PREVENTION GENETICS
DISEASE PREVENTION THROUGH GENETIC TESTING

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Achondrogenesis Type 1B (ACG1B) via *SLC26A2* Gene Sequencing (Test #782)

Brief Description of Clinical Features: Achondrogenesis type 1B (OMIM #600972) is characterized by extremely short limbs with short fingers and toes, flat face, short neck, hypoplasia of the thorax, protuberant abdomen, and hydropic fetal appearance caused by the abundance of soft tissue relative to the short skeleton (Superti-Furga *Am J Hum Genet* 55:1137-1145, 1994). Death occurs prenatally or shortly after birth.

Genetics: Achondrogenesis type 1B is inherited in an autosomal recessive manner with complete penetrance. *SLC26A2* is the only gene currently known to be associated with ACG1B. *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). Most mutations found in ACG1B are rare, private null mutations. The only common *SLC26A2* mutations that may be associated with ACG1B are p.Arg178X and c.-26+2T>C. Besides ACG1B, mutations in *SLC26A2* can result in three other skeletal dysplasia conditions, including atelosteogenesis type 2 (AO2; OMIM#256050), Diastrophic dysplasia (DTD; OMIM#222600) and recessive multiple epiphyseal dysplasia (rEMD; OMIM#226900). The predicted severity of the mutations can be correlated with the residual activity of the sulfate transporter. The same mutations found in the ACG1B phenotype can also be found in the milder phenotypes (AO2 and DTD), if the second allele is a relatively mild mutation. Indeed, missense mutations located outside the transmembrane domain of the sulfate transporter are often associated with a residual activity that can "rescue" the effect of a null allele (Rossi & Superti-Furga *Hum Mutat* 17:159–171, 2001).

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 newborns with abnormal clinical and radiologic/histologic features consistent with ACG1B, and patients with abnormal prenatal ultrasound showing features suggestive of ACG1B in the fetus.

Sensitivity of Test: This test is predicted to detect disease mutations in >95% of individuals affected with ACG1B (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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