

FAMILIAL
MEDULLARY
THYROID
CARCINOMA

Orderable – E-order/Requisition

Turnaround Time: 3 months

Alternate Name(s):

FMTC

Specimen:

Whole blood-2 x 4 mL Lavender EDTA top Vacutainer tube

Collection Information:

Blood samples must be maintained at room temperature.

Reference Ranges:

See report

Interpretive Comments:

Multiple endocrine neoplasia type 2 (MEN2) is an autosomal dominant form of inheritable cancer affecting tissues derived from the neural ectoderm. It is characterised by medullary thyroid carcinoma and pheochromocytoma. Co-inheritance of activating mis-sense mutations in the RET oncogene with FMTC, MEN 2A and MEN 2B has been demonstrated. It has been reported that specific RET mutations can predict both phenotypic expression and tumour grade in patients with MEN 2 and the vast majority of RET mutations can be detected by direct sequence analysis of RET exons 8, 10, 11, 13, 14, 15 and 16. *MEN2A Approx. 95% of families with MEN 2A have a RET mutation in exon 10 or 11 (PMID:7907913, PMID:7595170). Mutations of codon 634 Cys occur in about 85% of families; mutation of cysteine residues at codons 609, 611, 618, & 620 together account for the rest of identifiable mutations in exons 10 and 11. Other rare mutations, including codon 804 alterations, have been reported in a few cases (PMID:7915822, PMID:9097963, PMID:9452064, PMID:15386323) *FMTC Approx. 88% of families with FMTC have an identifiable RET mutation (PMID:7907913, PMID:7595170). These mutations occur at one of the five cysteine residues (codons 609, 611, 618, 620 & 634) with mutations of codons 618,



Laboratory:

Molecular Diagnostics Lab



Requisition:

[MOLECULAR DIAGNOSTIC REQUISITION](#)



Method of Analysis:

All coding exons and 20 bp of flanking intronic sequence are enriched using an LHSC custom targeted hybridization protocol (Roche Nimblegen), followed by high throughput sequencing (Illumina). Sequence variants and copy number changes are assessed and interpreted using clinically validated algorithms and commercial software (SoftGenetics: Nextgene, Geneticist Assistant, Mutation Surveyor; and Alamut Visual). All exons have >300x mean read depth coverage, with a minimum 100x coverage at a single nucleotide resolution. This assay meets the sensitivity and specificity of combined Sanger sequencing and

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MLPA copy number analysis. All variants interpreted as either ACMG category 1, 2, or 3 (pathogenic, likely pathogenic, VUS; PMID: 25741868) are confirmed using Sanger sequencing, MLPA, or other assays. ACMG category 4 and 5 variants (likely benign, benign) are not reported, but are available upon request. This assay has been validated at a level of sensitivity equivalent to the Sanger sequencing and standard copy number analysis (>99%; PMID: 27376475).

**Test Schedule:**

As required,
Monday to Friday 0800-
1600 hours

620 & 634 each accounting for 25%-35% of mutations. Mutations in exons 13 & 14 (at codons 768 & 804) appear to account for a small percent of mutations in families with FMTC (PMID:7845675, PMID:9111992, PMID:10876191, PMID:11114642). Mutations in codons 533, 630, 631, 790, 791, 844 & 891 (exons 8, 11, 13, 14 & 15) have also been identified in a few families (PMID:9398735, PMID:9506724, PMID:10024437, PMID:11849247, PMID:14602786).

Comments:

*FMTC Approx. 88% of families with FMTC have an identifiable RET mutation (PMID:7907913, PMID:7595170). These mutations occur at one of the five cysteine residues (codons 609, 611, 618, 620 & 634) with mutations of codons 618, 620 & 634 each accounting for 25%-35% of mutations. Mutations in exons 13 & 14 (at codons 768 & 804) appear to account for a small percent of mutations in families with FMTC (PMID:7845675, PMID:9111992, PMID:10876191, PMID:11114642). Mutations in codons 533, 630, 631, 790, 791, 844 & 891 (exons 8, 11, 13, 14 & 15) have also been identified in a few families (PMID:9398735, PMID:9506724, PMID:10024437, PMID:11849247, PMID:14602786).

Critical Information Required:

Please note that these samples will be subjected to direct mutational analysis. As this is an inheritable disorder, a family pedigree will be required.

Storage and Shipment:

Must be received within 5 days of collection, shipped at room temperature by courier/overnight delivery.