Prenatal Skeletal Dysplasia Panel

Disorder also known as: Osteochondrodysplasias

Panel Gene List: *AGPS, ALPL, ARSE, BMP1, CEP120, COL11A1, COL11A2, COL1A1, COL1A2, COL2A1, COMP, CRTAP, DLL3, DYNC2H1, EBP, EVC, EVC2, FGFR1, FGFR2, FGFR3, FKBP10, FLNA, FLNB, GNPAT, HSPG2, IFITM5, IFT172, INPPL1, KIAA0586, LBR, LEPRE1, LIFR, NEK1, PEX7, PLOD2, POR, PPIB, RUNX2, SERPINH1, SLC26A2, SLC35D1, SOX9, TMEM38B, TRIP11, TRPV4, TTC21B, WDR34, WDR35*

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.[1,6,9] 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.[6] There are over 450 currently recognized skeletal dysplasias, which are divided into 40 categories based on molecular, biochemical and radiographic criteria.[1,6,9] 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. [1,6,9]

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)[5,7]
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.[5,7] 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.[5,7] Hypochondroplasia (HCH) has a similar, but milder, phenotype to that of ACH and presents with micromelia, short stature and lumbar lordosis.[5,7] 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.[5] 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.[5] 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.[6] 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.[5,7]

Osteogenesis Imperfecta (OI)
(*COL1A1 & COL1A2, BMP1, CRTAP, FKBP10, IFITM5, LEPRE1 (P3H1), PPIB*)[2,8,10,20,27,34,39]
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.[2,8] Other common characteristics include dentinogenesis imperfecta, blue sclerae, short stature and hearing loss in adulthood.[8] 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.[8] 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*.[2, 8]

Achondrogenesis
(*COL2A1, SLC26A2, TRIP11*)[3,47,50]
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.[3] 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.[3] Type 1A is due to pathogenic variants in the *SLC26A2* (*DTDST*) gene, and type IB is due to pathogenic variants in the *TRIP11* gene.[3] All three types are usually lethal in the perinatal period.

Chondrodysplasia Punctata
(PEX7, GNPAT, AGPS, ARSE, EBP) [4,15,17,33,38]
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.[17] Less common disorders result from pathogenic variants in the *GNPAT* gene causing RCDP2, *AGPS* gene pathogenic variants causing RCDP3, *ARSE* pathogenic variants causing X-linked chondrodysplasia punctata 1 (CDPX1) and *EBP*

pathogenic variants 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.[17, 33]

Short-rib/asphyxiating thoracic dysplasias
(NEK1, DYNC2H1, EVC, EVC2, IFT172, WDR34, WDR35, CEP120, KIAA0586)[21,24,35,41,42,43,54,55]

Short-rib/asphyxiating thoracic dysplasias (SRTDs) with or without polydactyly are typically perinatal lethal, autosomal recessive skeletal ciliopathies characterized by bone abnormalities resulting from abnormal function or formation of cilia. Clinical presentations of SRTDs include constricted thoracic cage, short ribs, shortened tubular bones, and a 'trident' appearance of the acetabular roof (lateral surface of the hip bone). This group of disorders encompasses Ellis-van Creveld syndrome (EVC) and the disorders previously designated as Jeune syndrome or asphyxiating thoracic dystrophy (ATD), short rib-polydactyly syndrome (SRPS), and Mainzer-Saldino syndrome (MZSDS). Short-rib thoracic dysplasia-6 with or without polydactyly (SRTD6) is caused by pathogenic variants in the *NEK1* gene and short-rib thoracic dysplasia-3 with or without polydactyly (SRTD3) is caused by pathogenic variants in the *DYNC2H1* gene. Ellis-van Creveld syndrome (EVC) is an autosomal recessive condition additionally characterized by disproportionate short stature, congenital heart disease (most commonly ASD), postaxial polydactyly, dysplastic nails and teeth, and retinal degeneration.[18] This disorder, caused by pathogenic variants in *EVC* and *EVC2*, may present prenatally with narrow thorax, shortening of the long bones, polydactyly and cardiac defects.[42] Less common causes of SRTDs include pathogenic variants in IFT172, WDR34, WDR35, CEP120, and KIAA0856.

