

Multiple Endocrine Neoplasia Type 1 via *MEN1* Gene Sequencing – Test #715

Brief Description of Clinical Features: Multiple Endocrine Neoplasia Type 1 (MEN1; OMIM 131100) is an autosomal dominant disorder distinguished by tumors of the parathyroid glands, pancreatic islet cells and anterior pituitary gland (reviewed by Pannett and Thakker *Endocrine-Related Cancer* 6:449-473, 1999). Some patients with MEN1 may also develop adrenal cortical tumors, carcinoid tumors, facial angiofibromas, collagenomas, and/or lipomas. Neoplasia of endocrine glands typically leads to excessive hormone production. As a result, the clinical manifestations of MEN1 are clearly related to the sites of the tumors. For example, ~95% of patients exhibit hypercalcemia, nephrolithiasis, or osteitis fibrosa cystica due to parathyroid tumors; ~40% have recurrent peptic ulcers, hypoglycemia, or hyperglucagonaemia due to pancreatic tumors; and ~30% have hyperprolactinaemia, hypercorticism (i.e. Cushing’s syndrome) or acromegaly due to anterior pituitary tumors.

Genetics: Heterozygous germline mutations in the Menin gene (*MEN1*) predispose individuals to MEN type 1. For mutant carriers, the penetrance of MEN1 is greater than 75% by the age of 25, and approaches 100% by the age of 60 (Pannett and Thakker, 1999). To date, at least 565 distinct causative mutations have been found scattered throughout the *MEN1* gene (Lemos and Thakker *Hum Mut* 29:22-32, 2008). Greater than 80% of these mutations are inactivating (i.e. nonsense, frameshifts, splice-site), consistent with the role of *MEN1* as a tumor suppressor gene (Larsson et al. *Nature* 332:85-87, 1988). Although the precise molecular function of the Menin protein is still not known, data from protein interaction studies suggest it is involved in many vital processes, including transcription regulation, DNA replication, and DNA repair (reviewed in Lemos and Thakker, 2008). In addition to familial cases of MEN1, heterozygous mutations have also been found in patients with apparently sporadic cases of MEN1, as well as in patients diagnosed with Familial Isolated Hyperparathyroidism (FIHP; OMIM 145000) (Warner et al. *J Med Genet* 41:155-160, 2004). Interestingly, ~40% of the causative mutations found in FIHP cases are missense, compared to only ~20% for MEN1 (Lemos and Thakker, 2008). These observations suggest a likely association between weak missense mutations and the mild clinical FIHP variant.

Description of This Particular Test: This test involves bidirectional DNA sequencing of all 9 coding exons (3-11) of the *MEN1* gene, plus ~50 bp of flanking non-coding DNA on either side of each exon. As indicated, we will also sequence a single exon (Test #100) in family members of patients with a known mutation, or to confirm research results (\$190).

Reference Sequences: Genomic: NC_000011.9 mRNA: NM_000244.3 Protein: NP_000235.2 CCDS 8083.1

Indications for Test: Candidates for this test are patients diagnosed with multiple endocrine neoplasia type 1 (MEN1) or familial isolated hyperparathyroidism (FIHP). This test is specifically designed for heritable germline mutations and is not appropriate for the detection of somatic mutations in tumor tissue.

Sensitivity of Test: This test is predicted to detect a causative mutation in ~50-95% of patients with autosomal dominant MEN1, ~70% of patients with sporadic, or isolated, MEN1, or ~20% of patients with FIHP (Agarwal et al. *Hum Mol Genet* 6:1169-1175, 1997; Teh et al. *J Clin Endo Metab* 83:2621-2626, 1998; Warner et al., 2004).

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.

Price:	Sequencing of the <i>MEN1</i> Gene:	\$ 690
CPT Codes:		
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1 83891 \$ 40
Amplification x11	83898 \$ 180	Sequencing x11 83904 \$ 280
Separation x1	83894 \$ 50	Interpretation/Report x1 83912 \$ 110

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

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