

Multiple Epiphyseal Dysplasia (MED) Panel via Sequential COMP, MATN3, SLC26A2, COL9A1, COL9A2 and COL9A3 Gene Sequencing (Test #815)

Brief Description of Clinical Features: Multiple epiphyseal dysplasia is a clinically and genetically heterogeneous chondrodysplasia with either autosomal dominant or recessive inheritance. Dominant MED presents early in childhood, usually with pain in the hips and/or knees after exercise. Waddling gait may be present. Adult height is either in the lower range of normal or mildly shortened. The limbs are relatively short in comparison to the trunk. Pain and joint deformity can progress, resulting in early-onset osteoarthritis, particularly of the large weight-bearing joints (Briggs et al. *GeneReviews* 2011). Recessive MED is characterized by joint pain (usually in the hips or knees) occurring in late childhood; malformations of hands, feet, and knees; and scoliosis. Stature is usually within the normal range prior to puberty; in adulthood, stature is only slightly diminished (Bonafé et al. *GeneReviews* 2010).

Genetics: Mutations in five different genes (*COMP*, *MATN3*, *COL9A1*, *COL9A2* and *COL9A3*) can cause dominant MED. Many individuals with dominant MED have inherited the mutant allele from one parent. The prevalence of new mutations is not known. There is evidence for reduced penetrance in MED caused by *MATN3* mutations (Mortier et al. *Eur J Hum Genet* 9:606–612, 2001; Makitie et al. *Am J Med Genet A* 125:278–284, 2004). About 70% of dominant MED is caused by mutations in *COMP* (Briggs et al. *GeneReviews* 2011). MED-causing *COMP* mutations are located in the exons encoding calmodulin-like calcium-binding repeat domain (exons 8-14) as well as C-terminal domain (exons 15-19), and are mostly missense and small in-frame indels (Unger & Hecht *Am J Med Genet* 106:244–250, 2001; Briggs & Chapman *Hum Mutat* 19:465–478, 2002). Mutations in *MATN3* account for ~20% of dominant MED. With one exception (c.449delT), all the reported *MATN3* mutations are missense mutations found within exons 1-2 encoding the single A-domain of matrilin-3. All the reported MED-causing mutations in *COL9A1*, *COL9A2* and *COL9A3* are splice junction mutations clustered near exons encoding the collagenous domain of these collagen proteins, accumulatively accounting for ~10% of dominant MED. The five genes code for three structural macromolecules of the cartilage extracellular matrix (cartilage oligomeric matrix protein, matrilin-3, and type IX collagen), which have been shown to interact with each other (Thur et al. *J Biol Chem* 276:6083–6092, 2001; Mann et al. *J Biol Chem* 279:25294–25298, 2004). The recessive form of MED (EDM4/rMED) is caused by mutations in *SLC26A2*. Three most common *SLC26A2* mutations (p.Arg279Trp, c.-26+2T>C, p.Cys653Ser) account for >90% EDM4/rMED cases (Ballhausen et al. *J Med Genet* 40:65–71, 2003). Some genotype-phenotype correlations have been established. MED resulting from *COMP* mutations is characterized by significant involvement at the capital femoral epiphyses and irregular acetabuli (Unger et al. *Pediatr Radiol* 31:10–18, 2001); while type IX collagen defects result in more severe involvement of the knees and relative sparing of the hips. Intra- and interfamilial variability have been noticed for MED caused by *MATN3* mutations (Makitie et al. 2004).

| Gene | Disorder | Inheritance | OMIM# | Protein |
|----------------|-----------|-------------|--------|-------------------------------------|
| <i>COMP</i> | EDM1 | AD | 132400 | Cartilage oligomeric matrix protein |
| <i>COL9A1</i> | EDM6 | AD | 120210 | Collagen alpha-1(IX) chain |
| <i>COL9A2</i> | EDM2 | AD | 600204 | Collagen alpha-2(IX) chain |
| <i>COL9A3</i> | EDM3 | AD | 600969 | Collagen alpha-3(IX) chain |
| <i>MATN3</i> | EDM5 | AD | 607078 | Matrilin-3 |
| <i>SLC26A2</i> | EDM4/rMED | AR | 226900 | Solute carrier family 26 member 2 |

