Multiple Endocrine Neoplasia Type 2: RET Gene Sequencing

Condition Description

Multiple endocrine neoplasia type 2 (MEN2) is an autosomal dominant disorder classified into three subtypes: MEN2A, FMTC (familial medullary thyroid carcinoma), and MEN2B. All three subtypes carry a high risk for development of medullary carcinoma of the thyroid (MTC). MEN2A and MEN2B carry an increased risk for pheochromocytoma. MEN2A carries an increased risk for parathyroid adenoma or hyperplasia. Additional features in MEN2B include mucosal neuromas of the lips and tongue, distinctive facies with enlarged lips, ganglioneuromatosis of the gastrointestinal tract, and an asthenic “Marfanoid” body habitus. The onset of MTC is typically in early childhood in MEN2B, early adulthood in MEN2A, and middle age in FMTC.

MEN2A is diagnosed clinically by the occurrence of two or more specific endocrine tumors [medullary carcinoma of the thyroid (MTC), pheochromocytoma, or parathyroid adenoma/hyperplasia] in a single individual or in close relatives.

Familial medullary thyroid carcinoma (FMTC) is diagnosed in families with four cases of MTC in the absence of pheochromocytoma or parathyroid adenoma/hyperplasia.

MEN 2B is diagnosed clinically by the presence of mucosal neuromas of the lips and tongue, as well as medullated corneal nerve fibers, distinctive facies with enlarged lips, an asthenic “Marfanoid” body habitus, and MTC.

RET (10q11.2) is the only gene known to be associated with MEN type 2. Molecular genetic testing of the RET gene identifies disease-causing mutations in 95% of individuals with MEN2A and MEN2B and in about 88% of families with FMTC. All MEN2 subtypes are inherited in an autosomal dominant manner. The probability of a de novo gene mutation is 5% or less in index cases with MEN2A and 50% in index cases with MEN2B.

Hirschsprung disease (HSCR) is a disorder of the enteric plexus of the colon that typically results in enlargement of the bowel and constipation or obstipation in neonates. Overall, about 20%-40% of all cases of HSCR are caused by germline mutations in the RET and are designated HSCR1. However, most of the mutations that cause HSCR1 occur outside of the codons that are mutated in MEN2A.

For patients with suspected MEN2 or HSCR, sequence analysis is recommended as the first step in mutation identification. For HSCR patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate. Deletion/duplication analysis is available for MEN2 patients in whom mutations are not identified by full gene sequencing, although no large rearrangements of the RET gene causative of MEN2 have been reported.

Click here for the GeneTests summary on this condition.

Genes

RET

Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of MEN2
- Individuals at-risk for MEN2 due to family history

Methodology

Next Generation Sequencing: In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

Detection

Clinical Sensitivity: 95% in individuals with MEN2A and MEN2B and 88% in individuals FMTC. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's biochemical phenotype.

Analytical Sensitivity: ~99%

Specimen Requirements

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood
Type: Whole Blood

Specimen Requirements:

In EDTA (purple top) tube:
Infants (2 years): 3-5 ml
Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

Type: Saliva

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

Special Instructions

Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed.

Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of EGL Genetics, please submit a copy of the sequencing report with the test requisition.

Related Tests

- Deletion/duplication analysis of the RET gene by CGH array is available for those individuals in whom sequence analysis is negative (VU).
- Custom diagnostic mutation analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available to individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.