Skeletal Dysplasia: Short-Rib Thoracic Dysplasia (SRTD) Panel Sequence Analysis and Deletion/Duplication Testing of 14 Genes

Panel Gene List:
DYNC2H1, EVC, EVC2, IFT122, FT140, IFT172*, IFT43, IFT80, NEK1, TTC21B*, WDR19, WDR34, WDR35, and WDR60
*Deletion/Duplication testing is not included.

Clinical Features:
The short-rib thoracic dysplasias (SRTDs) are a group of autosomal recessive skeletal ciliopathies characterized by a narrow thorax, short ribs, short limbs, and a ‘trident’ appearance of the acetabular roof (lateral surface of the hip bone)\(^1\). Polydactyly is variably present, and there is phenotypic overlap in the various forms of SRTDs, which differ by visceral malformation and metaphyseal appearance. Other features may include anomalies of the brain, eye, heart, kidneys, liver, pancreas, intestines, and genitalia\(^1,2\). SRTD types 2-11 with or without polydactyly are caused by pathogenic variants in the following genes, respectively: IFT80, DYNC2H1, TTC21B, WDR19, NEK1, WDR35, WDR60, IFT140, IFT172, and WDR34.

Cranioectodermal dysplasia (CED) is an autosomal recessive ciliopathy that overlaps phenotypically with the SRTDs. The characteristic features include sagittal craniosynostosis, facial dysmorphism, ectodermal abnormalities of the teeth, hair, skin, and skeletal anomalies such as a narrow thorax, shortened proximal limbs, and brachydactyly\(^3\). Pathogenic variants in the following genes cause CED: IFT122, WDR35, WDR19, and IFT43.

Ellis-van Creveld syndrome (EVC) is an autosomal recessive condition that phenotypically overlaps with the SRTDs and is additionally characterized by disproportionate short stature, congenital heart disease (most commonly atrial septal defect), postaxial polydactyly, dysplastic nails and teeth, and retinal degeneration\(^4,5\). This disorder, caused by pathogenic variants in EVC and EVC2, may present prenatally with narrow thorax, shortening of the long bones, polydactyly and cardiac defects\(^6\).

Inheritance Pattern/Genetics:
The short-rib thoracic dysplasias, cranioectodermal dysplasia, and Ellis-van Creveld syndrome are all autosomal recessive conditions.

Test Methods:
Using genomic DNA obtained from the submitted specimen, the coding exons and flanking splice junctions of the genes on this panel are enriched using a proprietary targeted capture method developed by GeneDx. These targeted regions are simultaneously by massively
parallel (NextGen) sequencing on an Illumina platform with paired-end reads. Bidirectional sequence is assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Capillary sequencing is used to confirm all potentially pathogenic variants and to obtain sequence for regions where fewer than 15 reads are achieved by NextGen sequencing. Concurrent deletion/duplication testing is performed for the genes in the panel (except IFT172 and TTC21B) using exon-level oligo array CGH (ExonArrayDx). Data analysis is performed using gene-specific filtering. Probe sequences and locations are based on human genome build GRCh37/UCSC hg19. The array is designed to detect most intragenic deletions and duplications. Confirmation of copy number changes is performed by MLPA, qPCR, or repeat array CHG analysis. Sequence and array CGH array CGH alterations are reported according to the Human Genome Variation Society (HGVS) or International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. Benign and likely benign variants, if present, are not included in this report but are available upon request.

Test Sensitivity:
The clinical sensitivity of sequencing and deletion/duplication analysis of the genes included in this panel depends in part on the patient’s clinical phenotype. For Ellis-van Creveld syndrome, the sensitivity is approximately 74% for pathogenic variants in EVC and 26% for EVC2 as reported in one study. Pathogenic variants in DYNC2H1 are detectable in one-third of cases with a clinical diagnosis of SRTD type 3.

The technical sensitivity of the sequencing test is estimated to greater than 99%. It will not detect deletions, insertions, or rearrangements greater than or equal to ten base pairs. The deletion/duplication testing can detect deletions or duplications encompassing one or more exons, including variants as small as 150-300 base pairs. Note that small sections of a few individual genes have inherent sequence properties that yield suboptimal data and variants in those regions may not be identified.

References: