Skeletal Dysplasia Panel: Sequencing and CNV Analysis

**Test Code:** MM170
**Turnaround time:** 6 weeks
**CPT Codes:** 81406 x1, 81407 x1, 81408 x1

### Condition Description

Skeletal dysplasias are a heterogeneous group of more than 450 disorders with complex mechanisms. Clinical and biochemical features continue to be used reliably to assign patients to this general disease category. Identification of the precise genetic defect is important; however, to permit carrier testing and early prenatal diagnosis. Molecular analysis is likely to expand the clinical spectrum of skeletal dysplasia and may also provide data relevant to prognosis and future therapeutic intervention.

Collectively, the incidence of skeletal dysplasia is estimated to be 1 in 5,000 births. Skeletal dysplasia is referred to as generalized disorders of cartilage and bone, frequently resulting in disproportionate short stature. These disorders can range greatly in severity, from precocious arthopathy in relatively average stature individuals to severe dwarfism with perinatal mortality. A variety of complications can be associated with skeletal dysplasia, including orthopedic, neurologic, auditory, visual, pulmonary, cardiac, renal, and psychological. Five major groups are included in this panel: proportionate short stature; disproportionate short stature; skeletal dysplasias with increased bone density; skeletal dysplasias with decreased bone density osteolysis; and limb malformations.

**References:**


### Genes

ACAN, ACP5, AGPS, ALPL, ANOS1, ARHGDIP1, ARSL, ATP6V0A2, B3GALT6, B4GALT7, BMP1, BMP2, BMP1B, CASR, CC2D2A, CCDC1, CDH3, CDKN1A, CEP290, CHST14, CHST3, CHSY1, CLCN5, CLCN7, COL10A1, COL11A1, COL11A2, COL1A1, COL1A2, COL2A1, COL9A1, COL9A2, COL9A3, COMP, CRTAP, CTSL, CTSL2, DHCPR4, DILC3, DMP1, DYM, DYNC2H1, EBF, EID2, EID4, ENS1P1, ESCO2, EVC, EVC2, EX11, EXT1, EXT2, FAM20C, FBXN1, FBXN3, FBLN4, FBN1, FBN2, FLNB, FLNC, FNG, FN1, FMN1, GALNT3, GDF5, GLI3, GNAS, GORAB, GPO6, GREM1, HAC1, HDAC4, HES7, HOXD13, HPGD, HSPG2, ICK, IFITM5, IFT122, IFT1140, IFT80, IHH, KIF22, KIF7, LEMD3, LFNG, LIFR, LMRB1, LMPA1, LMPH3, LPRP5, MABF, MATN3, MSP2, MGP, MKS1, MMP13, MMP2, MMP9, MYCN, NEK1, NIPBL, NKX3-2, NOG, NOTCH2, NPR2, OBSL1, OSTM1, P3H1, PAPSS2, PCNT, PHEX, PIGV, PITX1, PLOC2, PPIB, PRKAR1A, PTH1R, PTHH, PTEN, PYCR1, RASGRF2, RBJLQ, ROR2, RPGRIP1L, RUNX2, SALL1, SALL4, SERPINF1, SERPINH1, SH3PXD2B, SHH, SHOX, SLC26A2, SLC34A1, SLC35D1, SLC39A13, SMCAL1, SOST, SOX9, SP7, SULF1, TBE, TBX15, TBX3, TBX5, TBX6, TBXAS1, TCRG1, TCL1, TGFBI, TMEM216, TMEM67, TNFRSF11A, TNFRSF11B, TNFSF11, TP63, TREM2, TRIF1, TRPS1, TRPV4, TYROBP, WDR35, WNT3, WNT5A, WNT7A, ZMPSTE24

### Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of skeletal dysplasias.
- Carrier testing in adults with a family history of skeletal dysplasias.

### Methodology

**Next Generation Sequencing:** In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

**Copy Number Analysis:** Comparative analysis of the NGS read depth (coverage) of the targeted regions of genes on this panel was performed to detect copy number variants (CNV). The accuracy of the detected variants is highly dependent on the size of the event, the sequence context and the coverage obtained for the targeted region. Due to these variables and limitations a minimum validated CNV size cannot be determined; however, single exon deletions and duplications are expected to be below the detection limit of this analysis.

### Detection

**Next Generation Sequencing:** Clinical Sensitivity: Unknown. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's
clinical/biochemical phenotype.

Analytical sensitivity for sequence variant detection is ~99%.

**Copy Number Analysis:** The sensitivity and specificity of this method for CNV detection is highly dependent on the size of the event, sequence context and depth of coverage for the region involved. The assay is highly sensitive for CNVs of 500 base pairs or larger and those containing at least 3 exons. Smaller (< 500 base pairs) CNVs and those that involving only 1 or 2 exons may or may not be detected depending on the sequence context, size of exon(s) involved and depth of coverage.

**Specimen Requirements**

**Submit only 1 of the following specimen types**

**Type: Saliva**

**Specimen Requirements:**
Orangene™ Saliva Collection Kit
Orangene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

**Specimen Collection and Shipping:**
Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

**Type: Whole Blood (EDTA)**

**Specimen Requirements:**
EDTA (Purple Top)
- Infants and Young Children (2 years of age to 10 years old): 3-5 ml
- Older Children & Adults: 5-10 ml
- Autopsy: 2-3 ml unclotted cord or cardiac blood

**Specimen Collection and Shipping:**
Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

**Type: DNA, Isolated**

**Specimen Requirements:**
Microtainer
- 8µg
- Isolation using the Perkin Elmer™Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

**Specimen Collection and Shipping:**
Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

**Related Tests**

- Skeletal Dysplasia: Deletion/Duplication Panel