Multiple Endocrine Neoplasia Type 2, RET Sequencing

Last Literature Review: December 2021 Last Update: November 2023

Multiple endocrine neoplasia type 2 (MEN2) is a hereditary syndrome caused by pathogenic variants in the *RET* gene. MEN2 is classified into subtypes MEN2A, MEN2B, and familial medullary thyroid cancer (FMTC). All MEN2 subtypes have an increased risk of medullary thyroid cancer (MTC). Additionally, MEN2A is associated with benign parathyroid adenomas/hyperplasia and pheochromocytoma (PCC). MEN2B is associated with more aggressive MTC that can occur during childhood, PCC, neuromas, eye anomalies, and distinctive physical features. FMTC is considered a variant of MEN2A and is characterized as multiple cases of MTC in a family, typically without the presence of PCC or hyperparathryoidism.

Featured ARUP Testing

Multiple Endocrine Neoplasia Type 2 (MEN2), RET Sequencing 3004572

Method: Massively Parallel Sequencing

Use for diagnostic or predictive testing for multiple endocrine neoplasia type 2 (MEN2) syndrome, caused by pathogenic variants in the *RET* gene

If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information.

Disease Overview

Epidemiology

- Approximately 1 in 35,000 individuals have MEN2[1]
- Approximately 25-30% of all individuals with MTC have a germline *RET* pathogenic variant[2]

Symptoms

Clinical Characteristics by MEN2 Subtype

Subtype	Proportion of MEN2 Cases	Presence of MTC	Presence of PCC	Presence of Parathyroid Disease
MEN2A	70-80%	95%	50%	20-30%
MEN2B[a]	~5%	100%	50%	Uncommon
FMTC[b]	10-20%	100%	0%	0%

[a]Additional findings for the MEN2B subtype may include mucosal neuromas, gastrointestinal ganglioneuromatosis, medullated corneal nerve fibers, distinctive facies with enlarged lips, or marfanoid habitus.

[b]The FMTC subtype may be part of an MEN2A disease spectrum, with decreased penetrance of PCC and hyperparathryoidism.[3]

Sources: Eng, 2019[2]; Raue, 2012[4]

Genetics

Gene

RET (NM_020975)

Inheritance

Autosomal dominant

De novo Pathogenic Variants

- 5% of MEN2A[5]
- 50% of MEN2B[6]

Test Description

Clinical Sensitivity

- MEN2A: >95%[2,7,8]
- MEN2B: >98%[2,7,9]
- FMTC: >88-95%[2,7,8]

Analytic Sensitivity/Specificity

For massively parallel sequencing:

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region (%)	Analytic Specificity (NPA) (%)
SNVs	>99 (96.9-99.4)	>99.9
Deletions 1-10 bp[b]	93.8 (84.3-98.2)	>99.9
Insertions 1-10 bp[b]	94.8 (86.8-98.5)	>99.9

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

[b]Variants greater than 10 bp may be detected, but the analytical sensitivity may be reduced.

bp, base pairs; NPA, negative percent agreement; PPA, positive percent agreement; SNVs, single nucleotide variants

Results

Result	Variant(s) Detected	Clinical Significance
Positive	One *RET* pathogenic variant detected	Consistent with a diagnosis of MEN2; MEN2 subtype depends on clinical features and specific variant identified
Negative	No *RET* pathogenic variants detected	Diagnosis of MEN2A, MEN2B, or FMTC is unlikely but not excluded
Inconclusive	*RET* variant of unknown clinical significance detected	Uncertain; it is unknown whether variant is benign or pathogenic

Limitations

- A negative result does not exclude a diagnosis of MEN2.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of the *RET* gene
  - Regulatory region and deep intronic variants
  - Large deletions/duplications in the *RET* gene
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Noncoding transcripts
  - Low-level somatic variants
  - Certain other variants due to technical limitations in the presence of pseudogenes or repetitive/homologous regions

References

1. DeLellis RA, Lloyd RV, Heitz PU. Pathology and genetics: tumours of the endocrine organs. *World Health Organization Classification of Tumours Series*. Vol 8. International Agency for Research on Cancer; 2004.

2. Eng C. Multiple endocrine neoplasia type 2. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. *GeneReviews*. University of Washington, Seattle. Last update Aug 2019; accessed Dec 2022.

3. Wells SA, Asa SL, Dralle H, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. *Thyroid*. 2015;25(6):567-610.

4. Raue F, Frank-Raue K. Genotype-phenotype correlation in multiple endocrine neoplasia type 2. *Clinics (Sao Paulo)*. 2012;67 Suppl 1(Suppl 1):69-75.

5. Schuffenecker I, Ginet N, Goldgar D, et al. Prevalence and parental origin of de novo RET mutations in multiple endocrine neoplasia type 2A and familial medullary thyroid carcinoma. *Am J Hum Genet*. 1997;60(1):233-237.

6. Carlson KM, Bracamontes J, Jackson CE, et al. Parent-of-origin effects in multiple endocrine neoplasia type 2B. *Am J Hum Genet*. 1994;55(6):1076-1082.

7. Kloos RT, Eng C, Evans DB, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. *Thyroid*. 2009;19(6):565-612.

8. Mulligan LM, Marsh DJ, Robinson BG, et al. Genotype-phenotype correlation in multiple endocrine neoplasia type 2: report of the International RET Mutation Consortium. *J Intern Med*. 1995;238(4):343-346.

9. Moline J, Eng C. Multiple endocrine neoplasia type 2: an overview. *Genet Med*. 2011;13(9):755-764.

Additional Resources

Mathiesen JS, Effraimidis G, Rossing M, et al. Multiple endocrine neoplasia type 2: A reveiw. *Semin Cancer Biol*. 2021:S1044-579X(21)00085-7.

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: thyroid carcinoma. Version 3.2021. Updated Oct 2021; accessed Nov 2021.

Related Information

Hereditary Cancer Germline Genetic Testing
Multiple Endocrine Neoplasias - MEN
Pheochromocytoma - Paraganglioma
Thyroid Cancer

ARUP Laboratories is a nonprofit enterprise of the University of Utah and its Department of Pathology. 500 Chipeta Way, Salt Lake City, UT 84108
(800) 522-2787 | (801) 583-2787 | aruplab.com | arupconsult.com