

Multiple Endocrine Neoplasia Type 2 (MEN 2): *RET* Proto-oncogene Targeted Mutation Analysis or Sequencing

FOR DIAGNOSTIC AND PRESYMPTOMATIC IDENTIFICATION OF MULTIPLE ENDOCRINE NEOPLASIA TYPE 2 (MEN 2A OR 2B) OR FAMILIAL MEDULLARY THYROID CARCINOMA (FMTC)

Disease Overview

- Multiple endocrine neoplasia type 2 (MEN 2) is classified into three clinically defined subtypes: MEN 2A (60–90 percent of cases), FMTC (5–35 percent of cases), and MEN 2B (~5 percent of cases). Subtype determination is useful for determining prognosis and management.
 - MEN 2A is associated with an increased risk for medullary thyroid carcinoma (MTC) (onset in early adulthood), pheochromocytoma, and parathyroid adenoma/hyperplasia.
 - MEN 2B is associated with an increased risk for MTC (onset in childhood), pheochromocytoma, mucosal neuromas, gastrointestinal ganglioneuromatosis, eye abnormalities including corneal nerve thickening, and skeletal findings, including marfanoid body habitus.
 - FMTC carries a high risk for development of MTC (adult onset).
- Between 1–7 percent of individuals with apparently sporadic MTC and an estimated 5 percent of individuals with sporadic, nonsyndromic pheochromocytoma may carry a causative germline mutation in the *RET* gene.
- MTC has nearly a 100 percent penetrance in MEN 2 syndromes, but the aggressiveness and clinical course may differ between the subtypes.
- Because chemotherapy and radiation are less effective against MTC, prophylactic thyroidectomy is the primary preventative measure for patients with *RET* germline mutations.
- Timing of prophylactic thyroidectomy and risk prediction for aggressive MTC may be guided by the codon position of the *RET* mutation.

Epidemiology

- Prevalence of MEN 2 is approximately 1 in 30,000.
- Medullary thyroid carcinoma (MTC) accounts for approximately 5–10 percent of all diagnosed thyroid carcinomas; about 25 percent of these cases are believed to be familial.

Genetics

- Inheritance of the MEN 2 syndromes is autosomal dominant.
- Approximately 5 percent of MEN 2A and 50 percent of MEN 2B causing mutations are de novo.
- The *RET* proto-oncogene is the only gene known to be associated with MEN 2.
- Approximately 95 percent of families with MEN 2A have a *RET* mutation in exon 10 or 11.
- About 85 percent of FMTC is caused by a *RET* mutation in exon 10 or 11, although rare mutations in exons 13, 14, or 15 can be causative.
- MEN 2B is caused by a point mutation at codon 918 in exon 16 in 95 percent of cases and at codon 883 in exon 15 in 3–4 percent; rarely, the phenotype results from a mutation in other exons of the *RET* gene.
- ARUP maintains the MEN 2 (*RET*) database, a repository for MEN 2-associated *RET* sequence variation and a reference for genotype/phenotype correlations (http://www.arup.utah.edu/database/MEN2/MEN2_welcome.php).

Indications for Ordering

- MEN 2: *RET* Sequencing Exons 10, 11, 13–16.
 - To determine if a *RET* mutation is present in an individual with MTC or pheochromocytoma.
 - To identify the causative mutation for MEN 2A or FMTC in an affected individual.
 - To identify the causative mutation for an individual with MEN 2B after a negative test for the M918T and A883F *RET* mutations.
- MEN 2B: *RET* Gene Mutation Analysis (M918T & A883F)
 - To confirm a clinical diagnosis of MEN 2B.
 - Pre-symptomatic testing for at-risk family members when a MEN 2B mutation (M918T or A883F) has been previously identified in an affected relative.

Interpretation

- MEN 2: *RET* Sequencing Exons 10, 11, 13–16.
 - Positive: A *RET* proto-oncogene mutation was identified; therefore, this individual is predicted to be affected with MEN 2.
 - Negative: No mutations were identified in exons 10, 11, and 13–16 of the *RET* proto-oncogene. Five percent of *RET* mutations causing MEN 2A and 12 percent of mutations causing FMTC will not be identified by this assay.
- MEN 2B: *RET* Gene Mutation Analysis (M918T & A883F)
 - Positive: A mutation in the *RET* proto-oncogene (M918T or A883F) was identified; therefore, this individual is predicted to be affected with MEN 2B.
 - Negative: No mutations were identified. This result does not exclude the possibility of MEN 2B resulting from a *RET* mutation not identified by this assay.

Limitations

- MEN 2: *RET* Sequencing Exons 10, 11, 13–16
 - Sequencing of exons 10, 11, 13, 14, 15, and 16 of the *RET* gene will detect approximately 95 percent, 88 percent, and 98 percent of mutations causative for MEN 2A, FMTC, and MEN 2B, respectively. Mutations in other *RET* exons, introns, or regulatory regions will not be identified.
- MEN 2B: *RET* Gene Mutation Analysis (M918T & A883F)
 - Detects approximately 98 percent of mutations causative for MEN 2B; *RET* mutations other than M918T and A883F will not be identified.

Methodology

- MEN 2: *RET* Sequencing Exons 10, 11, 13–16
 - Exons 10, 11, 13, 14, 15, and 16 of the *RET* proto-oncogene are bidirectionally sequenced.
 - The analytic specificity and sensitivity is 99 percent.

- MEN 2B: *RET* Gene Mutation Analysis (M918T & A883F)
 - MEN 2B mutations, c.2753T>C (p.M918T) and c.2647_2648delinsTT (p.A883F), in the *RET* gene are analyzed by polymerase chain reaction (PCR) followed by unlabeled probe and melting-curve analysis.
 - The analytic specificity and sensitivity are 99 percent.

Related Test

Custom PCR and Sequencing (0050358): Testing of at-risk relatives once the familial *RET* mutation, other than M918T or A883F, has been identified in an affected relative.

References

1. de Groot, et al. RET as a diagnostic and therapeutic target in sporadic and hereditary endocrine tumors. *Endocr Rev* 2006; 27:535–60.
2. Kouvaraki, et al. RET proto-oncogene: a review and update of Genotype-phenotype correlations in hereditary medullary thyroid cancer and associated endocrine tumors. *Thyroid* 2005; 15:531–44.
3. Eng C, et al. The relationship between specific RET proto-oncogene mutations and disease phenotype in multiple endocrine neoplasia type 2. International *RET* mutation consortium analysis. *JAMA* 1996; 276:1575–9.
4. Brandi, et al. Consensus: guidelines for diagnosis and therapy of MEN type 1 and type 2. *J Clin Endocrinol Metab* 2001; 86:5658–71.

Test Information

0051390
0051492

Multiple Endocrine Neoplasia Type 2 (MEN2), *RET* Gene Mutations by Sequencing
Multiple Endocrine Neoplasia Type 2B (MEN2B), *RET* Gene M918T & A883F Mutations

For specific collection, transport, and testing information, refer to the ARUP Web site at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.