Multiple Endocrine Neoplasia Type 2, RET Sequencing

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 hyperparathyroidism.

Disease Overview

Epidemiology

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

Symptoms

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Proportion of MEN2 Cases</th>
<th>Presence of MTC</th>
<th>Presence of PCC</th>
<th>Presence of Parathyroid Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN2A</td>
<td>70-80%</td>
<td>95%</td>
<td>50%</td>
<td>20-30%</td>
</tr>
<tr>
<td>MEN2B</td>
<td>~5%</td>
<td>100%</td>
<td>50%</td>
<td>Uncommon</td>
</tr>
<tr>
<td>FMTC</td>
<td>10-20%</td>
<td>100%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

| Additional findings for the MEN2B subtype may include mucosal neuromas, gastrointestinal ganglioneuromatosis, medullated corneal nerve fibers, distinctive facies with enlarged lips, or marfanoid habitus. |
| The FMTC subtype may be part of an MEN2A disease spectrum, with decreased penetrance of PCC and hyperparathyroidism. |

Sources: Eng, 2019; Raue, 2012

Genetics

Gene

RET (NM_020975)

Tests to Consider

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

Familial Targeted Sequencing 3005867
Method: Massively Parallel Sequencing

- Testing for a known familial sequence variant by sequencing gene of interest. A copy of the family member’s test result documenting the familial gene variant is REQUIRED.
- To determine if the variant(s) of interest are detectable by this assay, contact an ARUP genetic counselor at 800-242-2787.

Related Test

Hereditary Cancer Panel, Sequencing and Deletion/Duplication 2012032
Method: Massively Parallel Sequencing/Sequencing/Multiplex Ligation-dependent Probe Amplification

Use to confirm a diagnosis of a hereditary cancer syndrome with personal or family history consistent with features of more than one cancer syndrome
Inheritance
Autosomal dominant

De novo Pathogenic Variants

- 5% of MEN2A
- 50% of MEN2B

Test Description

Clinical Sensitivity

- MEN2A: >95%\(^2,7,8\)
- MEN2B: >98%\(^2,7,9\)
- FMTC: >88-95%\(^2,7,8\)

Analytical Sensitivity/Specificity

For massively parallel sequencing:

<table>
<thead>
<tr>
<th>Variant Class</th>
<th>Analytical Sensitivity (PPA) Estimate(^a) (%) and 95% Credibility Region (%)</th>
<th>Analytical Specificity (NPA) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNVs</td>
<td>&gt;99 (96.9-99.4)</td>
<td>&gt;99.9</td>
</tr>
<tr>
<td>Deletions 1-10 bp(^b)</td>
<td>93.8 (84.3-98.2)</td>
<td>&gt;99.9</td>
</tr>
<tr>
<td>Insertions 1-10 bp(^b)</td>
<td>94.8 (86.8-98.5)</td>
<td>&gt;99.9</td>
</tr>
</tbody>
</table>

\(^a\)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

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

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 \textit{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


Additional Resources


Related Information

\textbf{Hereditary Cancer Germline Genetic Testing}
- \textit{Multiple Endocrine Neoplasias - MEN}
- \textit{Pheochromocytoma - Paraganglioma}
- \textit{Thyroid Cancer}