

## Osteogenesis Imperfecta Panel Sequence Analysis and Deletion/Duplication

**PANEL GENE LIST:** *ALPL, ANO5, B3GAT3, BMP1, COL1A1, COL1A2, CREB3L1, CRTAP, FKBP10, IFITM5, LRP5, P3H1(LEPRE1), P4HB, PLOD2, PLS3, PP1B, SEC24D, SERPINF1, SERPINH1, SP7, SPARC, TAPT1, TMEM38B, and WNT1*

Test	Description
<b>J797</b>	Osteogenesis Imperfecta Panel (All genes listed above)
<b>T992</b>	Autosomal Dominant Osteogenesis Imperfecta (Testing of COL1A1, COL1A2, IFITM5 only)

### CLINICAL FEATURES:

Osteogenesis Imperfecta (OI) is characterized by bone fragility and consequent susceptibility to bone fractures. The severity of OI can range from severe perinatal lethal to asymptomatic with mild predisposition to fractures and a normal lifespan.<sup>1,2,3</sup> Other common characteristics include dentinogenesis imperfecta, blue sclerae, short stature and hearing loss in adulthood.<sup>3</sup> The most lethal form of OI is type II, which is characterized by compressible thin calvaria, severe micromelia and bowing of long bones with multiple fractures and a narrow thorax.<sup>4</sup> Together, all types of OI have a combined prevalence of between 1 in 15,000 and 1 in 30,000 births with about 90% of cases caused by variants in either *COL1A1* or *COL1A2*.<sup>2,3</sup>

About 90% of all pathogenic variants causing Osteogenesis imperfecta are within *COL1A1* or *COL1A2*. At least 1832 different OI-causing pathogenic variants have been identified, of which 682 are glycine substitution pathogenic variants in the triple helix domain of the proteins and 150 are splice site pathogenic variants. Pathogenic variants in these two genes can lead to variable phenotypes ranging in severity from mild to lethal. Other genes which can contain pathogenic variants causing OI, may also cause a variable phenotype, while certain genes are known to correlate with certain levels of severity. For example, pathogenic variants in *SERPINH1* and *BMP1* are associated with a severe phenotype, while pathogenic variants in *IFITM5* and *SP7* lead to a moderate phenotype, and pathogenic variants in *PLS3* produce a mild phenotype. Additionally, *FKBP10* pathogenic variants are specifically associated with progressive deformity and contractures.<sup>4</sup>

### INHERITANCE PATTERN/GENETICS:

Osteogenesis Imperfecta due to pathogenic variants in *COL1A1*, *COL1A2*, and *IFITM5* is an autosomal dominant condition. Autosomal recessive osteogenesis imperfecta is caused by pathogenic variants in *BMP1*, *CREB3L1*, *CRTAP*, *FKBP10*, *P3H1 (LEPRE1)*, *WNT1*, *PP1B*, *SERPINF1*, *SERPINH1*, *SP7*, *SPARC*, and *TMEM38B*. Bruck syndrome-2 is an autosomal recessive condition of congenital contractures and bone fragility caused by the *PLOD2* gene. *PLS3* is an X-linked dominant gene associated with bone fractures in males and potential osteoporosis in females. Hypophosphatasia, a condition affecting bone mineralization caused by the *ALPL* gene, is an autosomal recessive condition in its severe form and either dominant or recessive when phenotypically mild. The *ANO5* gene is associated with autosomal dominant gnathodiaphyseal dysplasia. The autosomal recessive *B3GAT3* gene causes multiple joint dislocations, short stature, craniofacial dysmorphism, and congenital heart defects. The *LRP5* gene causes autosomal recessive osteoporosis-pseudoglioma syndrome. Cole-Carpenter

syndrome, an OI-like disorder, is caused by the autosomal dominant *P4HB* gene, while Cole-Carpenter syndrome type 2 is caused by the autosomal recessive *SEC24D* gene. Finally, the *TAPT1* gene causes osteochondrodysplasia

## TEST METHODS:

Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be > 99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

## TEST SENSITIVITY:

The clinical sensitivity of sequencing and deletion/duplication analysis of the genes included in this panel depends in part on the patient's clinical phenotype. Pathogenic variants in *COL1A1* or *COL1A2* are found in about 90% of cases of Osteogenesis imperfecta.<sup>4,5</sup>

The technical sensitivity of the sequencing test is estimated to greater than 99%. It will not detect deletions, insertions, or rearrangements greater than or equal to ten base pairs. The deletion/duplication testing can detect deletions or duplications encompassing one or more exons, including variants as small as 150-300 base pairs. Note that small sections of a few individual genes have inherent sequence properties that yield suboptimal data and variants in those regions may not be identified.

## REFERENCES:

1. Barkova, E et. al. (2014). Clinical Genetics, PMID: 24863959
2. Dighe, M, et. al. (2008). Radiographics 28(4), 1061-1077. PMID: 18635629
3. Valadares, ER, et. al (2014). Jornal De Pediatria, 90(6), 536-541. PMID: 25046257
4. Noel, AE & Brown RN (2014). International Journal of Women's Health, 6, 489-500. PMID: 24868173
5. Steiner RD, Adsit J, Basel D. COL1A1/2-Related Osteogenesis Imperfecta. 2005 Jan 28 [Updated 2013 Feb 14]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK1295/>