Campomelic dysplasia
(SOX9)[32]

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.[11] 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.[12,32]

Hypophosphatasia (HPP) (ALPL)[30,31]

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.[28] 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.[30,31]

Other Genes Involved in Skeletal Dysplasias and Related Disorders (COL11A1, COL11A2, COMP, DLL3, FGFR1, FGFR2, FLNA, FLNB, INPPL1, HSPG2, LBR, LIFR, PLOD2, POR, RUNX2, SLC35D1,TRPV4, TTC21B) [3,13,14,16,19,23,29,36,40,44,45,48,52,53]

Other rarer conditions that may present with skeletal abnormalities in the prenatal period include fibrochondrogenesis, pseudoachondroplasia, spondylocostal dysostosis, frontometaphyseal dysplasia, Greenberg skeletal dysplasia, Bruck syndrome, and others. See the full list of genes and their related conditions in the table below.

Prenatal Ultrasound Findings:

Skeletal dysplasias are commonly identified in the prenatal period by the presence of shortened long bones or other abnormal skeletal findings such as narrow thorax, polydactyly, frontal bossing, or poor mineralization of the calvarium in an ultrasound.[1,6,9] Use of first-trimester combined screening with or without detailed anomaly scanning, will result in early detection of more skeletal dysplasias.[23] Other imaging methods, such as 3D ultrasound, MRI and CT scan, can be used to evaluate and diagnose a skeletal dysplasia in utero. [1,6,9] Due to genetic heterogeneity and overlapping phenotypes, the specific fetal skeletal dysplasia cannot be determined accurately with imaging alone. When available, molecular, genetic and/or biochemical testing can aid in determining the precise diagnosis after the differential has been established by imaging.[1,6,9]

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.[1,6,9]

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. 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.

Test Sensitivity:
Skeletal dysplasias are a genetically heterogeneous group of disorders with a wide pathogenic variant spectrum. The clinical sensitivity of this 48-gene panel in prenatal cases ascertained based on fetal ultrasound abnormalities is not well established and depends in part on the clinical phenotype of the fetus Review of testing of 280 fetuses with suspected skeletal dysplasia using a smaller 23-gene panel at GeneDx yielded positive diagnostic results in approximately 55% of cases. Among those (n=153), 66% had a molecular diagnosis of thanatophoric dysplasia or osteogenesis imperfecta. Additional information about the general clinical sensitivity of each gene in selected postnatal populations is included in the table below.

Gene	Inheritance	Disease Associations	Diagnostic Yield for Disorder in Postnatal Populations
AGPS	Autosomal recessive	Rhizomelic chondrodysplasia punctata type 3	Unknown[38]
ALPL	Autosomal dominant, Autosomal recessive	Hypophosphatasia	~95%[30]
ARSE	X-Linked recessive	Chondrodysplasia punctate	60-75% for sequence variants, multi-exonic and whole-gene deletions in affected males[33]
BMP1	Autosomal recessive	Osteogenesis imperfecta type XIII	<4% of individuals with OI[34]
CEP120	Autosomal recessive	Short-rib thoracic dysplasia 13 with or without polydactyly, Joubert syndrome w/Jeune asphyxiating thoracic dystrophy features	~1% of patients with JS[35]
COL11A1	Autosomal recessive	Fibrochondrogenesis type 1	Unknown[36]
COL11A2	Autosomal dominant, Autosomal recessive	Fibrochondrogenesis Otospondylomegaepiphyseal dysplasia, autosomal dominant Otospondylomegaepiphyseal dysplasia, autosomal recessive	Unknown[37]
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]

		(Namaqualand type) Spondyloepimetaphyseal (SMED) (Strudwick type) Otospondylomegaepiphyseal dysplasia Spondyloperipheral dysplasia Platyspondylic skeletal dysplasia (Torrance type) Kniest dysplasia	
COMP	Autosomal dominant	Pseudoachondroplasia Multiple epiphyseal dysplasia	>96% of individuals with pseudoachondroplasia and 70% of those with MED[29]
CRTAP	Autosomal resessive	Osteogenesis Imperfecta, type IIB and VII	Unknown[39]
DLL3	Autosomal recessive	Spondylocostal dysostosis type 1	~60% of individuals with SCDO[40]
DYNC2H1	Autosomal recessive	Asphyxiating thoracic dystrophy 3	~33% of patients with SRP type II [41,43]
EBP	X-Linked dominant	Chondrodysplasia punctata	~85 of females with suspected XLD chondroplasia punctata%[4]
EVC	Autosomal recessive	Ellis-Van Creveld Syndrome	~63% of individuals with Ellis-Van Creveld syndrome[42]
EVC2	Autosomal recessive	Ellis-van Creveld syndrome	~22% of individuals with Ellis-Van Creveld syndrome[42]
FGFR1	Autosomal dominant	Pfeiffer syndrome	~5% of individuals with Pfeiffer syndrome[19]
FGFR2	Autosomal dominant	Bent bone dysplasia Apert syndrome Crouzon syndrome Jackson-Weiss syndrome Pfeiffer syndrome	~95-100% of individuals with Pfeiffer syndrome[19]
FGFR3	Autosomal dominant	Achondroplasia Thanatophoric dysplasia, type I / II Hypocondroplasia	>99% [5,7]
FKBP10	Autosomal recessive	Osteogenesis imperfecta type XI Bruck syndrome 1	Unknown[27,43]
FLNA	X-linked dominant, X-linked	Frontometaphyseal dysplasia 1 Otopalatodigital syndrome type 1 and 2	~100% for all otopalatodigital spectrum disorders except for frontometaphyseal dysplasia