Description of This Particular Test: This test involves sequential sequencing of all six MED genes. When a likely causative mutation(s) is detected, testing stops at that point. The order of genes may be specified by the client. The default order is *COMP*, *MATN3*, *SLC26A2*, *COL9A1*, *COL9A2*, and *COL9A3*. For patients who have specific signs of EDM4/rMED (see Test #782), or have likely recessive inheritance, *SLC26A2* will be sequenced first (Jakkula et al. *Eur J Hum Genet* 13:292–301, 2005). As indicated, we will also sequence any single exon (Test #100, \$190) or pair of exons (Test #200, \$340) in any of these genes for family members of patients with known mutations, or to confirm research results. Tests for individual sequencing of these six genes are also available (see Tests #782, 805, 809, 816-818).

Reference Sequences:

| Gene | Genomic | mRNA | Protein | CCDS |
|----------------|--------------|-------------|-------------|---------|
| <i>COMP</i> | NC_000019.9 | NM_000095.2 | NP_000086.2 | 12385.1 |
| <i>COL9A1</i> | NC_000006.11 | NM_001851.4 | NP_001842.3 | 4971.1 |
| <i>COL9A2</i> | NC_000001.10 | NM_001852.3 | NP_001843.1 | 450.1 |
| <i>COL9A3</i> | NC_000020.10 | NM_001853.3 | NP_001844.3 | 13505.1 |
| <i>MATN3</i> | NC_000002.11 | NM_002381.4 | NP_002372.1 | 46226.1 |
| <i>SLC26A2</i> | NC_000005.9 | NM_000112.3 | NP_000103.2 | 4300.1 |

Indications for Test: Candidates for this test are patients with clinical and radiologic features consistent with MED and family members of patients who have known MED-causing mutations.

Sensitivity of Test: Sequencing of *COMP* is predicted to detect disease mutations in ~70% of cases with dominant MED. Mutations in *MATN3* and the three type IX collagen genes are estimated to account for ~20% and ~10% of dominant MED cases, respectively (Briggs et al. *GeneReviews* 2011). Sequencing of *SLC26A2* identifies at least one pathogenic mutation in >99% of cases and both mutations in ~90% of cases with EDM4/rMED (Ballhausen et al. 2003).

Turnaround Time: Maximum of 40 calendar days for the first gene and 10 days each for subsequent gene, although most tests are completed much more rapidly.

Specimen Requirements: See page 4 of the Requisition Form.

Prices: \$ 990 - \$5670

| Test | CPT Codes | | | | | | Totals |
|-----------------|-----------|-----------|--------------|--------------|------------|------------|----------|
| | 83890 | 83891 | 83898 | 83904 | 83894 | 83912 | |
| <i>COMP</i> | \$30 (x1) | \$40 (x1) | \$290 (x19) | \$440 (x19) | \$70 (x1) | \$120 (x1) | \$ 990 |
| <i>MATN3</i> | \$30 (x1) | \$40 (x1) | \$190 (x10) | \$280 (x10) | \$30 (x1) | \$90 (x1) | \$ 660 |
| <i>SLC26A2</i> | \$30 (x1) | \$40 (x1) | \$150 (x8) | \$220 (x8) | \$40 (x1) | \$90 (x1) | \$ 570 |
| <i>COL9A1</i> | \$30 (x1) | \$40 (x1) | \$570 (x39) | \$860 (x39) | \$120 (x1) | \$140 (x1) | \$1760 |
| <i>COL9A2</i> | \$30 (x1) | \$40 (x1) | \$380 (x25) | \$570 (x25) | \$80 (x1) | \$140 (x1) | \$1240 |
| <i>COL9A3</i> | \$30 (x1) | \$40 (x1) | \$460 (x31) | \$690 (x31) | \$100 (x1) | \$140 (x1) | \$1460 |
| Complete Panel* | \$30 (x1) | \$40 (x1) | \$1980(x132) | \$2960(x132) | \$390 (x1) | \$270 (x1) | \$ 5670* |

*When three or more genes in the Panel are tested, the price will be 85% of the sum of the individual gene prices.

Accreditation: CLIA ID:52D1027685 (expires 1/18/13) CAP ID:7185561, AU ID:1407125 (expires 12/20/12)

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