Skeletal Dysplasia Panel, Sequencing and Deletion/Duplication

Last Literature Review: May 2022 Last Update: January 2024

Skeletal dysplasias are a heterogeneous group of more than 400 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. Symptoms are dependent on the specific skeletal dysplasia and include the shortening of the bones of the arms and legs >3 standard deviations below the mean; head circumference >75th percentile, bone abnormalities (eg, bowed or fractured, irregular, thickened, or thin) undermineralization of bones, abnormal ribs and/or small chest circumference, and polydactyly.

When skeletal dysplasia is suspected prenatally, the fetal skeletal dysplasia panel is the recommended first-line test because providers correctly predict the accurate 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.

Featured ARUP Testing

Skeletal Dysplasia Panel, Sequencing and Deletion/Duplication 2012015

Method: Massively Parallel Sequencing

Use to assess for causative gene variant(s) in individuals with clinical features of a skeletal dysplasia.

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

Method: Massively Parallel Sequencing

- Use to assess for causative variant(s) in a fetus with clinical features of a skeletal dysplasia.
- May also be used as predictive testing in a fetus known to be at risk for a skeletal dysplasia based on family history

If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information.

Genetics

Genes

See Genes Tested table for genes included in this panel.

Prevalence

Approximately 1/5,000 births[1]

Etiology

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

Test Interpretation

Methodology

This test is performed using the following sequence of steps:

- Selected genomic regions, primarily coding exons and exon-intron boundaries, from the targeted genes are isolated from extracted genomic DNA using a probe-based hybrid capture enrichment workflow.
- Enriched DNA is sequenced by massively parallel sequencing (MPS; also known as next generation sequencing, or NGS) followed by paired-end read alignment and variant calling using a custom bioinformatics pipeline. The pipeline includes an algorithm for the detection of large deletions and duplications.
- Sanger sequencing is performed as necessary to fill in regions of low coverage and in certain situations, to confirm variant calls.
- Large deletion/duplication calls made using MPS are confirmed by an orthogonal exon-level microarray when sample quality and technical conditions allow.

Clinical Sensitivity

- Variable, dependent on specific skeletal dysplasia
- Clinical sensitivity of the most common prenatally detected skeletal dysplasias:
  - Thanatophoric dysplasia, 99%[2]
  - *COLA1/2*-related osteogenesis imperfecta, >97%[3]
  - Achondroplasia, 99%[4]

- Achondrogenesis type IB, >90%[5]
- Campomelic dysplasia, approximately 92%[6]
- Diastrophic dysplasia, >90%[5]

Analytic Sensitivity

For massively parallel sequencing:

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region	Analytic Specificity (NPA)
SNVs	>99 (96.9-99.4)	>99.9
Deletions 1-10 bp[b]	93.8 (84.3-98.2)	>99.9
Insertions 1-10 bp[b]	94.8 (86.8-98.5)	>99.9
Exon-level[c] deletions	97.8 (90.3-99.8) [2 exons or larger] 62.5 (38.3-82.6) [Single exon]	>99.9
Exon-level[c] duplications	83.3 (56.4-96.4) [3 exons or larger]	>99.9

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived. These values do not apply to testing performed by multiplex ligation-dependent probe amplification (MLPA).

[b]Variants greater than 10 bp may be detected, but the analytic sensitivity may be reduced.

[c]In most cases, a single exon deletion or duplication is less than 450 bp and 3 exons span a genomic region larger than 700 bp.

bp, base pairs; PPA, positive percent agreement; NPA, negative percent agreement; SNVs, single nucleotide variants

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 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 and deep intronic variants
  - Deletions/duplications in the upstream regulatory region of *SOX9*
  - Breakpoints of large deletions/duplications
  - Sequence variants in *EVC* (NM_153717) exon 1 due to technical limitations of the assay
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Large duplications less than 3 exons in size
  - Noncoding transcripts
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Variants in the chr17:70,119,704-70,119,743 region of *SOX9* exon 3
  - Low-level somatic variants

Genes Tested

Gene	MIM Number	Disorder	Inheritance
AGPS	603051	Rhizomelic chondrodysplasia punctata, type 3	AR
ALPL	171760	Hypophosphatasia, adult Odontohypophosphatasia	AD, AR

