

Paget Disease of Bone via *SQSTM1* Gene Sequencing (Test #853)

Brief Description of Clinical Features: Paget disease of bone (PDB, OMIM#602080) is the second most common metabolic bone disorder affecting ~2% of the population aged >40 years. The disorder is characterized by focal areas of increased and disorganized bone turnover, leading to bone pain, deformity, pathological fracture, neurological complications, and an increased risk of osteosarcoma (Laurin et al. *Am J Hum Genet* 70:1582-1588, 2002). The axial skeleton is preferentially affected. Common sites of involvement include the pelvis (70% of cases), femur (55%), lumbar spine (53%), skull (42%), and tibia (32%) (Ralston et al. *The Lancet* 372:155-163, 2008). PDB can be both inherited and sporadic, with the inherited form accounting for about one-third of patients with PDB (Michou et al. *Joint Bone Spine* 73:243-248, 2006).

Genetics: The familial form of PDB is inherited in an autosomal dominant manner with ~80% penetrance (Michou et al. *Joint Bone Spine* 73:243-248, 2006). At least 8 loci have been described in familial PDB cases by linkage studies, suggesting extensive genetic heterogeneity; however the disease-causing genes within most of these loci have not yet been discovered. The most important gene underlying PDB is *SQSTM1*, which encodes a scaffold protein (Sequestosome 1) in the nuclear factor κB (NFκB) signaling pathway. Mutations in *SQSTM1* have been reported to account for 20–50% of familial cases and 5–20% of sporadic cases (Eekhoff et al. *Arthritis Rheum* 50:1650–1654, 2004; Laurin et al. *Am J Hum Genet* 70: 1582–1588, 2002; Hocking et al. *Hum Mol Genet* 11:2735–2739, 2002; Beyens et al. *Calcif Tissue Int* 75:144–152, 2004; Cundy et al. *Calcif Tissue Int* 2011 July 7 epub). Although different types of mutations have been reported, including missense, nonsense, splice site and frameshift mutations, loss of ubiquitin binding is the unifying mechanism by which *SQSTM1* mutations cause this disease (Cavey et al. *Calcif Tissue Int* 78:271-277, 2006; Daroszewska et al. *Hum Mol Genet* 20:2734–2744, 2011). Patients with *SQSTM1* mutations have severe PDB and a high degree of penetrance with increasing age (Ralston et al. 2008). A minority of PDB cases are caused by mutation in the *TNFRSF11A* gene, which encodes the receptor activator of NFκB (RANK), a protein essential in osteoclast formation (see Test #854 for more information).

Description of This Particular Test: This test involves bidirectional sequencing using genomic DNA of all coding exons of the *SQSTM1* gene plus ~50 bp of flanking non-coding DNA on each side. As indicated, we will also sequence any single exon (Test #100, \$190) in family members of patients with known mutations, or to confirm research results.

Reference Sequences: Genomic: NC_000005.9 mRNA: NM_003900.4
 Protein: NP_003891.1 mRNA and Protein: CCDS 34317.1

Indications for Test: Candidates for this test are patients with features consistent with PDB, and family members of patients who have a known *SQSTM1* mutation.

Sensitivity of Test: This test is predicted to detect disease mutations in 20–50% of familial cases and 5–20% of sporadic cases with PDB (Eekhoff et al. 2004; Laurin et al. 2002; Hocking et al. 2002; Beyens et al. 2004; Cundy et al. 2011)

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 *SQSTM1* gene \$ 740

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x12	83898 \$210	Sequencing x12	83904 \$310
Separation x1	83894 \$ 40	Interpretation/Report x1	83912 \$110

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

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