

Assay Summary

Lamin A/C (LMNA) Gene Mutation Analysis

Emery-Dreifuss Muscular Dystrophy (Autosomal), Limb-Girdle Muscular Dystrophy (Type 1B), Dilated Cardiomyopathy, Charcot-Marie-Tooth Neuropathy Type 2, Familial Partial Lipodystrophy, Dunnigan Type, Hutchinson-Gilford Progeria Syndrome, Atypical Werner Syndrome, Mandibuloacral Dysplasia

Synopsis

Germline mutations in the LMNA gene encoding lamins A and C have been found in patients with Emery-Dreifuss muscular dystrophy (autosomal dominant, autosomal recessive, and sporadic forms of the disease¹⁻⁴), in limb-girdle muscular dystrophy (Type 1B)⁵, in Charcot-Marie-Tooth disorder type 2⁶, and in Dunnigan type familial partial lipodystrophy⁷. Mutations in the LMNA gene have also been detected in patients with Hutchinson-Gilford progeria syndrome^{8,9}, atypical Werner syndrome¹⁰, and mandibuloacral dysplasia. Mutations in this gene also have been reported to cause familial dilated cardiomyopathy, a genetically heterogeneous disease caused by perhaps as many as eleven different genes, only a few of which have been identified^{11,12}. Identification of lamin A/C gene mutations in patients with any of these diseases may permit identification of carriers as well as individuals who are at high risk for dilated cardiomyopathy in these families.

Indications for testing

Patients with non-X-linked Emery-Dreifuss muscular dystrophy, limb-girdle muscular dystrophy (Type 1B), an inherited form of dilated cardiomyopathy, or other diseases listed above may consider, with genetic counseling, lamin A/C (LMNA) gene sequence analysis. If a mutation is identified in the patient, other at-risk family members may be tested for carrier status.

Methodology

All coding 12 exons and associated intron junctions of the lamin A/C (LMNA) gene are analyzed by direct DNA sequence analysis using an automated fluorescent sequencing machine. Divergent regions of lamins A and C are included in the analysis. When a mutation is detected, confirmation is carried out on an independent amplification of PCR using a second prep (B-prep) by sequencing in the opposite direction. If no mutation is found, sequence analysis is performed in both directions. At-risk family members can be offered DNA sequence analysis of only the region of the gene with the previously identified mutation.

Performance

The sensitivity of DNA sequence analysis for detection of heterozygous point mutations is estimated to be greater than 99%.

Limitations

The mutation analysis will not detect mutations located in regions of the LMNA gene that are not analyzed (non-coding exon regions, intron regions other than the splice junctions, and upstream and downstream regions). The method also will not detect gross genetic alterations including most duplications, inversions,

or deletions. Some sequence alterations that may be detected (such as those causing missense or synonymous changes) will be of unknown clinical significance. 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

(a) 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.

(b) Prenatal samples: 2 T25 flasks of confluent cells sent padded to arrive on M/Tu/W. A blood sample from the mother maybe required (2 tubes with a total of 6 ccs in ACD (yellow top) or EDTA (lavender top) tubes) for use as positive control. Maternal cell contamination studies are not done here but are required for autosomal disorders and dosage analysis on X-linked disorders. We would be happy to assist in coordinating sending out a specimen for this purpose.

Test Request Form (TRF)

A completed MDL [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.

<i>Order Codes</i>	<i>CPT Codes</i>	<i>TAT</i>
LMNA-SEQ (Lamin A/C (LMNA) gene, full gene sequencing)	83890, 83898(x12), 83904(x11), 83894, 83912	4 wks
LMNA-CAS (Lamin A/C (LMNA) gene, targeted mutation analysis, known mutation)	83890, 83898, 83904, 83894, 83912	3 wks
LMNA-PD (LMNA gene, known mutation detection, prenatal)	83890, 83898, 83894, 83904, 83912	2 wks

References

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