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 hyperparathyroidism.

DISEASE OVERVIEW

Prevalence

1/35,000

Symptoms

MEN2 has three defined subtypes¹

- 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 hyperparathyroidism

GENETICS

Gene

RET

Inheritance

Autosomal dominant

Penetrance

- Clinical course differs between subtypes
- Penetrance of MTC²
  - 95% for MEN2A
  - Nearly 100% for FMTC and MEN2B
De novo Pathogenic Variants
- 5% of MEN2A
- 50% of MEN2B pathogenic variants

TEST INTERPRETATION

Sensitivity/Specificity
- Clinical sensitivity
  - MEN2A: 95%
  - MEN2B: 98%
  - FMTC: 88%
- 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

RELATED INFORMATION
Multiple Endocrine Neoplasias - MEN