PREVENTION GENETICS
DISEASE PREVENTION THROUGH GENETIC TESTING

CLIA #: 52D1027685 ● CAP #: 7185561
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Diastrophic dysplasia (DTD) via *SLC26A2* Gene Sequencing (Test #782)

Brief Description of Clinical Features: Diastrophic dysplasia (OMIM#222600) is characterized by limb shortening, normal-sized skull, hitchhiker thumbs, spinal deformities (scoliosis, exaggerated lumbar lordosis, cervical kyphosis), and contractures of the large joints with deformities and early-onset osteoarthritis. Other typical findings are ulnar deviation of the fingers, gap between the first and second toes, and clubfoot. On occasion the disease can be lethal at birth, but most affected individuals survive the neonatal period and develop physical limitations with normal intelligence (Bonafé & Superti-Furga *GeneReview* 2007).

Genetics: Diastrophic dysplasia is inherited in an autosomal recessive manner with complete penetrance. *SLC26A2* is the only gene currently known to be associated with DTD. *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 DTD, mutations in *SLC26A2* can result in three other skeletal dysplasia conditions, from lethal achondrogenesis type 1B (ACG1B; OMIM#600972) and atelosteogenesis type 2 (AO2; OMIM#256050) to mild recessive multiple epiphyseal dysplasia (rEMD; OMIM#226900). The predicted severity of the mutations can be correlated with the residual activities of the sulfate transporter and the severity of the phenotypes (Rossi & Superti-Furga *Hum Mutat* 17:159–171, 2001). Five mutations appear to be common (p.Arg279Trp, c.-26+2T>C, p.Val340del, p.Arg178X, p.Cys653Ser), together accounting for ~70% of the pathogenic alleles in *SLC26A2*. The mutation c.-26+2T>C, is also referred to as the "Finish allele" and has a carrier frequency of ~1% in the Finish population.

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 DTD and family members of patients who have known *SLC26A2* mutations.

Sensitivity of Test: This test is predicted to detect disease mutations in >90% of individuals affected with DTD (Rossi & Superti-Furga *Hum Mutat* 17:159–171, 2001).

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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