-976, 2006.