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

Gene	MIM Number	Disorder	Inheritance
		Hypophosphatasia, infantile Hypophosphatasia, childhood	AR
ARSL	300180	Chondrodysplasia punctata, XL	XL
CANT1	613165	Desbuquois dysplasia 1 Epiphyseal dysplasia, multiple, 7	AR
CCN6	603400	Progressive pseudorheumatoid dysplasia	AR
CILK1	612325	Endocrine-cerebro-osteodysplasia Epilepsy, juvenile myoclonic, susceptibility to, 10	AR, AD
COL1A1	120150	Caffey disease Combined osteogenesis imperfecta and Ehlers-Danlos syndrome 1 Ehlers-Danlos syndrome, arthrochalasia type, 1 Osteogenesis imperfecta, types I, II, III, and IV	AD
COL1A2	120160	Combined osteogenesis imperfecta and Ehlers-Danlos syndrome 2 Osteogenesis imperfecta, types II, III, and IV Osteoporosis, postmenopausal	AD
		Ehlers-Danlos syndrome, cardiac valvular type	AR
COL2A1	120140	Achondrogenesis, type II or hypochondrogenesis Avascular necrosis of the femoral head Czech dysplasia Kniest dysplasia Legg-Calve-Perthes disease Osteoarthritis with mild chondrodysplasia Platyspondylic lethal skeletal dysplasia, Torrance type SMED Strudwick type Spondyloepiphyseal dysplasia Spondyloepiphyseal dysplasia, Stanescu type Stickler syndrome, type 1 Stickler syndrome, type 1 nonsyndrome ocular	AD
COL10A1	120110	Metaphyseal chondrodysplasia, Schmid type	AD
COL11A1	120280	Marshall syndrome Stickler syndrome, type II Otospondylomegaepiphyseal dysplasia, autosomal dominant	AD
		Fibrochondrogenesis 2	AD, AR
		Fibrochondrogenesis 1 Otospondylomegaepiphyseal dysplasia, autosomal recessive	AR
COMP	600310	Carpal tunnel syndrome 2 Epiphyseal dysplasia, multiple, 1 Pseudoachondroplasia	AD

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Gene	MIM Number	Disorder	Inheritance
CRTAP	605497	Osteogenesis imperfecta, type VII	AR
DDR2	191311	Warburg-Cinotti syndrome	AD
		Spondylometaepiphyseal dysplasia, short limb-hand type	AR
DLL3	602768	Spondylocostal dysostosis 1, AR	AR
DYM	607461	Dyggve-Melchior-Clausen disease Smith-McCort dysplasia	AR
DYNC2H1	603297	Short-rib thoracic dysplasia 3 with or without polydactyly	AR, Digenic
EBP	300205	Chondrodysplasia punctata 2, X-linked dominant MEND syndrome	XL
EVC	604831	Ellis-van Creveld syndrome	AR
EVC2	607261	Weyers acrofacial dysostosis	AD
		Ellis-van Creveld syndrome	AR
FGFR1	136350	Hartsfield syndrome Hypogonadotropic hypogonadism 2 with or without anosmia Jackson-Weiss syndrome Osteoglophonic dysplasia Pfeiffer syndrome Trigonocephaly 1	AD
FGFR2	176943	Antley-Bixler syndrome without genital anomalies or disordered steroidogenesis Apert syndrome Beare-Stevenson cutis gyrata syndrome Bent bone dysplasia syndrome Craniofacial-skeletal-dermatologic dysplasia Craniosynostosis, nonspecific Crouzon syndrome Jackson-Weiss syndrome Lacrimoauriculodentodigital (LADD) syndrome Pfeiffer syndrome Saethre-Chotzen syndrome Scaphocephaly and Axenfeld-Rieger anomaly Scaphocephaly, maxillary retrusion, and mental retardation	AD
FGFR3	134934	Achondroplasia Achondroplasia, severe, with developmental delay and acanthosis nigricans (SADDAN) Crouzon syndrome with acanthosis nigricans Hypochondroplasia Lacrimoauriculodentodigital (LADD) syndrome Muenke syndrome Thanatophoric dysplasia, type I	AD

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Gene	MIM Number	Disorder	Inheritance
		Thanatophoric dysplasia, type II	
		Captodactyly, tall stature, and hearing loss syndrome (CATSHL)	AD, AR
FKBP10	607063	Bruck syndrome 1 Osteogenesis imperfecta, type XI	AR
FLNA	300017	Cardiac valvular dysplasia, X-linked Frontometaphyseal dysplasia 1 Heterotopia, periventricular, 1 Intestinal pseudoobstruction, neuronal Melnick-Needles syndrome Otopalatodigital syndrome, type I Otopalatodigital syndrome, type II Terminal osseous dysplasia	XL
FLNB	603381	Atelosteogenesis, type I Atelosteogenesis, type III Boomerang dysplasia Larsen syndrome	AD
		Spondylocarpotarsal synostosis syndrome	AR
GDF5	601146	Brachydactyly, type A2 Brachydactyly, type C Multiple synostoses syndrome 2 Symphalangism, proximal 1B	AD
		Brachydactyly, type A1, C	AD, AR
		Acromesomelic dysplasia 2A Acromesomelic dysplasia 2B	AR
GNPAT	602744	Rhizomelic chondrodysplasia punctata, type 2	AR
HSPG2	142461	Dyssegmental dysplasia, Silverman-Handmaker type Schwartz-Jampel syndrome, type 1	AR
IFT80	611177	Short-rib thoracic dysplasia 2 with or without polydactyly	AR
INPPL1	600829	Opsismodysplasia	AR
LBR	600024	Greenberg dysplasia	AR
		Pelger-Huet anomaly	AD
LIFR	151443	Stuve-Wiedemann syndrome/Schwartz-Jampel type 2 syndrome	AR
NEK1	604588	Short-rib thoracic dysplasia 6 with or without polydactyly	AR, Digenic
		Amyotrophic lateral sclerosis, susceptibility to, 24	AD
NPR2	108961	Acromesomelic dysplasia 1, Maroteaux type	AR

