Skeletal Dysplasia Panels

Indications for Ordering

- Confirm diagnosis of a specific skeletal dysplasia to aid in prognosis and recurrence risk in
  - Pregnancies with ultrasound findings suggestive of a skeletal dysplasia in the fetus
  - Newborns or children suspected to be affected with a skeletal dysplasia
  - Pregnancies in which both parents are affected and
    - Fetus is at risk for homozygosity or compound heterozygosity
- Determine the specific causative variant(s) in affected adults prior to pregnancy

Test Description

- Targeted capture of all coding exons and intron/exon junctions followed by massively parallel sequencing
  - Reported variants are confirmed by Sanger sequencing
- Deletion/duplication analysis by tiled, custom-designed comparative genomic hybridization (CGH) array

Tests to Consider

Primary tests

Skeletal Dysplasia Panel, Sequencing (39 Genes) and Deletion/Duplication (36 Genes), Fetal 2012010

- Prenatal diagnosis for suspected fetal skeletal dysplasia

Skeletal Dysplasia Panel, Sequencing (39 Genes) and Deletion/Duplication (36 Genes) 2012015

- Preferred test for individuals with an undetermined skeletal dysplasia

Related test

Familial Mutation, Targeted Sequencing 2001961

- Useful when a pathogenic familial variant identifiable by sequencing is known

Tests for specific genes or components of the skeletal dysplasia panel may be available individually at ARUP

- For test availability and further information, see ARUP's Genetics test directory (www.aruplab.com/genetics)

Disease Overview

- Skeletal dysplasias are a heterogeneous group of >350 disorders characterized by abnormal growth of cartilage or bone
  - Also known as osteochondrodysplasias
- Half of affected fetuses are stillborn or die within 6 weeks of birth
- The most common skeletal dysplasias detected prenatally include
  - Thanatophoric dysplasia
  - Osteogenesis imperfecta
  - Achondroplasia
  - Achondrogenesis types IB and II
  - Campomelic dysplasia
  - Diastrophic dysplasia
- Some skeletal dysplasias are detected prenatally, while others are not detected until after birth or in later childhood
  - Only 40% of affected fetuses presenting prenatally are correctly identified by ultrasound alone

Symptoms

- Dependent on the specific skeletal dysplasia
- Symptoms 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 the bones
  - Abnormal ribs and/or small chest circumference
  - Polydactyly

Incidence – ~1/5,000 births

- Skeletal dysplasias represent 5% of all genetic disorders in newborns
- In >160 skeletal dysplasias, the responsible genetic defect is known

Genetics

Genes – for gene-specific information, see table below

Variants

- Majority of causative variants are detected by sequencing
- Most of the genes tested have some variants represented by large deletions or duplications
  - Will not be identified by sequencing
    - Require deletion/duplication analysis for detection

Test Interpretation

Clinical sensitivity/specificity – dependent on the specific skeletal dysplasia

Results

- Positive
  - One pathogenic variant detected
    - Confirms diagnosis of a skeletal dysplasia in genes with autosomal dominant inheritance
      - Individuals with a pathogenic dominant germline variant have a 50% risk of passing the variant on to their offspring
  - Two pathogenic variants detected
    - Confirms diagnosis of a skeletal dysplasia in genes with autosomal recessive inheritance
      - Parents who both carry pathogenic variants for a skeletal dysplasia in the same recessive gene have a 25% risk for having affected offspring
  - One pathogenic X-linked variant detected in a male
    - Confirms diagnosis of a skeletal dysplasia
- Negative
  - No pathogenic variants detected in any of the genes tested
    - Reduces the likelihood of, but does not exclude, a diagnosis of a skeletal dysplasia
- Inconclusive
  - Variants of unknown clinical significance may be identified

Limitations

- Not detected
  - Deep intronic or regulatory region variants
  - Breakpoints for large deletions/duplications
  - Large deletions and duplications in the *COMP, HSPG2,* and *TRPV4* genes
- Not all variants in the tested genes are identified
- Not all predisposing genes are interrogated
- Diagnostic errors can occur due to rare sequence variations

Gene Symbol	Gene Description	NM #	OMIM #	Associated Skeletal Dysplasia(s)	Inheritance
AGPS	Alkylglycerone phosphate synthase	003659	603051	Rhizomelic chondrodysplasia punctata type 3	AR
ALPL	Alkaline phosphatase (liver/bone/kidney)	000478	171760	Hypophosphatasia	Perinatal/ infantile forms are AR; milder forms are AD or AR
ARSE	Arylsulphatase E (chondrodysplasia punctata 1)	000047	300180	Chondrodysplasia punctata	XLR
COL1A1	Collagen, type I, alpha 1	000088	120150	Osteogenesis imperfecta types I, II, III, IV	AD
COL1A2	Collagen, type I, alpha 2	000089	120160	Osteogenesis imperfecta types II, III, IV	AR, AD
COL2A1	Collagen, type II, alpha 1	001844	120140	Achondrogenesis type II; hypochondrogenesis; Czech dysplasia; Kniest dysplasia; otospondylomegaepiphyseal dysplasia; platyspondylic skeletal dysplasia; spondyloepiphyseal dysplasia congenita; spondyloperipheral dysplasia	AD
COMP	Cartilage oligomeric matrix protein	000095	600310	Pseudoachondroplasia (PSACH)	AD
CRTAP	Cartilage associated protein	006371	605497	Osteogenesis imperfecta, types IIB and VII	AR
DLL3	Delta-like 3 (Drosophila)	016941	602768	Spondylocostal dysostosis	AR
DYNC2H1	Dynein, cytoplasmic 2, heavy chain 1	001080463	603297	Short rib thoracic dystrophy 3 (with or without polydactyly)/asphyxiating thoracic dysplasia-3/Jeune syndrome	AR
EBP	Emopamil binding protein (sterol isomerase)	006579	300205	Chondrodysplasia punctata	XLD
EVC	Ellis van Creveld syndrome	153717	604831	Ellis van Creveld syndrome	AR
EVC2	Ellis van Creveld syndrome 2	147127	607261	Ellis-van Creveld syndrome 2; Weyers acrofacial dysostosis	Ellis-van Creveld is AR; Weyers is AD
FGFR1	Fibroblast growth factor receptor 1	023110	136350	Osteoglophonic dysplasia	AD

