MEN1 Gene Analysis in Multiple Endocrine Neoplasia Type 1 and Familial Isolated Hyperparathyroidism

Disorder Also Known As: MEN1; Endocrine adenomatosis, multiple; MEA I; Wermer syndrome; Menin; FIHP; Hyperparathyroidism 1; HRPT1

Clinical Features:
Multiple endocrine neoplasia type 1 (MEN1) is characterized by endocrine tumors, particularly parathyroid, gastro-entero-pancreatic neuroendocrine tumors, anterior pituitary tumors, carcinoid tumors, and adrenocortical tumors. Primary tumors may be found in more than one endocrine organ and may be multi-focal. MEN1-associated endocrine tumors have the potential to cause an array of clinical and biochemical manifestations secondary to hormone hypersecretion: hyperparathyroidism (the most frequent MEN1-symptom leading to hypercalcemia), hypercortisolism, gigantism and acromegaly, prolactinoma, gastrinoma, and insulinoma. Non-endocrine tumors also are common and can include facial angiofibromas and collagenomas of the skin, lipomas, meningioma and ependymoma of the CNS, and leiomyomas. Although many MEN1-related tumors have a low risk of malignancy, others such as gastrinomas and thymic and bronchial carcinoids carry high malignant potential and are the leading cause of morbidity and mortality.[1]

Familial Isolated Hyperparathyroidism (FIHP), a disorder characterized by parathyroid tumors in the absence other associated endocrinopathies, is also associated with pathogenic variants in the *MEN1* gene.

Inheritance Pattern:
MEN1 and **FIHP** are inherited in an autosomal dominant manner. Approximately 10% of cases are *de novo* (new).[2]

Test Methods:
Using genomic DNA from the submitted specimen, the coding regions and splice junctions of *MEN1* are PCR amplified and capillary sequencing is performed. Bi directional sequence is assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Capillary sequencing or another appropriate method is used to confirm all variants with clinical or uncertain significance. If present, apparently homozygous variants are confirmed using alternate primer pairs to significantly reduce the possibility of allele drop-out. All sequence alterations are described according to the Human Genome Variation Society (HGVS) nomenclature guidelines.

Concurrent deletion/duplication testing is performed using either exon-level array CGH or MLPA. Confirmation of copy number changes is performed by MLPA, qPCR, or repeat aCGH analysis. The array is designed to detect most single-exon deletions and duplications. Array CGH alterations are reported according to the International System for Human Cytogenetic Nomenclature (ISCN) guidelines. Benign and likely benign variants, if present, are not reported but are available upon request.

Test Sensitivity:

The clinical sensitivity of sequencing and deletion/duplication analysis of *MEN1* depends in part on the patient's clinical phenotype and family history. In general, the sensitivity is highest for individuals with features suggestive of MEN1/ FIHP as outlined above. Germline *MEN1* variants have been found in 75-90% of patients with a clinical diagnosis of MEN1, regardless of family history.[2,3] Of patients who do not harbor a variant identifiable on sequencing, it is estimated that 1-8% of patients with familial MEN1 will have a heterozygous partial or whole deletion of the *MEN1* gene.[4,6,13] Additionally, 23%-57% of patients with clinically diagnosed FIHP are expected to have a variant in the MEN1 gene.[16,18,19]

DNA sequencing will detect nucleotide substitutions and small insertions and deletions, while array CGH, or MLPA will detect exon-level deletions and duplications. These methods are expected to be greater than 99% sensitive in detecting pathogenic variants identifiable by sequencing or CNV technology.

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