Multiple Endocrine Neoplasia Type 1 (MEN1) Sequencing and Deletion/Duplication

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Multiple endocrine neoplasia type 1 (MEN1) is a hereditary syndrome caused by pathogenic variants in the *MEN1* gene and is associated with a combination of endocrine and nonendocrine tumors. In MEN1, tumors are most often found in the parathyroid gland, islet cells of the pancreas, and the pituitary gland. Tumors can also form in other endocrine glands and the digestive tract. The majority of MEN1 tumors are benign, but tumors of the gastroenteropancreatic tract and thymic carcinoids may be malignant. Endocrine tumors cause an increased hormone production based on tumor type, resulting in a wide range of symptoms.

Featured ARUP Testing

Multiple Endocrine Neoplasia Type 1 (MEN1) Sequencing and Deletion/Duplication 3004437

Method: Massively Parallel Sequencing

Preferred initial test to confirm diagnosis of MEN1

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

Incidence

1/10,000–1/100,000[1]

Symptoms

MEN1 can include development of multiple endocrine and nonendocrine tumors.[1]

- Common endocrine tumors:
  - Parathyroid
  - Gastroenteropancreatic tract (gastrinoma, insulinoma, glucagonoma, pancreatic islet cell tumor)
  - Pituitary (prolactinoma)
  - Gastrinoma
  - Carcinoid (thymic, bronchial, gastric)
  - Adrenal
  - Medullary carcinoma of the thyroid
- Nonendocrine tumors:
  - Facial angiofibromas
  - Collagenomas
  - Lipomas
  - Meningiomas
  - Ependymomas
  - Leiomyomas

Genetics

Gene

MEN1 (NM_130799)

Variants

MEN1 is caused by pathogenic germline variants in the *MEN1* tumor suppressor gene. Approximately 10% of these variants are de novo variants.[1]

Inheritance

Autosomal dominant

Penetrance

The penetrance for all clinical features of MEN1 syndrome is approximately 50% by 20 years of age and is >95% by 40 years of age.[2,3,4]

Test Interpretation

Clinical Sensitivity

A pathogenic *MEN1* variant is identified in 80-90% of individuals who meet clinical criteria for MEN1 syndrome and have a family history of related cancers. Approximately 4% of pathogenic variants are large deletions or duplications.[1]

Analytic Sensitivity

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region (%)	Analytic Specificity (NPA) (%)
SNVs	>99 (96.9 to 99.4)	>99.9
Deletions 1-10 bp[b]	93.8 (84.3 to 98.2)	>99.9
Insertions 1-10 bp[b]	94.8 (86.8 to 98.5)	>99.9
Exon-level[c] deletions	97.8 (90.3 to 99.8) [2 exons or larger] 62.5 (38.3 to 82.6) [single exon]	>99.9
Exon-level[c] duplications	83.3 (56.4 to 96.4) [3 exons or larger]	>99.9

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived. These values do not apply to testing performed by multiplex ligation-dependent probe amplification (MLPA).

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

[c]In most cases, a single exon deletion or duplication is less than 450 bp and 3 exons span a genomic region larger than 700 bp.

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

Methodology

This test is performed using the following sequence of steps:

- Selected genomic regions, primarily coding exons and exon-intron boundaries, from the targeted genes are isolated from extracted genomic DNA using a probe-based hybrid capture enrichment workflow.
- Enriched DNA is sequenced by massively parallel sequencing (MPS; also known as NGS) followed by paired-end read alignment and variant calling using a custom bioinformatics pipeline.
- Sanger sequencing is performed as necessary to fill in regions of low coverage and, in certain situations, to confirm variant calls.
- The pipeline includes an algorithm for detection of large (single exon-level or larger) deletions and duplications.
- Large deletion/duplication calls made using MPS are confirmed by an orthogonal exon-level microarray when sample quality and technical conditions allow.

Results

Result	Variant(s) Detected	Clinical Significance
Positive	One pathogenic variant detected in *MEN1*	Confirms diagnosis and etiology of MEN1
Negative	No pathogenic variants detected in *MEN1*	Reduces the likelihood, but does not exclude, a diagnosis of MEN1

Limitations

- A negative result does not exclude a diagnosis of MEN1.
- 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 *MEN1*
- Regulatory region and deep intronic variants
- Breakpoints of large deletions/duplications

- The following may not be detected:
  - Deletions, duplications, or insertions of any size by massively parallel sequencing
  - Large duplications less than three exons in size
  - Noncoding transcripts
  - Certain other variants, due to technical limitations in the presence of pseudogenes or repetitive/homologous regions
  - Low-level somatic variants

References

1. Giusti F, Marini F, Brandi ML. Multiple endocrine neoplasia type 1. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews, University of Washington; 1993-2022. [Last update: Mar 2022; Accessed: Dec 2022]

2. Online Mendelian Inheritance in Man. Multiple endocrine neoplasia type 1. [Edited: Feb 2017; Accessed: Mar 2020]

3. Bassett JH, Forbes SA, Pannett AA, et al. Characterization of mutations in patients with multiple endocrine neoplasia type 1. *Am J Hum Genet*. 1998;62(2):232-244.

4. Carroll RW. Multiple endocrine neoplasia type 1 (MEN1). *Asia Pac J Clin Oncol*. 2013;9(4):297-309.

Related Information

Multiple Endocrine Neoplasias - MEN

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