

Hereditary Multiple Osteochondromas (HMO)

EXT1 & EXT2 Gene Sequential Sequencing (Test #806) EXT1 Only (Test #807) EXT2 Only (Test #808)

Brief Description of Clinical Features: Hereditary multiple osteochondromas, also known as hereditary multiple exostoses (OMIM#133700 for type I and #133701 for type II), are benign cartilage-capped bone tumors (exostoses) that grow outward from the metaphyses of long bones. Osteochondromas can be associated with a reduction in skeletal growth, bony deformity, restricted joint motion, shortened stature, premature osteoarthritis, and compression of peripheral nerves (Schmale et al. *GeneReviews* 2008). The lifetime risk for malignant osteochondrosarcoma is low (1-5%), but the risk increases with age (Vink et al. *Eur J Hum Genet* 13:470-474, 2005).

Genetics: HMO is inherited as an autosomal dominant trait with high penetrance (~95%). About 10% of affected individuals have HMO as the result of a *de novo* mutation. Two genes (*EXT1* and *EXT2*) are known to be associated with HMO. A possible third locus is thought to account for a small number of cases, but the gene has not yet been identified. Both *EXT* gene products (Exostosin-1, Exostosin-2) are involved in the biosynthesis of heparan sulfate. *EXT1* and *EXT2* encode glycosyltransferases that interact as heterooligomeric complexes and participates in cell signaling and chondrocyte proliferation and differentiation (McCormick et al. *Proc Natl Acad Sci* 97:668-673, 2000). *EXT1* mutations account for 56-78% of HMO, and *EXT2* mutations account for 21-44% of HMO (Schmale et al. *GeneReviews* 2008). In both genes, most of reported mutations are nonsense, frameshift and splice site mutations. Individuals with *EXT1* mutations were found to have a greater number of exostoses, a greater incidence of limb malalignment with shorter limb segments and height, and more frequent pelvic and flat bone involvement than those with *EXT2* mutations (Alvarez et al. *Clin Genet* 70:122-130, 2006). The risk of chondrosarcoma may also be higher in individuals with an *EXT1* mutation (Porter et al. *J Bone Joint Surg Br* 86:1041-1046, 2004).

Description of This Particular Test: This test involves bidirectional sequencing using genomic DNA of all coding exons of the *EXT1* and *EXT2* genes plus ~50 bp of flanking non-coding DNA on each side. Unless specially requested, we will sequence *EXT1* first. If a pathogenic mutation is found, testing will stop; if no mutation (or a variant of unknown significance) is found in *EXT1*, we will proceed with sequencing *EXT2*. Sequencing of either gene may also be ordered separately. As indicated, we will sequence any single exon (Test #100, \$190) in family members of patients with known mutation, or to confirm research results.

Reference Sequences:	Gene	Genomic	mRNA	Protein	CCDS
	<i>EXT1</i>	NC 000008.10	NM 000127.2	NP 000118.2	6324.1
	<i>EXT2</i>	NC 000011.9	NM 207122.1	NP 997005.1	7908.1

Indications for Test: Candidates for this test are patients with clinical and radiographic features consistent with HMO, and family members of patients who have known *EXT1* or *EXT2* mutations.

Sensitivity of Test: Combining *EXT1* and *EXT2*, this test is predicted to detect disease mutations in 70-85% of affected individuals with HMO (Schmale et al. *GeneReviews* 2008). Large deletions that are not detectable by sequencing may be found in up to 10% of patients with HMO (Vink et al. *Eur J Hum Genet* 13:470-474, 2005)

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 both *EXT1* and *EXT2* Genes \$ 1350

Test	CPT Codes						Totals
	83890	83891	83898	83904	83894	83912	
<i>EXT1</i> Only (#807)	\$30 (x1)	\$40 (x1)	\$ 240 (x14)	\$ 350 (x14)	\$50 (x1)	\$110 (x1)	\$820
<i>EXT2</i> Only (#808)	\$30 (x1)	\$40 (x1)	\$ 240 (x14)	\$ 350(x14)	\$50 (x1)	\$110 (x1)	\$820
Both <i>EXT1</i> & <i>EXT2</i> (#806)	\$30 (x1)	\$40 (x1)	\$ 410 (x28)	\$ 610 (x28)	\$90 (x1)	\$170 (x1)	\$1350

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

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