Osteogenesis Imperfecta and Low Bone Density Panel, Sequencing

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Polygenetic factors are responsible for 80% of bone mineral density. Although osteoporosis is present in 10% of the U.S. population, monogenetic causes of osteoporosis, such as osteogenesis imperfecta (OI), are rare. OI comprises a continuum of phenotypes ranging from individuals with perinatal lethal OI, severe skeletal deformities, dentinogenesis imperfecta (DI), and severe short stature to individuals with normal stature, dentition, and lifespan but with mild predisposition to fractures.

Featured ARUP Testing

Osteogenesis Imperfecta and Low Bone Density Panel, Sequencing 3001607

Method: Massively Parallel Sequencing

- Use to confirm a clinical diagnosis of OI or monogenic cause of low bone density.
- Do not order this test to confirm a diagnosis of hypophosphatemic rickets or osteopetrosis.
- Regions of low coverage and reported variants are confirmed by Sanger sequencing as necessary.

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.

Disease Overview

Prevalence

6-7/100,000 for OI

Symptoms of Osteogenesis Imperfecta

- Predisposition to fractures, especially long bones, ribs, skull, spine
- Low bone mass or osteoporosis
- Skeletal deformities
- Variable DI
- Short stature
- Blue/gray scleral hue
- Joint hypermobility, early onset arthritis, scoliosis
- Progressive postpubertal mixed conductive/sensorineural hearing loss
- Protrusion acetabuli

Phenotype-Based Classification System for *COL1A1*- and *COL1A2*-Related OI

	Severity	Features
Type I	Classic nondeforming (mild)	Predisposition to fractures Blue sclera Rarely DI 50% have hearing loss Bone density can be normal
Type II	Perinatal lethal	Severe skeletal deformities Severe short stature DI
Type III	Severe progressively deforming	Very short stature DI Blue sclera Hearing loss frequent
Type IV	Mild to moderate	Variable short stature Mild to moderate bone deformities Multiple fractures

	Normal to gray sclera Some with hearing loss Some with DI

Genetics

Genes

ALPL, *ANO5*, *BMP1*, *CASR*, *CLCN5*, *COL1A1*, *COL1A2*, *CREB3L1*, *CRTAP*, *CYP27B1*, *FKBP10*, *GORAB*, *IFITM5*, *LRP5*, *P3H1*, *P4HB*, *PLOD2*, *PLS3*, *PPIB*, *SEC24D*, *SERPINF1*, *SERPINH1*, *SLC34A3*, *SP7*, *SPARC*, *TMEM38B*, *WNT1*

Etiology

Pathogenic variants in collagen 1 genes, collagen 1 processing genes, and osteoblast genes

- Pathogenic *COL1A1* and *COL1A2* variants are causative for approximately 90% of OI.
- Pathogenic variants in more than 25 other genes are causative for rarer forms of OI or other monogenic forms of decreased bone density.

Inheritance

- 60% of mild and 100% of severe OI cases are caused by de novo variants or a pathogenic variant inherited from a parent with somatic and/or germline mosaicism.
- Parental germline mosaicism is present in up to 16% of families.
- *COL1A1* and *COL1A2* variants are autosomal dominant (AD), but variants in other causative genes may be autosomal recessive (AR), X-linked, or AD (see table of Genes Tested).

Penetrance

Varies depending on causative gene; complete for *COL1A1* and *COL1A2* variants

Test Description

Clinical Sensitivity

OI: >90%

Other monogenic forms of osteoporosis or low bone density: unknown

Analytic Sensitivity

The analytical sensitivity of this test is approximately 99% for single nucleotide variants (SNVs) and greater than 93% for insertions/duplications/deletions from 1-10 base pairs in size. Variants greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced.

Limitations

- A negative result does not exclude a diagnosis of OI or low bone density.
- 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 targeted genes
  - Regulatory region and deep intronic variants
  - Large deletions/duplications
  - Noncoding transcripts
  - The following exons are not sequenced due to technical limitations of the assay:
    - LRP5 (NM_002335) exon 1
- The following may not be detected:

- Deletions/duplications/insertions of any size by massively parallel sequencing
- Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
- Low-level somatic variants

Genes Tested

Gene	MIM Number	Associated Disorders	Inheritance
ALPL	171760	Hypophosphatasia, adult	AD/AR
		Hypophosphatasia, infantile Hypophosphatasia, childhood	AR
ANO5	608662	Gnathodiaphyseal dysplasia	AD
BMP1	112264	OI, type XIII	AR
CASR	601199	Hyperparathyroidism, neonatal severe	AD/AR
CLCN5	300008	Hypophosphatemic rickets Dent disease 1	XLR
COL1A1	120150	Caffey disease OI types I, II, III, and IV Ehlers-Danlos syndrome, Arthrochalasia type 1	AD
COL1A2	120160	OI, Types II, III, and IV Ehlers-Danlos syndrome, Arthrochalasia type 2	AD
CREB3L1	616215	OI, type XVI	AR
CRTAP	605497	OI, type VII	AR
CYP27B1	609506	Vitamin D hydroxylation-deficient rickets, type 1A	AR
FKBP10	607063	Bruck syndrome 1 OI, type XI	AR
GORAB	607983	Geroderma osteodysplasticum	AR
IFITM5	614757	OI, type V	AD
LRP5	603506	Endosteal hyperostosis, AD Osteoporosis Van Buchem disease, type 2 Osteopetrosis, AD 1	AD
		Osteoporosis-pseudoglioma syndrome	AR
		Exudative vitreoretinopathy 4	AD/AR
P3H1	610339	OI, type VIII	AR

XLR, X-linked recessive

Gene	MIM Number	Associated Disorders	Inheritance
P4HB	176790	Cole-Carpenter syndrome 1	AD
PLOD2	601865	Bruck syndrome 2	AR
PLS3	300131	Bone mineral density quantitative trait locus 18	AR
PPIB	123841	OI, type IX	AR
SEC24D	607186	Cole-Carpenter syndrome 2	AR
SERPINF1	172860	OI, type VI	AR
SERPINH1	600943	OI, type X	AR
SLC34A3	609826	Hypophosphatemic rickets with hypercalciuria, hereditary	AR
SP7	606633	OI, type XII	AR
SPARC	182120	OI, type XVII	AR
TMEM38B	611236	OI, type XIV	AR
WNT1	164820	OI, type XV	AR

XLR, X-linked recessive

Related Information

Skeletal Dysplasias
Skeletal Dysplasia Panel, Sequencing and Deletion/Duplication

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