

Achondrogenesis Type II (ACG2)-Hypochondrogenesis via *COL2A1* Gene Sequencing (Test #788)

Brief Description of Clinical Features: Achondrogenesis type II (OMIM#200610) is characterized grossly by severe micromelic dwarfism with small chest and prominent abdomen, radiographically by incomplete ossification of the vertebral bodies, and histologically by disorganization of the costochondral junction. Hypochondrogenesis shares phenotypic characteristics with ACG2, but can be much milder. ACG2 and hypochondrogenesis likely reflect the spectrum of severity of the same disorder (Borochowitz et al. *Am J Med Genet* 24:273-288, 1986).

Genetics: Achondrogenesis type II/hypochondrogenesis is inherited in an autosomal dominant manner occurring mostly as a result of *de novo* mutations. Familial cases have been reported, suggesting both germline and somatic mosaicism (Comstock et al. *Am J Med Genet* 152A: 1822-1824, 2010). *COL2A1* is the only gene known to be associated with ACG2. This gene encodes the alpha 1 chain of type II collagen, a major structural component of cartilaginous tissues. *COL2A1* mutations can also cause several different skeletal disorders, including Stickler dysplasia type I (OMIM#108300), Spondyloepiphyseal dysplasia congenita (OMIM#183900), Spondyloepimetaphyseal dysplasia Strudwick type (OMIM#184250), Spondyloperipheral dysplasia (OMIM#271700), Kniest dysplasia (OMIM#156550), Osteoarthritis with mild chondrodysplasia (OMIM#604864), and Platyspondylic lethal skeletal dysplasia, Torrance type (OMIM#151210). The majority of ACG2/hypochondrogenesis-associated *COL2A1* mutations are missense mutations.

Description of This Particular Test: This test involves bidirectional sequencing using genomic DNA of all coding exons of the *COL2A1* gene plus ~50 bp of flanking non-coding DNA on each side. As indicated, we will also sequence any single exon (Test #100) in family members of patients with a known mutation, or to confirm research results (\$190).

Reference Sequences: Genomic: NC_000012.11
Protein: NP_001835.3

mRNA: NM_001844.4
mRNA and Protein: CCDS 41778.1

Indications for Test: Candidates for this test are patients with clinical and radiographic findings consistent with ACG2/hypochondrogenesis, and family members of patients who have a known *COL2A1* mutation.

Sensitivity of Test: This test is predicted to detect disease mutations in >99% of individuals with a clinical diagnosis of ACG2/hypochondrogenesis (Körkkö et al. *Am J Med Genet* 92:95-100, 2000; Mortier et al. *J Med Genet* 37:263-271, 2000; Nishimura et al. *Hum Mutat* 26:36-43, 2005).

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 *COL2A1* gene \$ 1990

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x47	83898 \$660	Sequencing x47	83904 \$990
Separation x1	83894 \$140	Interpretation/Report x1	83912 \$130

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

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