Assay Summary

Marfan and Marfan-related Panel (FBN1, TGFBR2, TGFBR1 Genes)

Marfan Syndrome, Familial Ectopia Lentis, Loeys-Dietz syndrome and Familial Aortic Aneurysm

Synopsis

Marfan syndrome is a systemic disorder of connective tissue with a high degree of clinical variability. Cardinal manifestations involve the cardiovascular, musculoskeletal, ocular, and central nervous systems. Of particular concern is the risk for the development of a life threatening, aortic aneurysm or dissection. The syndrome shows autosomal dominant inheritance (only one copy of a mutation is necessary for expression of disease) and complete penetrance, but is notable for variability in the age of onset, tissue distribution, and severity of clinical manifestations, both between and within affected families. Because mutations are heterogeneous and approximately 30% of cases are due to de novo mutations of FBN1, direct testing often requires complete gene analysis. Mutations in the FBN1 gene are detected in approximately 80% and 40% of patients that meet and do not meet Ghent diagnostic criteria for MS, respectively. Mutations in fibrillin-1 (FBN1) are the primary cause of Marfan, but can also be found in other related conditions such as familial ectopia lentis, and certain inherited forms of aortic aneurysm.

Mutations in TGFBR1 and TGFBR2 cause Loeys-Dietz syndrome (LDS), a syndrome involving aortic aneurysms and/or dissection and skeletal findings, with features overlapping Marfan syndrome1,2. LDS may also include craniofacial findings of hypertelorism, bifid uvula and/or cleft palate1,2. Approximately 20% and 70% of LDS has been attributed to mutations in TGFBR1 and TGFBR2 genes, respectively (either sequence variants or deletion/duplications)3. While there are some overlapping features between Marfan and LDS, ectopia lentis seems to be a very rare finding in individuals with TGFBR mutations, and LDS patients often have craniofacial abnormalities such as hypertelorism, and bifid uvula.

FBN1 large deletions are found in ~2% of Marfan syndrome cases7-10. Large deletions of TGFBR2 or TGFBR1 have also been reported, although they are less commonly seen and may be associated with distinct clinical presentations11-12.

Indications for testing

Individuals with a diagnosis or suspected diagnosis of Marfan syndrome, Loeys-Dietz syndrome, or Marfan-like phenotype including familial ectopic lentis, and familial aortic aneurysm. Once a specific mutation is known in a family, presymptomatic testing for appropriate family members can be performed.

Methodology

Sequence analysis: Coding exons and associated intron junctions are captured and enriched using custom Agilent SureSelect technology. Next-generation sequencing is performed on Illumina MiSeq. Additional Sanger sequencing is performed for any regions with insufficient depth of coverage or for verification of suspect variant calls. Targeted testing for known familial mutation is performed by Sanger sequencing.

Large deletion/duplication analysis: SALSA MLPA (Multiplex Ligation-dependant Probe amplification) technology is used to detect large (one or more exons) deletions/duplications in the FBN1, TGFBR2, and TGFBR1 genes.
**Performance/Limitations**

Mutations in the FBN1 gene are detected in approximately 80% and 40% of patients that meet and do not meet Ghent diagnostic criteria for MS, respectively. For patients presenting with a diagnosis of Loeys-Dietz syndrome, the detection rates range from 100% to 30% for Type I and II respectively. This method will not detect mutations located in regions of the genes that are not analyzed (non-coding exon sequences, intron sequences other than the splice junctions, and upstream and downstream sequences). The method also will not detect gross genetic alterations including inversions. Some sequence alterations that may be detected (such as those causing missense or synonymous changes) will be of unknown clinical significance. The MLPA method is designed to detect deletions of one or more exons of the FBN1 gene. However, mutations and/or polymorphisms very close to the probe ligation site may also result in a reduced relative peak area. Therefore, apparent deletions detected by a single probe will be confirmed by a second method whenever possible. Interpretation of test results should be in the context of the patient's ethnicity, clinical and family histories, and other laboratory test results.

**Specimen Requirements**

Blood samples: 2 tubes with a total of 6 ccs in ACD (yellow top) or EDTA (lavender top) tubes. Keep at ambient temperature and ship by overnight courier. Samples must be received in our laboratory within 72 hours of draw. 

**Note:**

i) for infants, a minimum of 3 ccs is sufficient.

ii) we accept DNA; at least 10 micrograms is required.

**Test Request Form (TRF)**

a) A completed CMDL TRF is required for each specimen. Please submit the completed TRF with the specimen. Complete testing and billing information must be provided before the specimen is processed.

b) Marfan Patient Information Form: Include a completed Marfan Patient Information.

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<th>Order Codes</th>
<th>CPT Codes</th>
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**References**


NOTE: This test is performed pursuant to a license agreement with Roche Molecular Systems, Inc.