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FGFR2	Fibroblast growth factor receptor 2	000141	176943	Bent bone dysplasia	Most are AD; some are sporadic
FGFR3	Fibroblast growth factor receptor 3 (murine mammary tumor virus integration site (v-int-2) oncogene homologue)	000142	134934	Achondroplasia; hypochondroplasia; thanatophoric dysplasia types I and II	AD
FKBP10	FK506 binding protein 10, 65 kDa	021939	607063	Osteogenesis imperfecta type X1/ Bruck syndrome 1	AR
FLNA	Filamin A, alpha	001456	300017	Frontometaphyseal dysplasia; terminal osseous dysplasia	XLD
FLNB	Filamin B, beta	001457	603381	Atelosteogenesis types I and III; Larsen syndrome; spondylocarpotarsal synostosis syndrome	AR
GNPAT	Glyceronephosphate O-acyltransferase	014236	602744	Rhizomelic chondrodysplasia punctata type 2	AR
HSPG2	Heparan sulphate proteoglycan 2	005529	142461	Dyssegmental dysplasia, Silverman-Handmaker type; Schwartz-Jampel syndrome type 1	AR
IFT80	Intraflagellar transport 80	020800	611177	Asphyxiating thoracic dystrophy 2; short rib-polydactyly type 2	AR
LBR	Lamin B receptor	002296	600024	Greenburg dysplasia	AR
LIFR	Leukaemia inhibitory factor receptor alpha	002310	151443	Stuve-Wiedemann syndrome/Schwartz-Jampel syndrome type 2	AR
NEK1	NIMA-related kinase 1	012224	604588	Short-rib thoracic dysplasia 6 with or without polydactyly/short rib-polydactyly syndrome type II (Majewski type)	AR or digenic (*NEK1/DYNC2H1*)
*P3H1 (*previously *LEPRE1)*	Prolyl 3-hydoxylase 1	022356	610339	Osteogenesis imperfecta, type VIII	AR
PEX7	Peroxisome biogenesis factor 7	000288	601757	Rhizomelic chondrodysplasia punctata type 1	AR
POR	P450 (cytochrome) oxidoreductase	000941	124015	Disordered steroidogenesis; Antley-Bixler syndrome	AR
PPIB	Peptidylprolyl isomerase B (cyclophilin B)	000942	123841	Osteogenesis imperfecta, type IX	AR
RUNX2	Runt-related transcription factor 2	001024630	600211	Metaphyseal dysplasia with maxillary hypoplasia with or without brachydactyly; cleidocranial dysplasia	AD
SERPINH1	Serpin peptidase inhibitor, clade h (heat shock protein 47), member 1, (collagen binding protein 1)	001235	600943	Osteogenesis imperfecta, type 10	AR
SLC26A2	Solute carrier family 26 (sulphate transporter), member 2	000112	606718	Diastrophic dysplasia; achondrogenesis type Ib; atelosteogenesis type II	AD
SLC35D1	Solute carrier family 35(UDP-GlcA/UDP- GalNAc transporter), member D1	015139	610804	Schneckenbecken dysplasia	AR
SOX9	SRY (sex-determining region Y)-box 9	000346	608160	Campomelic dysplasia	AD
TRIP11	Thyroid hormone receptor interactor 11	004239	604505	Achondrogenesis type 1A	AR
TRPV4	Transient receptor potential cation channel, subfamily V, member 4	021625	605427	Metatropic dysplasia; parastremmatic dwarfism; SED, Marteaux type; spondylometaphyseal dysplasia, Kozlowski type	AD
TTC21B	Tetratricopeptide repeat domain 21B	024753	612014	Short-rib thoracic dysplasia 4 with or without polydactyly	AR

Gene Symbol	Gene Description	NM #	OMIM #	Associated Skeletal Dysplasia(s)	Inheritance
WDR19	WD repeat domain 19	025132	608151	Cranioectodermal dysplasia 4/ Sensenbrenner syndrome; short-rib thoracic dysplasia 5 with or without polydactyly/Jeune syndrome	AR
WDR35	WD repeat domain 35	001006657	613602	Cranioectodermal dysplasia 2/ Sensenbrenner syndrome; short rib thoracic dysplasia 7 with or without polydactyly	AR
AD = autosomal dominant; AR = autosomal recessive; XLD = X-linked dominant; XLR = X-linked recessive					