RET Gene Analysis in Multiple Endocrine Neoplasia 2A and Familial Medullary Thyroid Carcinoma

**Disorder also known as:** MEN2A; Pheochromocytoma and amyloid-producing medullary thyroid carcinoma; PTC syndrome; Sipple syndrome; FMTC; Thyroid carcinoma, familial medullary; MTC

**Clinical Features:**
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.

RET gene variants also are associated with two other distinct disorders, MEN2B and Hirschsprung disease (see separate information sheets for GeneDx testing information), and in approximately 10% of isolated pheochromocytoma. Predisposition to pheochromocytoma is shared by other cancer predisposition syndromes, including Von Hippel Lindau syndrome (VHL gene), Hereditary PGL/PCC syndrome (SDHD, SDHB, SDHC genes), NF1 (NF1 gene) and rarely Carney Complex (PRKAR1A gene). Testing for all of these syndromes, with the exception of NF1, is available at GeneDx.

**Genetics:**
Autosomal dominant; de novo variants occur in 5% of cases

**Test Methods:**
Analysis is performed by bi-directional sequencing of exons 10, 11, 13, and 14 of the RET gene. If no variant is identified in these four exons, sequencing of remainder of the RET gene can be performed upon request. 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:
Germline RET variants have been found in 95% of patients with clinical MEN2A and in ~88% of patients with FMTC.\textsuperscript{1,2} One large study identified a germline RET variant in 35 of 481 (7.3%) of individuals with apparently sporadic MTC\textsuperscript{3}, while other smaller studies have found germline RET variants in 0-22.7% of apparently sporadic MTC cases.\textsuperscript{4,5,6}

References: