Multiple Endocrine Neoplasia Type 2

Multiple endocrine neoplasia type 2 (MEN2) is a rare hereditary syndrome caused by pathogenic variants in the *RET* gene. MEN2 can be further classified into subtypes MEN2A, MEN2B, and familial medullary thyroid cancer (FMTC). All MEN2 types have an increased risk of medullary thyroid cancer (MTC). MEN2A (70-80% of MEN2 cases) is also associated with benign parathyroid adenomas, adrenal gland tumors (pheochromocytoma), and nerve cell tumors (ganglioneuromatosis). MEN2B is associated with more aggressive MTC that can occur during childhood and with benign neuromas often found in the mucous membranes. Pheochromocytomas develop in approximately 50% of individuals with MEN2B. FMTC is considered a variant of MEN2A and is characterized as multiple cases (often four or more) of MTC in a family, without the presence of pheochromocytomas or hyperparathryoidism.

Tests to Consider

Multiple Endocrine Neoplasia Type 2 (MEN2), RET Gene Mutations by Sequencing (Temporary Referral as of 12/07/20) 0051390

Method: Polymerase Chain Reaction/Sequencing

Diagnostic test for MEN2

Familial Mutation, Targeted Sequencing 2001961

Method: Polymerase Chain Reaction/Sequencing

Useful when a pathogenic familial variant identifiable by sequencing is known

Related Test

Hereditary Cancer Panel, Sequencing and Deletion/Duplication 2012032

Method: Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray

Confirm diagnosis of a hereditary cancer syndrome with personal or family history consistent with features of more than one cancer syndrome

Disease Overview

Prevalence

1/35,000[1]

Symptoms

MEN2 has three defined subtypes[2]

- MEN2A: 70-80% of cases
  - Early onset MTC: typically prior to 35 years
  - Pheochromocytoma
  - Parathyroid adenoma/hyperplasia
- MEN2B: ~5% of cases
  - Early onset MTC: childhood
  - Pheochromocytoma
  - Mucosal abnormalities
  - Gastrointestinal ganglioneuromatosis
  - Eye abnormalities: eg, corneal nerve thickening
  - Skeletal abnormalities: eg, marfanoid body
- FMTC: 10-20% of cases
  - Associated with MTC only
  - FMTC is considered a variant of MEN2A and is characterized as multiple cases (often four or more) of MTC in a family, without the presence pheochromocytomas or hyperparathryoidism

Genetics

Gene

RET

Inheritance

Autosomal dominant

Penetrance

- Clinical course differs between subtypes
- Penetrance of MTC[3]
  - 95% for MEN2A
  - Nearly 100% for FMTC and MEN2B

De novo Pathogenic Variants

- 5% of MEN2A[4]
- 50% of MEN2B pathogenic variants[5]

Test Interpretation

Sensitivity/Specificity

- Clinical sensitivity
  - MEN2A: 95%[6,7]
  - MEN2B: 98%[6,8]
  - FMTC: 88%[6,7]
- Analytical sensitivity/specificity: 99%

Results

- Positive: one *RET* pathogenic variant detected
  - Confirms diagnosis and etiology
- Negative: no *RET* pathogenic variants detected
  - MEN2A, MEN2B, or FMTC is unlikely, but not excluded
- Inconclusive: *RET* variant detected, but whether variant is benign or pathogenic is unknown

Limitations

- Not evaluated
  - Regulatory region variants
  - Deep intronic variants
  - Large deletions/duplications
  - *RET* exons other than 5, 8, 10, 11, 13-16
- Diagnostic errors can occur due to rare sequence variations

References

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Related Information

Multiple Endocrine Neoplasias - MEN

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