Skeletal Dysplasia Panel

DISORDER ALSO KNOWN AS Osteochondrodysplasias

PANEL GENE LIST
ALPL, ARSE, COL10A1, COL11A1, COL11A2, COL1A1, COL1A2, COL2A1, DDR2, EBP, FGFR3, FLNB, HSPG2, INPPL1, LBR, LIFR, MMP9, MMP13, NKX3-2, NSDHL, PEX7, PTH1R, RMRP, SBDS, SLC26A2, SLC35D1, SOX9, TRIP11, TRPV4

CLINICAL FEATURES
Skeletal dysplasias are a highly variable group of disorders affecting the bone and cartilage of the skeletal system, which are estimated to occur in 2.4 to 4.5 per 10,000 births and 20 per 10,000 stillbirths.[1,2,3] They are characterized by generalized structural abnormalities of bone and cartilage growth and modeling caused by a disturbance in bone growth beginning in the early stages of fetal development and evolving throughout life.[2] There are over 450 currently recognized skeletal dysplasias, which are divided into 40 categories based on molecular, biochemical and radiographic criteria.[1,2,3] Although each disorder presents with its own clinical findings, as a group, these conditions are characterized by anomalies of bone shape, size and density, which manifest as abnormalities of the limbs, chest, or skull. These conditions have variable etiologies including, chromosomal abnormalities or single-gene pathogenic variants as well as environmental factors such as teratogen exposure and autoimmune response.[1,2,3]

While there are a number of different skeletal dysplasias, certain disorders are more common than others. A brief overview of some of the more common fetal skeletal dysplasias is given below.

FGFR3-Related Skeletal Dysplasias / Achondroplasia (FGFR3)[4,5]
FGFR3-related skeletal dysplasias refer to four distinct disorders caused by pathogenic variants in the FGFR3 gene. The most common of these is achondroplasia (ACH), which is nonlethal and the most common condition associated with disproportionate short stature or dwarfism.[4,5] Prenatally, this disorder often presents in the third trimester and is associated with rhizomelic micromelia, macrocephaly with frontal bossing and midface hypoplasia. Mild limb bowing, brachydactyly, increased space between the third and fourth digits, and a depressed nasal bridge are also common.[4,5] Hypochondroplasia (HCH) has a similar, but milder, phenotype to that of ACH and presents with micromelia, short stature and lumbar lordosis.[4,5]

The prevalence of HCH is estimated to be 1 in 50,000 births, and together ACH and HCD are estimated to account for 20% of all cases of skeletal dysplasia in live births.[4] Thanatophoric dysplasia (TD) is the most common lethal skeletal dysplasia and has an incidence estimated to be between 1 in 17,000 and 1 in 50,000 births.[4] This disorder is characterized by disproportionate dwarfism with very short extremities, normal trunk length, very narrow thorax, macrocephaly, depressed nasal bridge, prominent forehead with protruding eyes, brachydactyly, platyspondyly, and normal bone mineralization without fractures.[2] Severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN) is a very severe form of achondroplasia caused by a rare pathogenic variant in the FGFR3 gene.[4,5]

Osteogenesis Imperfecta (OI) (COL1A1 & COL1A2)[6,7]
Osteogenesis Imperfecta (OI) is characterized by bone fragility and consequent susceptibility to bone fractures. The severity of OI can range from severe perinatal lethal to asymptomatic with mild predisposition to fractures and a normal lifespan.[6,7] Other common characteristics include dentinogenesis imperfecta, blue sclerae, short stature

and hearing loss in adulthood.[7] The most lethal form of OI is type II, which is characterized by compressible thin calvaria, severe micromelia and bowing of long bones with multiple fractures and a narrow thorax.[7] Together, all types of OI have a combined prevalence of between 1 in 15,000 and 1 in 30,000 births with about 90% of cases caused by pathogenic variants in either COL1A1 or COL1A2.[6,7]

