Skeletal Dysplasias: Achondrogenesis Panel

Panel Gene List:
This panel is composed of 3 genes: COL2A1, SLC26A2, TRIP11.

Clinical Features:
Achondrogenesis is a severe skeletal dysplasia characterized by a lack of ossification of the vertebral bodies, extreme micromelia, a barrel-shaped short trunk, short ribs, and hydrops fetalis.\textsuperscript{1,2} There are three types with overlapping clinical features: type IA, type IB, and type II. Achondrogenesis type IA is due to pathogenic variants in the TRIP11 gene and type IB is due to pathogenic variants in the SLC26A2 (DTDST) gene. The most common type II accounts for approximately 80\% of cases of achondrogenesis and is due to de novo pathogenic variants in the COL2A1 gene.\textsuperscript{1,2} All three types are usually lethal in the perinatal period.\textsuperscript{2}

Inheritance Pattern/Genetics:
Achondrogenesis types IA and IB are autosomal recessive conditions. Achondrogenesis type II is autosomal dominant.

Test Methods:
Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the genes tested are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. 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.

The technical sensitivity of sequencing is estimated to be >99\% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.
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. Sensitivity for SLC26A2 is greater than 90% in individuals with the diagnosis of a sulfate transporter-related skeletal dysplasia which includes achondrogenesis type IB and the allelic disorders of atelosteogenesis type 2, diastrophic dysplasia, and autosomal recessive multiple epiphyseal dysplasia.

References: