

Osteogenesis Imperfecta and Low Bone Density Panel, Sequencing

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.

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

Tests to Consider

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.

Related Tests

Skeletal Dysplasia Panel, Sequencing and Deletion/Duplication 2012015

Method: Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray

- Use to confirm diagnosis of a skeletal dysplasia in a symptomatic individual.
- Use to determine the causative gene variant(s) in an affected individual.

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

Method: Massively Parallel Sequencing

- Use to confirm diagnosis of a skeletal dysplasia in a symptomatic fetus.
- Use to 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 familial variant is required.



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 ~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

Analytical 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
<i>ALPL</i>	171760	Hypophosphatasia, adult	AD/AR
		Hypophosphatasia, infantile	AR
		Hypophosphatasia, childhood	
<i>ANOS</i>	608662	Gnathodiaphyseal dysplasia	AD
<i>BMP1</i>	112264	OI, type XIII	AR
<i>CASR</i>	601199	Hyperparathyroidism, neonatal severe	AD/AR
<i>CLCN5</i>	300008	Hypophosphatemic rickets Dent disease 1	XLR
<i>COL1A1</i>	120150	Caffey disease	AD
		OI types I, II, III, and IV	
		Ehlers-Danlos syndrome, Arthrochalasia type 1	
<i>COL1A2</i>	120160	OI, Types II, III, and IV	AD
		Ehlers-Danlos syndrome, Arthrochalasia type 2	
<i>CREB3L1</i>	616215	OI, type XVI	AR
<i>CRTAP</i>	605497	OI, type VII	AR
<i>CYP27B1</i>	609506	Vitamin D hydroxylation-deficient rickets, type 1A	AR
<i>FKBP10</i>	607063	Bruck syndrome 1	AR
		OI, type XI	
<i>GORAB</i>	607983	Geroderma osteodysplasticum	AR
<i>IFITM5</i>	614757	OI, type V	AD



Gene	MIM Number	Associated Disorders	Inheritance
<i>LRP5</i>	603506	Endosteal hyperostosis, AD Osteoporosis Van Buchem disease, type 2 Osteopetrosis, AD 1	AD
		Osteoporosis-pseudoglioma syndrome	AR
		Exudative vitreoretinopathy 4	AD/AR
<i>P3H1</i>	610339	OI, type VIII	AR
<i>P4HB</i>	176790	Cole-Carpenter syndrome 1	AD
<i>PLOD2</i>	601865	Bruck syndrome 2	AR
<i>PLS3</i>	300131	Bone mineral density quantitative trait locus 18	AR
<i>PPIB</i>	123841	OI, type IX	AR
<i>SEC24D</i>	607186	Cole-Carpenter syndrome 2	AR
<i>SERPINF1</i>	172860	OI, type VI	AR
<i>SERPINH1</i>	600943	OI, type X	AR
<i>SLC34A3</i>	609826	Hypophosphatemic rickets with hypercalciuria, hereditary	AR
<i>SP7</i>	606633	OI, type XII	AR
<i>SPARC</i>	182120	OI, type XVII	AR
<i>TMEM38B</i>	611236	OI, type XIV	AR
<i>WNT1</i>	164820	OI, type XV	AR

XLR, X-linked recessive

Additional Resources

Basel D, Steiner RD. [Osteogenesis imperfecta: recent findings shed new light on this once well-understood condition](#). Genet Med. 2009;11(6):375-385.

Mäkitie RE, Costantini A, Kämpe A, et al. [New insights into monogenic causes of osteoporosis](#). Front Endocrinol (Lausanne). 2019;10:70.

Pyott SM, Pepin MG, Schwarze U, et al. [Recurrence of perinatal lethal osteogenesis imperfecta in sibships: parsing the risk between parental mosaicism for dominant mutations and autosomal recessive inheritance](#). Genet Med. 2011;13(2):125-130.

Wright NC, Looker AC, Saag KG, et al. [The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine](#). J Bone Miner Res. 2014;29(11):2520-2526.

Related Information



Skeletal Dysplasias
Skeletal Dysplasia Panel

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