Achondrogenesis
(COL2A1, SLC26A2, TRIP11)[8,9,10]
Achondrogenesis is a severe skeletal dysplasia classified into three types: type IA, type IB, and type II and characterized by a lack of ossification of the vertebral bodies as well as extreme micromelia, a barrel-shaped short trunk, and short ribs.[8] The most common Type II accounts for approximately 80% of cases of achondrogenesis and is due to de novo dominant pathogenic variants in the COL2A1 gene.[8] Type 1A is due to pathogenic variants in the SLC26A2 (DTDST) gene, and type IB is due to pathogenic variants in the TRIP11 gene.[8] All three types are usually lethal in the perinatal period.

Chondrodysplasia Punctata
(PEX7, ARSE, EBP) [11,12,13]
Chondrodysplasia Punctata is a group of disorders characterized by chondrodysplasia punctata (stippled epiphyses). The most common form, rhizomelic chondrodysplasia punctata type 1 (RCDP1), is caused by pathogenic variants in the PEX7 gene and 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.[12] Less common disorders result from pathogenic variants in the ARSE gene causing X-linked chondrodysplasia punctata 1 (CDPX1), and in the EBP gene causing X-linked chondrodysplasia punctata 2 (CDPX2). These related disorders have similar punctate cartilaginous changes with variable limb shortening and/or asymmetry, short stature, intellectual disability, cataracts, and skin changes.[12,13]

Campomelic dysplasia
(SOX9)[14]
Campomelic dysplasia (CD) is a rare, often lethal skeletal dysplasia characterized by angular bowing and shortening of the long bones, severe respiratory distress, and XY sex reversal. It is caused by chromosome abnormalities or pathogenic variants affecting expression of the SOX9 gene located on chromosome 17q24.3-q25.1. Approximately 75% of patients with CD with a 46, XY karyotype exhibit partial or complete sex reversal, ranging from ambiguous genitalia to normal female external genitalia.[15] In addition to bowing of the long bones, skeletal features of CD include club feet, a bell-shaped and underdeveloped thorax, eleven pairs of ribs, and hypoplastic scalpulae. Other variable features include micrognathia and Pierre-Robin malformation. Many infants die shortly after birth from respiratory compromise; however, those who survive the neonatal period can develop hearing loss, developmental delay, short stature and progressive kyphoscoliosis.[14,16]

Hypophosphatasia (HPP)
(ALPL)[17,18]
Pathogenic variants in the ALPL gene cause hypophosphatasia (HPP), an autosomal dominant or autosomal recessive disorder caused by low alkaline phosphatase activity resulting in defective bone mineralization and dental manifestations.[19] Six different clinical subtypes of HPP have been recognized, ranging in severity from a lethal perinatal type without mineralized bones, to a mild adult onset form characterized by an isolated finding of early tooth loss. The severe perinatal and infantile forms are inherited in an autosomal recessive fashion and may be accompanied by neurological findings including seizures, while the milder childhood and adult onset forms can be either autosomal dominant or autosomal recessive, and incomplete penetrance has been reported.[17,18]

See the full list of genes and their related conditions in the table below.

INHERITANCE PATTERN/GENETICS

Many severe skeletal dysplasias are due to single-gene disorders inherited in an autosomal dominant manner and are often sporadic pathogenic variants. Autosomal recessive and X-linked inheritance patterns are also observed.[1,2,3]

