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[1]

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%[2]
  - *COLA1/2*-related osteogenesis imperfecta, >97%[3]
  - Achondroplasia, 99%[4]
  - Achondrogenesis type IB, >90%[5]
  - Campomelic dysplasia, ~92%[6]
  - Diastrophic dysplasia, >90%[5]

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 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

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

- 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[a] (%)	Analytical Sensitivity (PPA) 95% Credibility Region[a] (%)
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

[a]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
AGPS	ADHAPS, ADAS, ALDHPSY, ADPS, ADAP-S	603051	Rhizomelic chondrodysplasia punctata, type 3	AR
ALPL	HOPS, TNSALP, TNALP, TNAP	171760	Hypophosphatasia, adult	AD
			Hypophosphatasia, infantile Hypophosphatasia, childhood	AR
ARSE	CDPX, CDPX1	300180	Chondrodysplasia punctata 1, XL	XL
CANT1	SHAPY, SCAN-1	613165	Desbuquois dysplasia 1	AR
COL1A1	OI4	120150	Caffey disease Osteogenesis imperfecta, types I, II, III, and IV	AD
COL1A2	OI4	120160	Osteogenesis imperfecta, types II, III, and IV	AD

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

Gene	Alias Symbol(s)	MIM Number	Disorder	Inheritance
COL2A1	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
COMP	PSACH, EDM1, EPD1, MED, THBS5	600310	Epiphyseal dysplasia, multiple, 1 Pseudoachondroplasia	AD
CRTAP	CASP, LEPREL3, P3H5	605497	Osteogenesis imperfecta, type VII	AR
DDR2	TYRO10, NTRKR3, TKT	191311	Spondylometaepiphyseal dysplasia, short limb-hand type	AR
DLL3	SCDO1	602768	Spondylocostal dysostosis 1, AR	AR
DYNC2H1	DNCH2, hdhc11, DHC2, DHC1b, DYH1B	603297	Short-rib thoracic dysplasia 3 with or without polydactyly	AR
EBP	CDPX2, CPX, CPXD, CHO2	300205	Chondrodysplasia punctata 2, X-linked dominant	XL
EVC	DWF-1	604831	Ellis-Van Creveld syndrome	AR
EVC2	LBN	607261	Ellis-Van Creveld syndrome	AR
FGFR1	FLT2, KAL2, H2, H3, H4, H5, CEK, FLG, BFGFR, N-SAM, CD331	136350	Osteoglophonic dysplasia Trigonocephaly 1	AD
FGFR2	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
FGFR3	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
FKBP10	hFKBP65, FLJ22041, FKBP6, FLJ20683, FLJ23833	607063	Bruck syndrome 1 Osteogenesis imperfecta, type XI	AR
FLNA	FLN1, FLN, OPD2, OPD1, ABP-280	300017	Terminal osseous dysplasia Otopalatodigital syndrome, type II Frontometaphyseal dysplasia 1 Otopalatodigital syndrome, type I	XL

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Gene	Alias Symbol(s)	MIM Number	Disorder	Inheritance
FLNB	FLN1L, LRS1, TAP, TABP, ABP-278, FH1	603381	Atelosteogenesis, type I Atelosteogenesis, type III Boomerang dysplasia Larsen syndrome	AD
			Spondylocarpotarsal synostosis syndrome	AR
GDF5	CDMP1, BMP14	601146	Chondrodysplasia, Grebe type Acromesomelic dysplasia, Hunter-Thompson type	AR
GNPAT	DHAPAT, DAPAT, DAP-AT	602744	Rhizomelic chondrodysplasia punctata, type 2	AR
HSPG2	SJS1, perlecan, PRCAN	142461	Dyssegmental dysplasia, Silverman-Handmaker type Schwartz-Jampel syndrome, type 1	AR
ICK	MRK, LCK2, KIAA0936, MGC46090	612325	Endocrine cerebro-osteodysplasia	AR
IFT80	WDR56, KIAA1374	611177	Short-rib thoracic dysplasia 2 with or without polydactyly	AR
LBR	DHCR14B, TDRD18	600024	Greenberg dysplasia	AR
LIFR	CD118	151443	Stuve-Wiedemann syndrome	AR
NEK1	NY-REN-55, KIAA1901	604588	Short-rib thoracic dysplasia 6 with or without polydactyly	AR
P3H1	LEPRE1, GROS1, LEPRECAN, MGC117314	610339	Osteogenesis imperfecta, type VIII	AR
PCNT	PCNT2, KEN, KIAA0402, PCN, PCNTB, SCKL4	605925	Microcephalic osteodysplastic primordial dwarfism, type II	AR
PEX7	PTS2R, RD	601757	Rhizomelic chondrodysplasia punctata, type 1	AR
POR	CYPOR, FLJ26468	124015	Antley-Bixler syndrome with genital anomalies and disordered steroidogenesis	AR
PPIB	CYPB, OI9, PPIase, B, CYP-S1, SCYLP	123841	Osteogenesis imperfecta, type IX	AR
PTH1R	PTHR, PTHR1	168468	Metaphyseal chondrodysplasia, Jansen type	AD
			Chondrodysplasia, Blomstrand type Eiken Syndrome	AR
RUNX2	CCD, CBFA1, CCD1, AML3, PEBP2A1, PEBP2aA1	600211	Cleidocranial dysplasia	AD
SERPINH1	CBP1, CBP2, SERPINH2, HSP47, colligen	600943	Osteogenesis imperfecta, type X	AR
SLC26A2	DTD, DTDST	606718	Diastrophic dysplasia Atelosteogenesis, type II Achondrogenesis, type IB	AR
SLC35D1	UGTREL7, KIAA0260	610804	Schneckenbecken dysplasia	AR
SOX9	CMD1, CMPD1, SRA1	608160	Campomelic dysplasia	AD

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Gene	Alias Symbol(s)	MIM Number	Disorder	Inheritance
TRIP11	CEV14, Trip230, GMAP-210, GMAP210	604505	Achondrogenesis, type IA	AR
TRPV4	OTRPC4, TRP12, VROAC, VRL-2, VR-OAC, CMT2C	605427	Metatropic dysplasia Parastremmatic dwarfism Spondyloepiphyseal dysplasia, Maroteaux type Spondylometaphyseal dysplasia, Kozlowski type	AD
TTC21B	FLJ11457, JBTS11, NPHP12, IFT139B, THM1	612014	Short-rib thoracic dysplasia 4 with or without polydactyly	AR
WDR19	Pwdmp, KIAA1638, FLJ23127, ORF26, DYF-2, Oseg6, IFT144, NPHP13	608151	Short-rib thoracic dysplasia 5 with or without polydactyly	AR
WDR35	MGC33196, KIAA1336, IFT121, IFTA1	613602	Short-rib thoracic dysplasia 7 with or without polydactyly	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, de Luna RIOrtiz, 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.

Additional Resources

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

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 Monitoring

Achondroplasia (FGFR3) 2 Mutations, Fetal 0051265

Method: Polymerase Chain Reaction/Fluorescence Monitoring

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