Menin Gene Analysis in Multiple Endocrine Neoplasia Type 1 and Familial Isolated Hyperparathyroidism (FIHP)

Disorder also known as: MEN1; Endocrine adenomatosis, multiple; MEA I; Wermer syndrome; Menin; Familial Isolated Hyperparathyroidism; FIHP; Hyperparathyroidism 1; HRPT1

Clinical Features:
Multiple endocrine neoplasia type 1 (MEN1) is characterized by endocrine tumors, particularly in the parathyroid glands, anterior pituitary, and pancreatic islet cells. Primary tumors may be found in more than one endocrine organ and/or multiple tumors may be found in the same organ. MEN1-associated endocrine tumors cause an array of clinical and biochemical manifestations secondary to hormone hypersecretion: hyperparathyroidism (the most frequent MEN1-symptom with potential effects on the central nervous system (CNS), hypercalcemia, gastrointestinal, renal cardiovascular, and skeletal involvement), hypercortisolism, gigantism and acromegaly, prolactinoma (with associated oligomenorrhea, amenorrhea, and galactorrhea in females and sexual dysfunction in males), 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. MEN1 is caused by pathogenic variants in the menin gene (MEN1), which are highly penetrant. Approximately 50% of MEN1 variant carriers are symptomatic by age 20 and 95% are symptomatic by the age of 40.

Familial Isolated Hyperparathyroidism (FIHP), a disorder characterized by parathyroid adenoma/hyperplasia (and possibly carcinoma) in the absence other associated endocrinopathies, is also associated with pathogenic variants in the MEN1 gene. However, FIHP is genetically heterogeneous and can be caused by pathogenic variants in other genes, such as CASR and HRPT2, for which genetic testing also is available at GeneDx.

Inheritance Pattern/Genetics:
MEN1: Autosomal dominant; 10% of cases result from de novo variants
FIHP: Autosomal dominant

Over 400 different variants have been identified in the 9 coding exons of the MEN1 gene. Small deletions, small insertions, and nonsense changes constitute the majority of variants. Most variants in MEN1 result in premature truncation of the predicted protein; however, missense changes and, less frequently, partial/whole deletions have been detected. Individuals with FIHP are significantly more likely to have a missense pathogenic variant in the MEN1 gene than those with a diagnosis of MEN1.[1,2]

Test Methods:
Using genomic DNA of the submitted specimen, bi-directional sequencing analysis of the coding regions (exons 2-10) and splice sites of the MEN1 gene is performed. Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method. If no variant is found by sequencing, multiplex ligation-dependant probe amplification (MLPA) is available to evaluate for a deletion or duplication of one or more exons of this gene.

Test Sensitivity:

Multiple endocrine neoplasia type 1
Germline MEN1 variants have been found in 75-90% of patients with a clinical diagnosis of MEN1, regardless of family history.[1,2] 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.[4,5,6] Although the sequencing approach used by GeneDx is expected to identify >99% of existing small intragenic variants in the MEN1 gene, this method will miss a partial or whole gene deletion. Therefore, if indicated, MLPA analysis is available to screen for such deletions.

Familial Isolated Hyperparathyroidism (FIHP)
Based on three studies, 23%-57% of patients with clinically diagnosed FIHP are expected to have a variant in the MEN1 gene.[7,8,9]

References: (12 pt bold)

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