PREVENTION GENETICS
DISEASE PREVENTION THROUGH GENETIC TESTING

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Multiple Epiphyseal Dysplasia, Recessive (EDM4/rMED) via *SLC26A2* Gene Sequencing (Test #782)

Brief Description of Clinical Features: Recessive multiple epiphyseal dysplasia (OMIM#226900) is characterized by joint pain (usually in the hips or knees); malformations of hands, feet, and knees; and scoliosis. Approximately half of affected individuals have some abnormal finding at birth, e.g., clubfoot, clinodactyly. Onset of articular pain is variable but usually occurs in late childhood. Stature is usually within the normal range prior to puberty; in adulthood, stature is only slightly diminished. Functional disability is mild (Superti-Furga et al. *GeneReview* 2010).

Genetics: EDM4/rMED is inherited in an autosomal recessive manner. *SLC26A2* is the only gene currently known to be associated with rMED. *SLC26A2* encodes solute carrier family 26 member A2, a sulfate transporter. This transmembrane protein transports sulfate into chondrocytes to maintain adequate sulfation of proteoglycans. Undersulfation of proteoglycans affects the composition of the extracellular matrix and leads to impaired proteoglycan deposition, which is necessary for proper enchondral bone formation (Corsi et al. *Arch Pathol Lab Med* 125:1375–1378, 2001; Forlino et al. *Hum Molec Genet* 14: 859-871, 2005). Besides EDM4/rMED, mutations in *SLC26A2* can result in three other skeletal dysplasia conditions, achondrogenesis type 1B (ACG1B; OMIM#600972), atelosteogenesis type 2 (AO2; OMIM#256050) and diastrophic dysplasia (DTD; OMIM#222600). The predicted severity of the mutations can be correlated with the residual activity of the sulfate transporter (Rossi & Superti-Furga *Hum Mutat* 17:159–171, 2001). Three most common *SLC26A2* mutations associated with rMED are p.Arg279Trp, p.Cys653Ser, and c.-26+2T>C ("the Finnish allele", ~1% carrier frequency in Finns).

Description of This Particular Test: This test involves bidirectional sequencing using genomic DNA of all coding exons (exons 2-3) and partial 5'UTR of the *SLC26A2* gene plus ~50 bp of flanking non-coding DNA on each side. As indicated, we will also perform sequencing of any single exon (Test #100) or pair of exons (Test #200) for family members of patients with known mutations and to confirm previous research results ($190-340).

Reference Sequences: **Genomic: NC_000005.9** **mRNA: NM_000112.3**
Protein: NP_000103.2 **mRNA and Protein: CCDS 4300.1**

Indications for Test: Candidates for this test are patients with clinical and radiologic features consistent with EDM4/rMED and family members of patients who have known *SLC26A2* mutations.

Sensitivity of Test: This test is predicted to detect disease mutations in ~70% of individuals with clinical and radiologic features compatible with EDM4/rMED and no evidence of autosomal dominant inheritance (Superti-Furga et al. *GeneReview* 2010). The radiologic sign of double-layered patella in lateral knee radiograph is specific for rMED; mutations in *SLC26A2* were found in 100% of individuals with this sign (Superti-Furga et al. *J Med Genet* 36:621–624, 1999; Ballhausen et al. *J Med Genet* 40:65–71, 2003; Makitie et al. *Am J Med Genet* 122A:187–192, 2003)

Turnaround Time: Maximum of 40 calendar days, although many tests are completed in 2-3 weeks.

Specimen Requirements: See page four of the Requisition Form.

Prices: **Sequencing of *SLC26A2* gene** **$ 570**

CPT Codes:

Sample Ascertainment x1	83890 $ 30	DNA Isolation x1	83891 $ 40
Amplification x8	83898 $150	Sequencing x8	83904 $220
Separation x1	83894 $ 40	Interpretation/Report x1	83912 $ 90

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

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