# Chondrodysplasia Punctata Panel

## Panel Gene List

*AGPS, ARSL,* EBP, FAR1, GGCX, GNPAT, LBR, MGP, NSDHL, PEX5, 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. A single homozygous variant in the PEX5 gene (long isoform) has been reported to cause RCDP5.[14]

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 ARSL* (formerly *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]

Variants in FAR1 result in peroxisomal fatty acyl-CoA reductase-1 disorder, characterized by severe intellectual disability, microcephaly, cataracts, and growth retardation. While many features of this disorder overlap with rhizomelic chondrodysplasia punctata, patients are not reported to develop skeletal anomalies.[4,5]
Variants in the GGCX gene can cause vitamin K-dependent coagulation factor deficiency (VKCFD1), resulting in decreased levels of multiple coagulation factors and anticoagulant proteins. Patients have a mild to severe bleeding tendency and moderate predisposition to thrombotic events; other reported phenotypes include hearing loss, cardiac abnormalities; skeletal abnormalities such as chondrodysplasia punctata have also been reported.[6-8]

Biallelic LBR variants are associated with a range of skeletal dysplasia. A severe presentation, Greenberg skeletal dysplasia, results in fetal hydrops, short limbed dwarfism and abnormal chondroosseous calcification. Less severe forms of LBR-related skeletal dysplasia are characterized by spontaneously regressing bone dysplasia, spondylometaphyseal dysplasia, and disproportionate short stature.[9,10]

Pathogenic variants in MGP are the cause of Keutel syndrome, an autosomal recessive condition with a phenotype that overlaps with CDPX1. Keutel syndrome is characterized by abnormal cartilage calcification, short distal phalanges, peripheral pulmonary stenosis, hearing loss, short stature, and midface hypoplasia.[11,12]

Pathogenic variants in the NSDHL gene cause one of two X-linked disorders, CHILD and CK syndrome. The phenotype of CHILD syndrome overlaps with that of CDPX2. It is often embryonic lethal in males, and affected females present with congenital hemidysplasia with ichthyosiform nevus and limb defects.[13]

## Inheritance Pattern/Genetics

Autosomal recessive, X-linked recessive, X-linked dominant.

## Test Methods

Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel 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. For the GGCX gene, no copy number testing is performed; for the ARSL gene, exon-level coverage is limited to exons 2-8. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. 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.

| Gene | Protein | Inheritance | Disorder(s) |
|---|---|---|---|
| ***AGPS*** | Alkylglycerone phosphate synthase | AR | Rhizomelic chondrodysplasia punctata type 3 |
| ***ARSL*** | Arylsulfatase L | XL-R | Chondrodysplasia punctata |
| ***EBP*** | Emopamil binding protein | XL-D | Chondrodysplasia punctata |
| ***FAR1*** | Fatty acyl-CoA reductase 1 | AR | Peroxisomal fatty acyl-CoA reductase-1 disorder |
| ***GGCX*** | Gamma-glutamyl carboxylase | AR | Vitamin K-dependent coagulation factor deficiency (VKCFD1)<br>Pseudoxanthoma elasticum-like disorder with multiple coagulation factor deficiency |
| ***GNPAT*** | Glyceronephosphate O-acyltransferase | AR | Rhizomelic chondrodysplasia punctata type 2 |
| ***LBR*** | Lamin B receptor | AR | LBR-related skeletal dysplasias |
| ***MGP*** | Matrix Gla protein | AR | Keutel syndrome |
| ***NSDHL*** | NAD(P)-dependent steroid dehydrogenase-like | XL-D<br>XL-R | CHILD syndrome CK syndrome |
| ***PEX5*** | Peroxisomal biogenesis factor 5 | AR | Rhizomelic chondrodysplasia punctata type 5 Zellweger spectrum disorder |

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| ***PEX7*** | Peroxisomal biogenesis factor 7 | AR | Rhizomelic chondrodysplasia punctata type 1 |

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