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 *PEX7* gene. RCDP2 results from pathogenic variants in the *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 pigmentary 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 *ARSE* gene, while CDPX2 is caused by pathogenic variants in the *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 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. Specific information about the sensitivity of each gene in selected populations is included in the clinical sensitivity table below.

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.

Clinical Sensitivity of Genes Associated with Chondrodysplasia Punctata

Disorder(s)	Gene	Inh.	Diagnostic Yield for Disorder
Rhizomelic chondrodysplasia punctata type 3	AGPS	AR	Unknown
Chondrodysplasia punctata	ARSE	XL-R	60-75% for sequence variants, multi-exonic and whole-gene deletions in affected males 10% deletion/duplication analysis[2]
Chondrodysplasia punctata	EBP	XL-D	~90% in affected females[3]
Rhizomelic chondrodysplasia punctata type 2	GNPAT	AR	Unknown
Rhizomelic chondrodysplasia punctata type 1	PEX7	AR	94% detection of 2 variants 6% detection of only 1 variant[1]

References:

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2. Braverman NE, Bober M, Brunetti-Pierri N, et al. Chondrodysplasia Punctata 1, X-Linked. 2008 Apr 22 [Updated 2014 Nov 20]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1544/
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