Multiple Endocrine Neoplasia Type 2: RET Gene Deletion/Duplication

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.

Click here for the GeneTests summary on this condition.

Genes

RET

Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of MEN2 in individuals who have tested negative for sequence analysis
- Individuals at-risk for MEN2 due to family history who have tested negative for sequence analysis

Methodology

DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region. Please note that a “backbone” of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-target copy number variants causative of disease may be identified that may or may not be related to the patient's phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.

Detection

Detection is limited to duplications and deletions. The CGH array will not detect point or intronic mutations. Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

Specimen Requirements

Disclaimer: This information is confidential and subject to change without notice. It may not be reproduced in whole or part unless authorized in writing by an authorized EGL representative.
Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

**Type: Whole Blood**

Specimen Requirements:

In EDTA (purple top) or ACD (yellow 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**

- Sequencing analysis of the RET gene is available (VT) and is required before deletion/duplication 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.