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

Skeletal Dysplasia Panel, Sequencing, 39 Genes 2012018

- Acceptable test for individuals with an undetermined skeletal dysplasia

Skeletal Dysplasia Panel, Deletion/Duplication, 36 Genes 2012007

- Preferred test for individuals with a previously identified familial deletion/duplication
- Secondary diagnostic test if sequencing does not detect the causative variant

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

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 mutation 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

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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
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,	AD

Gene Symbol	Gene Description	NM #	OMIM #	Associated Skeletal Dysplasia(s)	Inheritance*
				Kozlowski type	
TTC21B	Tetratricopeptide repeat domain 21B	024753	612014	Short-rib thoracic dysplasia 4 with or without polydactyly	AR
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; XLR = X-linked recessive; XLD = X-linked dominant					