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 SBDS and RMRP genes, sequencing but not deletion/duplication analysis is performed. 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	Inheritance	Disease Association	Diagnostic Yield
ALPL	Autosomal dominant, Autosomal recessive	Hypophosphatasia	95%[17]
ARSE	X-linked	Chondrodysplasia punctata	60-75% for sequence variants, multi-exonic and whole-gene deletions in affected males[13]
COL10A1	Autosomal dominant	Metaphyseal chondrodysplasia, Schmid type	Unknown[20,21]
COL11A1	Autosomal recessive	Fibrochondrogenesis Stickler syndrome	10-20% of Stickler syndrome[22], unknown for fibrocondrogenesis[23]
COL11A2	Autosomal dominant; Autosomal recessive	Fibrochondrogenesis Stickler syndrome	Unknown for fibrocondrogenesis[24], unknown for Stickler[22]
COL1A1	Autosomal dominant	Osteogenesis imperfecta, types I, II, III & IV	>90%[2]
COL1A2	Autosomal dominant;Autosomal recessive	Osteogenesis imperfecta, types II, III & IV	>90%[2]

COL2A1	Autosomal dominant	Achondrogenesis, type II (ACH2) Hypochondrogenesis Spondyloepiphyseal dysplasia (SED) with metatarsal shortening (also called Czech dysplasia) Spondyloepiphyseal dysplasia (SED) congenita Spondyloepiphyseal dysplasia (SED)	>75% of COL2A1-related disorders[3]
DDR2	Autosomal recessive	Spondylo-meta-epiphyseal dysplasia, short limb-hand type	Unknown[25,26]
EBP	X-linked	Chondrodysplasia punctata	~85% of females with suspected XLD chondroplasia punctata%[11]
FGFR3	Autosomal dominant	Achondroplasia	99%[4,5]
FLNB	Autosomal dominant, Autosomal recessive	Atelosteogenesis, type I / III (AOI / AOIII) Boomerang dysplasia (BD) Larsen syndrome Spondylocarpotarsal synostosis syndrome (SCT) *Autosomal recessive	~100% of individuals with AOI[27]
HSPG2	Autosomal recessive	Schwartz-Jampel syndrome type 1 Dyssegmental dysplasia, Silverman-Handmaker Type	93% for SJS, unknown in DDSH[28,29]
INPPL1	Autosomal recessive	Opsismodysplasia	100% of probands with opsismodysplasia[30]
LBR	Autosomal recessive	Greenberg skeletal dysplasia	Unknown[31]
LIFR	Autosomal recessive	Stuve-Wiedemann syndrome / Schwartz-Jampel type 2 syndrome	>60% of individuals with Stuve- Wiedemann syndrome[32,33]
MMP9	Autosomal recessive	Metaphyseal anadysplasia	Unknown[34]
MMP13	Autosomal dominant; Autosomal recessive	Metaphyseal anadysplasia	Unknown[34,35]
NKX3-2	Autosomal recessive	Spondylo-megaepiphyseal-metaphyseal dysplasia	Unknown[36,37]
NSDHL	X-linked	CHILD syndrome CK syndrome	100% of CHILD[38,39]
PEX7	Autosomal recessive	Rhizomelic chondrodysplasia punctata type 1	>90% of patients with rhizomelic chondrodysplasia[12]

PTH1R	Autosomal dominant; Autosomal recessive	Ollier disease Chondrodysplasia Primary failure of tooth eruption and osteoarthritis	Unknown[40,41]
RMRP	Autosomal recessive	Cartilage-Hair hypoplasia Omenn syndrome	100% of CHH[42]
SBDS	Autosomal recessive	Shwachman-Diamond syndrome	75-89% will have at least 1 variant [43,44]
SLC26A2	Autosomal recessive	Achondrogenesis type 1B Atelosteogenesis type II Diastrophic dysplasia	>90% of patients with Achondrogeneis 1B[9]
SLC35D1	Autosomal recessive	Schneckenbecken dysplasia	<50% of individuals with Schneckenbecken dysplasia[10,45]
SOX9	Autosomal dominant	Campomelic dysplasia	~92%[14]
TRIP11	Autosomal recessive	Achondrogenesis type 1A	Unknown[46]
TRPV4	Autosomal dominant	Metatropic dysplasia	~99% for TRPV4-Related neuromusuclar and skeletal disorders[47]

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