

## Skeletal Dysplasia Panel

Skeletal dysplasias are a heterogeneous group of >350 disorders characterized by abnormal growth of cartilage or bone. Some skeletal dysplasias are detectable prenatally while others are not evident until after birth or in later childhood.

### Disease Overview

#### Symptoms

- Dependent on the specific skeletal dysplasia
- Common symptoms may include:
  - Shortening of bones of the arms and legs >3 standard deviations below the mean
  - Head circumference >75th percentile
  - Bowed or fractured bones
  - Irregular, thickened, or thin bones
  - Undermineralization of bones
  - Abnormal ribs and/or small chest circumference
  - Polydactyly

#### Prevalence

~1/5,000 births<sup>1</sup>

#### Etiology

Pathogenic variants in numerous genes with various inheritance patterns (see [table below](#))

### Test Description

See [Genes Tested](#) table for genes included in this panel.

#### Clinical Sensitivity

- Variable, dependent on specific skeletal dysplasia
- Clinical sensitivity of the most common prenatally detected skeletal dysplasias:
  - Thanatophoric dysplasia, 99%<sup>2</sup>
  - *COL1A1/2*-related osteogenesis imperfecta, >97%<sup>3</sup>
  - Achondroplasia, 99%<sup>4</sup>
  - Achondrogenesis type IB, >90%<sup>5</sup>
  - Campomelic dysplasia, ~92%<sup>6</sup>
  - Diastrophic dysplasia, >90%<sup>5</sup>

#### Limitations

- A negative result does not exclude diagnosis of a skeletal dysplasia.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if the individual has had an

### Tests to Consider

#### Skeletal Dysplasia Panel, Sequencing and Deletion/Duplication 2012015

**Method:** Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray

- Confirm diagnosis of a skeletal dysplasia in a symptomatic individual
- Determine the causative gene variant(s) in an affected individual

#### Skeletal Dysplasia Panel, Sequencing and Deletion/Duplication, Fetal 2012010

**Method:** Massively Parallel Sequencing

- Confirm diagnosis of a skeletal dysplasia in a symptomatic fetus
- Determine if a fetus at risk for a skeletal dysplasia based on a positive family history is affected

#### Familial Mutation, Targeted Sequencing 2001961

**Method:** Polymerase Chain Reaction/Sequencing

- Recommended test for a known familial sequence variant previously identified in a family member
- A copy of the family member's test result documenting the known familial variant is required

#### Testing Strategy

- When skeletal dysplasia is suspected prenatally, the skeletal dysplasia panel is the recommended first-line test because providers correctly predict the correct skeletal dysplasia diagnosis in only 40% of prenatal cases.
- When skeletal dysplasia is suspected postnatally, radiographs and medical genetic consultation are recommended. If a geneticist is confident in the clinical diagnosis, targeted testing for the specific disorder should be performed. If two or more diagnoses are being considered, the skeletal dysplasia panel is recommended.

See [Related Tests](#)

interpretation of the test result may be impacted if the individual has had an allogeneic stem cell transplantation.



- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of the targeted genes
  - Regulatory region variants and deep intronic variants
  - Breakpoints of large deletions/duplications
  - Deletions/duplications in *CANT1*, *COMP*, *DDR2*, *GDF5*, *HSPG2*, *PCNT*, *PTH1R*, *TRPV4*
  - Noncoding transcripts
  - Exon *EVC* (NM\_153717) 1 is not sequenced due to technical limitations of the assay
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Deletions/duplications less than 1kb in the targeted genes by array
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Low-level mosaic variants
  - Single exon deletions/duplications in the following exons:
    - *ARSE* (NM\_000047) 9; *ARSE* (NM\_001282631) 1; *COL1A1* (NM\_000088) 5; *COL1A2* (NM\_000089) 20, 22; *EVC* (NM\_001306092) 12; *PEX7* (NM\_000288) 1

## Analytical Sensitivity

For massively parallel sequencing:

Variant Class	Analytical Sensitivity (PPA) Estimate <sup>a</sup> (%)	Analytical Sensitivity (PPA) 95% Credibility Region <sup>a</sup> (%)
SNVs	99.2	96.9-99.4
Deletions 1-10 bp	93.8	84.3-98.2
Deletions 11-44 bp	100	87.8-100
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	100	62.1-100

<sup>a</sup>Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.  
bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