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Gene	MIM Number	Disorder	Inheritance
		Epiphyseal chondrodysplasia, Miura type Short stature with nonspecific skeletal abnormalities	AD
P3H1	610339	Osteogenesis imperfecta, type VIII	AR
PCNT	605925	Microcephalic osteodysplastic primordial dwarfism, type II	AR
PEX7	601757	Peroxisome biogenesis disorder 9B Rhizomelic chondrodysplasia punctata, type 1	AR
POR	124015	Antley-Bixler syndrome with genital anomalies and disordered steroidogenesis	AR
PPIB	123841	Osteogenesis imperfecta, type IX	AR
PTH1R	168468	Metaphyseal chondrodysplasia, Murk Jansen type Failure of tooth eruption, primary	AD
		Chondrodysplasia, Blomstrand type Eiken Syndrome	AR
RUNX2	600211	Cleidocranial dysplasia Cleidocranial dysplasia, forme fruste, dental anomalies only Cleidocranial dysplasia, forme fruste, with brachydactyly Metaphyseal dysplasia with maxillary hypoplasia with or without brachydacyly	AD
SERPINH1	600943	Osteogenesis imperfecta, type X	AR
SLC26A2	606718	Achondrogenesis, type IB Atelosteogenesis, type II De la Chapelle dysplasia Diastrophic dysplasia Diastrophic dysplasia, broad bone-platyspondylic variant Epiphyseal dysplasia multiple, 4	AR
SLC35D1	610804	Schneckenbecken dysplasia	AR
SMACRCAL1	606622	Schimke immunoosseous dysplasia	AR
SOX9	608160	Campomelic dysplasia Campomelic dysplasia Campomelic dysplasia with autosomal sex reversal	AD
TRIP11	604505	Achondrogenesis, type IA Odontochondrodysplasia 1	AR
TRPV4	605427	Brachyolmia type 3 Digital arthropathy-brachydactyly, familial Hereditary motor and sensory neuropathy, type IIc Metatropic dysplasia Neuronopathy, distal hereditary motor, type VIII Parastremmatic, dwarfism	AD

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Gene	MIM Number	Disorder	Inheritance
		Scapuloperoneal spinal muscular atrophy SED, Maroteaux type Spondylometaphyseal dysplasia, Kozlowski type	
TTC21B	612014	Nephronophthisis 12	AR, AD
		Short-rib thoracic dysplasia 4 with or without polydactyly	AR
WDR19	608151	Nephronophthisis 13 Senior-Loken syndrome 8	AR
WDR35	613602	Short-rib thoracic dysplasia 7 with or without polydactyly Cranioectodermal dysplasia 2	AR

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References

1. Orioli IM, Castilla EE, Barbosa-Neto JG. The birth prevalence rates for the skeletal dysplasias. *J Med Genet*. 1986;23(4):328-332.
2. Chen CP, Chern SR, Shih JC, et al. Prenatal diagnosis and genetic analysis of type I and type II thanatophoric dysplasia. *Prenat Diagn*. 2001;21(2):89-95.
3. van Dijk FS, Byers PH, Dalgleish R, et al. EMQN best practice guidelines for the laboratory diagnosis of osteogenesis imperfecta. *Eur J Hum Genet*. 2012;20(1):11-19.
4. Bellus GA, Hefferon TW, Ortiz de Luna RI, et al. Achondroplasia is defined by recurrent G380R mutations of FGFR3. *Am J Hum Genet*. 1995;56(2):368-373.
5. Rossi A, Superti-Furga A. Mutations in the diastrophic dysplasia sulfate transporter (DTDST) gene (SLC26A2): 22 novel mutations, mutation review, associated skeletal phenotypes, and diagnostic relevance. *Hum Mutat*. 2001;17(3):159-171.
6. Olney PN, Kean LS, Graham D, et al. Campomelic syndrome and deletion of SOX9. *Am J Med Genet*. 1999;84(1):20-24.

Related Information

Skeletal Dysplasias

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