RET Gene Analysis in Multiple Endocrine Neoplasia Type 2A and Multiple Endocrine Neoplasia Type 2B (Familial Medullary Thyroid Cancer, included)

Disorder also known as: MEN2A; Pheochromocytoma and amyloid-producing medullary thyroid carcinoma; PTC syndrome; Sipple syndrome; FMTC; Thyroid carcinoma, familial medullary; MTC; MEN2B; Neuromata, mucosal, with endocrine tumors; Mucosal neuroma syndrome; Wagenmann-Froboese syndrome

Clinical Features:
The endocrine disorders observed in MEN2 are medullary thyroid carcinoma (MTC) and/or its precursor, C-cell hyperplasia; pheochromocytoma; and parathyroid adenoma or hyperplasia. MEN2 traditionally has been classified into three clinical subtypes: MEN2A, FMTC, and MEN2B. All three subtypes involve high risk for MTC; MEN2A and MEN2B have an increased risk for pheochromocytoma; MEN 2A has an increased risk for parathyroid hyperplasia or adenoma. Although all three subtypes are caused by pathogenic variants in the RET gene, classifying an individual or family by MEN2 subtype is useful for determining prognosis and management.

The clinical diagnosis of MEN2A is made when an individual has two or more specific endocrine tumors: medullary carcinoma of the thyroid (>95%), pheochromocytoma (50%), or parathyroid adenoma/hyperplasia (20-30%). Prophylactic thyroidectomy in childhood is recommended when a RET variant is identified.

FMTC (Familial Medullary Thyroid Carcinoma) is diagnosed in families with four cases of medullary thyroid carcinoma (MTC) in the absence of pheochromocytoma or parathyroid adenoma. The medullary thyroid cancer associated with FMTC is typically later onset and may be subclinical; therefore, in some families RET genetic testing may be necessary to differentiate sporadic medullary thyroid cancer from FMTC.

MEN2B is characterized by multiple mucosal neuromas of the lips, tongue, and conjunctiva. Patients often have a tall, thin, Marfanoid body habitus. Muscle wasting and weakness are a complication. Gastrointestinal symptoms secondary to ganglioneuromas and colonic diverticula are observed. MEN2B is associated with an increased risk of malignancy, including pheochromocytoma (50% of patients) and medullary thyroid carcinoma (100% penetrance).

RET gene variants also are associated with another distinct disorder, Hirschsprung disease (see separate information sheet for clinical information and for GeneDx testing information), and in approximately 10% of isolated pheochromocytoma.

Genetics:
Autosomal dominant; de novo variants are estimated to occur in 5% of MEN2A cases and 50% of MEN2B cases.

Test Methods:
Analysis is performed by bi-directional sequencing of exons 1-20 of the RET gene. 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.

Test Sensitivity:
The largest international study to date identified germline RET variants in 95% of patients with a clinical diagnosis of MEN2A, 87% of patients with FMTC, and 94% of patients with MEN2B.[1] One large study identified a germline RET variant in 35 of 481 (7.3%) of individuals with apparently sporadic MTC2, while other smaller studies have found germline RET variants in 0-22.7% of apparently sporadic MTC cases.[3,4,5]

References:

1. Mulligan, L.M. et al., Genotype-phenotype correlation in multiple endocrine neoplasia type 2: report of the International RET Mutation Consortium. J Intern Med. 238: 343-6, 1995.
2. Elisei, R et al., RET genetic screening in patients with medullary thyroid cancer and their relatives: Experience with 807 individuals at one center. J Clin Endocrinol Metab 92(12)4725-4729, 2007.
3. Heshmati HM, et al. Genetic testing in medullary thyroid carcinoma syndromes: mutation types and clinical significance. Mayo Clin Proc 72(5):430-436, 1997.
4. Wiench M et al. Estimation of risk of inherited medullary thyroid carcinoma in apparent sporadic patients. J Clin Oncol 19(5):1374-1380, 2001.
5. Shirahama S et al. Mutational analysis of the RET proto-oncogene in 71 Japanese patients with medullary thyroid carcinoma. J Hum Genet 43:101-106, 1998.
6. Mulligan, L.M. et al., Specific mutations of the RET proto-oncogene are related to disease phenotype in MEN 2A and FMTC. Nat Genet. 6: 70-4, 1994.
7. Eng, C. et al., Point mutation within the tyrosine kinase domain of the RET-proto-oncogene in multiple endocrine neoplasia type 2B and related sporadic tumors. Hum Mol Genet. 3: 237-41, 1994.
8. Gimm, O. et al., Germline dinucleotide mutation in codon 883 of the RET proto-oncogene in multiple endocrine neoplasia type 2B without codon 918 mutation. J Clin Endocrinol Metab. 82: 3902-4, 1997.
9. Yip, L. et al., Multiple Endocrine Neoplasia Type 2: Evaluation of the Genotype-Phenotype Relationship. Arch Surg. 138: 409-16, 2003.