	recessive		(~68%)[13]
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[14]
GNPAT	Autosomal recessive	Rhizomelic chondrodysplasia punctata type 2	<10% of individuals with rhizomelic chondrodysplasia[15]
HSPG2	Autosomal recessive	Schwartz-Jampel syndrome type 1 Dyssegmental dysplasia, Silverman-Handmaker Type	Unknown[16]
IFITM5	Autosomal dominant	Osteogenesis imperfecta type 5	100% of probands with OI 5, ~5% of all OI individuals[20]
IFT172	Autosomal recessive	Short-rib thoracic dysplasia 10 with or without polydactyly	Unknown[21]
INPPL1	Autosomal recessive	Opsismodysplasia	100% of probands with opsismodysplasia[23]
KIAA0586	Autosomal recessive	Short-rib thoracic dysplasia 14 with polydactyly	Unknown[24]
LBR	Autosomal recessive	Greenberg skeletal dysplasia	Unknown[25]
LEPRE1	Autosomal recessive	Osteogenesis imperfecta type VIII	<<10% of patients with OI[10]
LIFR	Autosomal recessive	Stuve-Wiedemann syndrome Schwartz-Jampel type 2 syndrome	~60% of individuals with Stuve-Wiedemann syndrome[31]
NEK1	Autosomal recessive	Short rib-polydactyly syndrome, Majewski type Asphyxiating thoracic dystrophy 1	~50% of patients with SRP type II[43]
PEX7	Autosomal recessive	Rhizomelic chondrodysplasia punctata type 1	>90% of patients with rhizomelic chondrodysplasia[15]
PLOD2	Autosomal recessive	Bruck syndrome 2	Unknown[44]
POR	Autosomal recessive	Antley-Bixler syndrome with genital anomalies and disordered steroidogenesis	~50% of individuals with Antley-Bixler syndrome[45]
PPIB	Autosomal	Osteogenesis imperfecta, type IX	<<10% of patients with OI[10]

	recessive		
RUNX2	Autosomal dominant	Cleidocranial dysplasia	~70% of individuals with a cleidocranial dysplasia spectrum disorder[46]
SERPINH1	Autosomal recessive	Osteogenesis imperfecta type 10	<<10% of patients with OI[10]
SLC26A2 (DTDST)	Autosomal recessive	Achondrogenesis type 1B Atelosteogenesis type II Diastrophic dysplasia	>90% of patients with Achondrogeneis 1B[47]
SLC35D1	Autosomal recessive	Schneckenbecken dysplasia	<50% of individuals with Schneckenbecken dysplasia[48,49]
SOX9	Autosomal dominant	Campomelic dysplasia	~92% of individuals[32]
TMEM38B	Autosomal recessive	Osteogenesis imperfecta, type xiv	Unknown[50]
TRIP11	Autosomal recessive	Achondrogenesis, type IA	Unknown[51]
TRPV4	Autosomal dominant	Metatropic dysplasia	~99% for TRPV4-Related neuromusuclar and skeletal disorders[52]
TTC21B	Autosomal recessive	Asphyxiating thoracic dystrophy	~5% of pathogenic alleles involved in ciliopathy spectrum disorders[53]
WDR34	Autosomal recessive	Short-rib thoracic dysplasia 11 with or without polydactyly	Unknown[54]
WDR35	Autosomal recessive	Asphyxiating thoracic dystrophy (Jeune syndrome)	Unknown[55]

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