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.[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.[1, 2] All three types are usually lethal in the perinatal period.[2]

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

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 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. 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 austosomal recessive multiple epiphyseal dysplasia.

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:

1. Noel, AE & Brown RN (2014). *International Journal of Women's Health, 6*, 489-500 PMID: 24868173
2. Witters, I, Moerman, P & Fryns, JP (2008). *Genetic Counseling (Geneva, Switzerland),* 19(3), 267-275. PMID: 18990981