Skeletal Dysplasia: Chondrodysplasia Punctata Panel
Sequence Analysis and Deletion/Duplication Testing of 5 Genes

Panel Gene List:
AGPS, ARSE, EBP, GNPAT, and PEX7

Clinical Features:
Chondrodysplasia punctata is a group of clinically and genetically heterogeneous disorders whose common feature is punctate calcifications of the bones or stippled epiphyses. Rhizomelic chondrodysplasia punctata (RCDP) is a peroxisome biogenesis disorder characterized by proximal shortening of the humerus and femur, punctate calcifications in cartilage with epiphyseal and metaphyseal abnormalities, congenital cataracts, low birth weight, length, and head circumference, severe postnatal growth deficiency, profound intellectual disability and seizures.\(^1\) The most common form, rhizomelic chondrodysplasia punctata type 1 (RCDP1), is caused by pathogenic variants in the \textit{PEX7} gene. RCDP2 results from pathogenic variants in the \textit{GNPAT} gene while AGPS pathogenic variants cause RCDP3.

X-linked recessive chondrodysplasia punctata (CDPX1) also known as chondrodysplasia punctata, brachytelephalangic type, is characterized by abnormal cartilage and bone development, hypoplasia of distal phalanges (brachytelephalangy), stippled epiphyses especially in the hands and feet, hearing loss, and short stature.\(^2\) Clinical features for X-linked dominant chondrodysplasia punctata (CDPX2) include linear or whorl-like hyperkeratosis, atrophy and pigmented changes of the skin, coarse alopecia, cataracts, and skeletal abnormalities including short stature, rhizomelic shortening of the limbs, epiphyseal stippling, and craniofacial defects.\(^3\) CDPX1 is caused by pathogenic variants in the \textit{ARSE} gene, while CDPX2 is caused by pathogenic variants in the \textit{EBP} gene, both of which encode proteins critical for normal cholesterol metabolism.\(^2,3\)

Inheritance Pattern/Genetics:
All 3 types of rhizomelic chondrodysplasia punctata are autosomal recessive. CDPX1 is X-linked recessive. CDPX2 is X-linked 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. Specific information about the sensitivity of each gene in selected populations is included in the clinical sensitivity table below.

Clinical Sensitivity of Genes Associated with Chondrodysplasia Punctata

<table>
<thead>
<tr>
<th>Disorder(s)</th>
<th>Gene</th>
<th>Inh.</th>
<th>Diagnostic Yield for Disorder</th>
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</thead>
<tbody>
<tr>
<td>Rhizomelic chondrodysplasia punctata type 3</td>
<td>AGPS</td>
<td>AR</td>
<td>Unknown</td>
</tr>
<tr>
<td>Chondrodysplasia punctata</td>
<td>ARSE</td>
<td>XL-R</td>
<td>60-75% for sequence variants, multi-exonic and whole-gene deletions in affected males 10% deletion/duplication analysis²</td>
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<tr>
<td>Chondrodysplasia punctata</td>
<td>EBP</td>
<td>XL-D</td>
<td>~90% in affected females³</td>
</tr>
<tr>
<td>Rhizomelic chondrodysplasia punctata type 2</td>
<td>GNPAT</td>
<td>AR</td>
<td>Unknown</td>
</tr>
<tr>
<td>Rhizomelic chondrodysplasia punctata type 1</td>
<td>PEX7</td>
<td>AR</td>
<td>94% detection of 2 variants 6% detection of only 1 variant¹</td>
</tr>
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References:

