

Paget Disease, Juvenile via *TNFRSF11B* Gene Sequencing (Test #855)

Brief Description of Clinical Features: Juvenile Paget disease (JPD, OMIM#239000) is a rare osteopathy characterized by rapidly remodeling woven bone, osteopenia, fractures, and progressive skeletal deformity (Whyte et al. *New Eng J Med* 347:175-184, 2002). Deafness and sometimes retinopathy also occur.

Genetics: JPD is inherited in an autosomal recessive manner. The only molecular defect known to cause JPD are mutations in *TNFRSF11B*, the gene that encodes osteoprotegerin (Whyte et al. *J Bone Miner Res* 22:938-946, 2007). Osteoprotegerin (OPG) suppresses bone turnover by functioning as a decoy receptor for osteoclast differentiation factor (also called RANK ligand). Most JPD patients have diminished OPG inhibition of osteoclastogenesis. Distinct genotype-phenotype relationships have been reported (Chong et al. *J Bone Miner Res* 18:2095-2104, 2003). Missense mutations in the cysteine residues, predicted to cause major disruption to the ligand-binding region, were associated with a severe phenotype in which deformity developed before 18 months of age and caused major disability. Non-cysteine missense mutations in the ligand-binding domain were associated with an intermediate phenotype, with deformity recognized around the age of 5 years and an increased rate of long bone fracture. Frameshift mutations in exon 5 (last exon) were associated with the mildest phenotype.

Description of This Particular Test: This test involves bidirectional sequencing using genomic DNA of all coding exons of the *TNFRSF11B* gene plus ~50 bp of flanking non-coding DNA on each side. As indicated, we will also sequence any single exon (Test #100, \$190) or pair of exons (Test #200, \$340) in family members of patients with known mutations, or to confirm research results.

Reference Sequences: Genomic: NC_000008.10 mRNA: NM_002546.3
 Protein: NP_002537.3 mRNA and Protein: CCDS 6326.1

Indications for Test: Candidates for this test are patients with features consistent with JPD, and family members of patients who have known *TNFRSF11B* mutations.

Sensitivity of Test: JPD is a rare condition, and analysis of a large series of patients for this disorder has not been published. Chong et al. studied 8 patients with JPD and identified homozygous *TNFRSF11B* mutations in 5 of them (Chong et al. *J Bone Miner Res* 18:2095-2104, 2003).

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 <i>TNFRSF11B</i> 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 ID:7185561, AU ID:1407125 (expires 12/20/12)

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