## Genes Tested

Gene	Alias Symbol(s)	MIM Number	Disorder	Inheritance
<i>AGPS</i>	ADHAPS, ADAS, ALDHPSY, ADPS, ADAP-S	603051	Rhizomelic chondrodysplasia punctata, type 3	AR
<i>ALPL</i>	HOPS, TNSALP, TNALP, TNAP	171760	Hypophosphatasia, adult	AD
			Hypophosphatasia, infantile	AR
			Hypophosphatasia, childhood	
<i>ARSE</i>	CDPX, CDPX1	300180	Chondrodysplasia punctata 1, XL	XL
<i>CANT1</i>	SHAPY, SCAN-1	613165	Desbuquois dysplasia 1	AR
<i>COL1A1</i>	O14	120150	Caffey disease	AD
			Osteogenesis imperfecta, types I, II, III, and IV	





AD, autosomal dominant; AR, autosomal recessive; XL, X-linked

Gene	Alias Symbol(s)	MIM Number	Disorder	Inheritance
<i>COL1A2</i>	OI4	120160	Osteogenesis imperfecta, types II, III, and IV	AD
<i>COL2A1</i>	SEDC, AOM, STL1	120140	Platyspondylic lethal skeletal dysplasia, Torrance type Kniest dysplasia Spondyloepiphyseal dysplasia congenita Spondyloepimetaphyseal dysplasia, Strudwick type Achondrogenesis, type II Spondyloperipheral dysplasia Czech dysplasia Spondyloepiphyseal dysplasia, Stanescu type	AD
<i>COMP</i>	PSACH, EDM1, EPD1, MED, THBS5	600310	Epiphyseal dysplasia, multiple, 1 Pseudoachondroplasia	AD
<i>CRTAP</i>	CASP, LEPREL3, P3H5	605497	Osteogenesis imperfecta, type VII	AR
<i>DDR2</i>	TYRO10, NTRKR3, TKT	191311	Spondylometaphyseal dysplasia, short limb-hand type	AR
<i>DLL3</i>	SCDO1	602768	Spondylocostal dysostosis 1, AR	AR
<i>DYNC2H1</i>	DNCH2, hdhc11, DHC2, DHC1b, DYH1B	603297	Short-rib thoracic dysplasia 3 with or without polydactyly	AR
<i>EBP</i>	CDPX2, CPX, CPXD, CHO2	300205	Chondrodysplasia punctata 2, X-linked dominant	XL
<i>EVC</i>	DWF-1	604831	Ellis-Van Creveld syndrome	AR
<i>EVC2</i>	LBN	607261	Ellis-Van Creveld syndrome	AR
<i>FGFR1</i>	FLT2, KAL2, H2, H3, H4, H5, CEK, FLG, BFGFR, N-SAM, CD331	136350	Osteoglophonic dysplasia Trigonocephaly 1	AD
<i>FGFR2</i>	KGFR, BEK, CFD1, JWS, CEK3, TK14, TK25, ECT1, K-SAM, CD332	176943	Lacrimoauriculodentodigital syndrome Antley-Bixler syndrome without genital anomalies or disordered steroidogenesis Bent bone dysplasia syndrome	AD
<i>FGFR3</i>	ACH, CEK2, JTK4, CD333	134934	Achondroplasia Hypochondroplasia Lacrimoauriculodentodigital syndrome Thanatophoric dysplasia, type I Thanatophoric dysplasia, type II Achondroplasia, severe, with developmental delay and acanthosis nigricans	AD
<i>FKBP10</i>	hFKBP65, FLJ22041, FKBP6, FLJ20683, FLJ23833	607063	Bruck syndrome 1 Osteogenesis imperfecta, type XI	AR





