

## Conradi-Hunermann syndrome / Chondrodysplasia Punctata, X-Linked Dominant via *EBP* Gene Sequencing (Test #781)

**Brief Description of Clinical Features:** Chondrodysplasia punctata (CDP) is a clinically and genetically heterogeneous disorder characterized by punctiform calcification of the bones. X-linked dominant CDP (CDPX2), also known as Conradi-Hunermann syndrome (OMIM #302960), is the best characterized form. CDPX2 patients display skin defects including linear or whorled atrophic and pigmentary lesions, striated hyperkeratosis, coarse lusterless hair and alopecia, cataracts, and skeletal abnormalities including short stature, rhizomelic shortening of the limbs, epiphyseal stippling, and craniofacial defects (Derry et al. *Nature Genet.* 22: 286-290, 1999).

**Genetics:** Conradi-Hunermann syndrome/CDPX2 is inherited in an X-linked dominant manner. Incomplete penetrance and variable expressivity have been noted (Ausavarat et al. *Eur. J. Derm.* 18: 391-393, 2008), which may reflect different patterns of X inactivation. CDPX2 has presumed male lethality prenatally, however hemizygous males with an *EBP* mutation have been reported (Traupe et al. *Am. J. Med. Genet.* 85:324-329, 1999; Metzenberg et al. *Am. J. Hum. Genet.* 65:A480, 1999; Milunsky et al. *Am. J. Med. Genet.*, 116A:249-254, 2003). These reported males have various features, ranging from mildly affected to typical CDPX2. *EBP* is the only gene currently known to be associated with CDPX2. *EBP* encodes the delta(8)-delta(7) sterol isomerase emopamil binding protein, an enzyme involved in postsqualene cholesterol biosynthesis. *EBP* is an integral membrane protein of the endoplasmic reticulum. It is similar to sigma receptors and may be a member of a superfamily of high affinity drug-binding proteins in the endoplasmic reticulum of different tissues. It has four putative transmembrane segments and contains two conserved glutamate residues which may be involved in the transport of cationic amphiphilics. Another prominent feature of this protein is its high content of aromatic amino acid residues (>23%) in its transmembrane segments. These aromatic amino acid residues have been suggested to be involved in the drug transport by the P-glycoprotein (Hanner et al. *J. Biol. Chem.* 270:7551-7557, 1995).

**Description of This Particular Test:** This test involves bidirectional sequencing using genomic DNA of all coding exons of the *EBP* gene plus ~50 bp of flanking non-coding DNA on each side. As indicated, we will also sequence any single exon (Test #100) or two exons (Test #200) in family members of patients with known mutations, or to confirm research results (\$190-340).

**Reference Sequences:** Genomic: **NC\_000023.1** mRNA: **NM\_006579.2** Protein: **NP\_006570.1** (CCDS 14300.1)

**Indications for Test:** Candidates for this test are patients with clinical/radiographic features or abnormal sterol profile consistent with CDPX2, and family members of patients who have known *EBP* mutations.

**Sensitivity of Test:** This test is predicted to detect disease mutations in ~90% of affected individuals with CDPX2 (Derry et al. *Nature Genet.* 22:286-290, 1999; Braverman et al. *Nature Genet.* 22:291-294, 1999; Ikegawa et al. *Am. J. Med. Genet.* 94:300-305, 2000; Herman et al. *Genet. Med.* 4:434-438, 2002; Has et al. *Hum. Mol. Genet.* 9:1951-1955, 2000).

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

**Specimen Requirements:** See page 4 of the Requisition Form.

**Prices:**                      **Sequencing of *EBP* gene**                      **\$ 490**

**CPT Codes:**

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x5	83898 \$120	Sequencing x5	83904 \$180
Separation x1	83894 \$ 30	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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