PREVENTION GENETICS
DISEASE PREVENTION THROUGH GENETIC TESTING

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Cleidocranial Dysplasia (CCD) via *RUNX2* Gene Sequencing (Test #786)

Brief Description of Clinical Features: Cleidocranial dysplasia (OMIM#119600) is a skeletal disorder characterized by delayed closure of the cranial sutures, hypoplastic or absent clavicles, increased head circumference, multiple dental abnormalities, and short stature (Otto et al. *Hum Mutat* 19:209–216, 2002). Hand abnormalities such as brachydactyly, tapering fingers, and short, broad thumbs are also common. Manifestations vary among individuals in the same family.

Genetics: Cleidocranial dysplasia is inherited in an autosomal dominant manner with high penetrance and extreme variability (Zhou et al. *Hum Mol Genet* 8:2311–2316, 1999). The proportion of cases caused by a *de novo* mutation is high. *RUNX2* (known previously as *CBFA1*) is the only gene known to be associated with CCD. *RUNX2* encodes runt-related transcription factor 2, which is involved in osteoblast differentiation and skeletal morphogenesis. RUNX2 is essential for osteoblast differentiation during intramembranous as well as chondrocyte maturation during endochondral ossification (Zheng et al. *Am J Hum Genet* 77:305–312, 2005). This protein contains an N-terminal stretch of consecutive polyglutamine and polyalanine repeats, known as the Q/A domain or the runt domain, and a C-terminal proline/serine/threonine-rich (PST) activation domain. The runt domain is a 128-amino-acid polypeptide motif that has the unique ability to independently mediate DNA binding and protein heterodimerization (Zhou et al. 1999). Most mutations in *RUNX2* are missense, nonsense, frameshift and splice site mutations. The majority of *RUNX2* mutations in individuals with classic CCD affect the runt domain and most mutations are predicted to abolish DNA binding (Lee et al. *Nat Genet* 16:307–310, 1997; Otto et al. 2002).

Description of This Particular Test: This test involves bidirectional sequencing using genomic DNA of all coding exons of the *RUNX2* 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_000006.11** **mRNA: NM_001024630.3**
Protein: NP_001019801.3 **mRNA and Protein: CCDS_43467.1**

Indications for Test: Candidates for this test are patients with clinical and radiographic findings consistent with CCD and family members of patients who have a known *RUNX2* mutation.

Sensitivity of Test: This test is predicted to detect disease mutations in 60-70% of individuals with a clinical diagnosis of CCD (Otto et al. 2002; Ott et al. *Hum Mutat* 31:1587-1593, 2010). Heterozygous deletions of all or part of the *RUNX2* gene, which would not be detected by sequencing, may be present in ~10% of all patients with CCD (Ott et al. 2010).

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 *RUNX2* gene** **$ 820**

CPT Codes:

Sample Ascertainment x1	83890 $ 30	DNA Isolation x1	83891 $ 40
Amplification x14	83898 $240	Sequencing x14	83904 $350
Separation x1	83894 $ 50	Interpretation/Report x1	83912 $110

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

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