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Gene	Alias Symbol(s)	MIM Number	Disorder	Inheritance
<i>FLNA</i>	FLN1, FLN, OPD2, OPD1, ABP-280	300017	Terminal osseous dysplasia Otopalatodigital syndrome, type II Frontometaphyseal dysplasia 1 Otopalatodigital syndrome, type I	XL
<i>FLNB</i>	FLN1L, LRS1, TAP, TABP, ABP-278, FH1	603381	Atelosteogenesis, type I Atelosteogenesis, type III Boomerang dysplasia Larsen syndrome	AD
			Spondylocarpotarsal synostosis syndrome	AR
<i>GDF5</i>	CDMP1, BMP14	601146	Chondrodysplasia, Grebe type Acromesomelic dysplasia, Hunter-Thompson type	AR
<i>GNPAT</i>	DHAPAT, DAPAT, DAP-AT	602744	Rhizomelic chondrodysplasia punctata, type 2	AR
<i>HSPG2</i>	SJS1, perlecan, PRCAN	142461	Dyssegmental dysplasia, Silverman-Handmaker type Schwartz-Jampel syndrome, type 1	AR
<i>ICK</i>	MRK, LCK2, KIAA0936, MGC46090	612325	Endocrine cerebro-osteodysplasia	AR
<i>IFT80</i>	WDR56, KIAA1374	611177	Short-rib thoracic dysplasia 2 with or without polydactyly	AR
<i>LBR</i>	DHCR14B, TDRD18	600024	Greenberg dysplasia	AR
<i>LIFR</i>	CD118	151443	Stuve-Wiedemann syndrome	AR
<i>NEK1</i>	NY-REN-55, KIAA1901	604588	Short-rib thoracic dysplasia 6 with or without polydactyly	AR
<i>P3H1</i>	LEPRE1, GROS1, LEPRECAN, MGC117314	610339	Osteogenesis imperfecta, type VIII	AR
<i>PCNT</i>	PCNT2, KEN, KIAA0402, PCN, PCNTB, SCKL4	605925	Microcephalic osteodysplastic primordial dwarfism, type II	AR
<i>PEX7</i>	PTS2R, RD	601757	Rhizomelic chondrodysplasia punctata, type 1	AR
<i>POR</i>	CYPOR, FLJ26468	124015	Antley-Bixler syndrome with genital anomalies and disordered steroidogenesis	AR
<i>PPIB</i>	CYPB, OI9, PPlase, B, CYP-S1, SCYLP	123841	Osteogenesis imperfecta, type IX	AR
<i>PTH1R</i>	PTHR, PTHR1	168468	Metaphyseal chondrodysplasia, Jansen type	AD
			Chondrodysplasia, Blomstrand type Eiken Syndrome	AR





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Gene	Alias Symbol(s)	MIM Number	Disorder	Inheritance
<b>RUNX2</b>	CCD, CBFA1, CCD1, AML3, PEBP2A1, PEBP2aA1	600211	Cleidocranial dysplasia	AD
<b>SERPINH1</b>	CBP1, CBP2, SERPINH2, HSP47, colligen	600943	Osteogenesis imperfecta, type X	AR
<b>SLC26A2</b>	DTD, DTDST	606718	Diastrophic dysplasia Atelosteogenesis, type II Achondrogenesis, type IB	AR
<b>SLC35D1</b>	UGTREL7, KIAA0260	610804	Schneckenbecken dysplasia	AR
<b>SOX9</b>	CMD1, CMPD1, SRA1	608160	Campomelic dysplasia	AD
<b>TRIP11</b>	CEV14, Trip230, GMAP-210, GMAP210	604505	Achondrogenesis, type IA	AR
<b>TRPV4</b>	OTRPC4, TRP12, VROAC, VRL-2, VR-OAC, CMT2C	605427	Metatropic dysplasia Parastremmatic dwarfism Spondyloepiphyseal dysplasia, Maroteaux type Spondylometaphyseal dysplasia, Kozlowski type	AD
<b>TTC21B</b>	FLJ11457, JBTS11, NPHP12, IFT139B, THM1	612014	Short-rib thoracic dysplasia 4 with or without polydactyly	AR
<b>WDR19</b>	Pwdmp, KIAA1638, FLJ23127, ORF26, DYF-2, Oseg6, IFT144, NPHP13	608151	Short-rib thoracic dysplasia 5 with or without polydactyly	AR
<b>WDR35</b>	MGC33196, KIAA1336, IFT121, IFTA1	613602	Short-rib thoracic dysplasia 7 with or without polydactyly	AR

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## References

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- Olney PN, Kean LS, Graham D, et al. [Campomelic syndrome and deletion of SOX9](#). Am J Med Genet. 1999;84(1):20-24. PubMed

## Additional Resources

Krakov D, Lachman RS, Rimoin DL. [Guidelines for the prenatal diagnosis of fetal skeletal dysplasias](#). Genet Med. 2009;11(2):127-133. PubMed





## Related Information

[Skeletal Dysplasias](#)

## Related Tests

[Thanatophoric Dysplasia, Types 1 and 2 \(FGFR3\) 13 Mutations, Fetal 0051508](#)

**Method:** Polymerase Chain Reaction/Fragment Analysis

[Thanatophoric Dysplasia, Types 1 and 2 \(FGFR3\) 13 Mutations 0051506](#)

**Method:** Polymerase Chain Reaction/Fragment Analysis

[Achondroplasia \(FGFR3\) 2 Mutations 0051266](#)

**Method:** Polymerase Chain Reaction/Fluorescence Resonance Energy Transfer

[Achondroplasia \(FGFR3\) 2 Mutations, Fetal 0051265](#)

**Method:** Polymerase Chain Reaction/Fluorescence Monitoring

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