

Assay Summary

X-linked EDMD: Emerin (EMD) Gene Mutation Analysis **Autosomal EDMD: Lamin A/C (LMNA) Gene Mutation Analysis**

Emery-Dreifuss Muscular Dystrophy

Synopsis

Emery-Dreifuss muscular dystrophy (EDMD), a rare muscle disorder that may be associated with potentially lethal cardiac arrhythmias, is caused by mutations in two different genes. Mutations in the EMD gene, encoding emerin, cause X-linked EDMD¹⁻⁶; mutations in the LMNA gene, encoding lamins A and C, cause autosomal dominant EDMD⁷⁻¹⁰ and a very rare autosomal recessive EDMD¹¹. Both types of Emery-Dreifuss muscular dystrophy have phenotypes that include joint contractures in early childhood, slowly progressive muscle weakness, and cardiac disease, including dilated cardiomyopathy, with conduction defects and arrhythmias. Identification of mutations in patients with Emery-Dreifuss muscular dystrophy may permit identification of carriers as well as individuals who are at high risk for dilated cardiomyopathy in these families.

Mutations in the LMNA gene may cause a variety of different diseases in addition to Emery-Dreifuss muscular dystrophy. Please also see our Assay Summary for lamin A/C gene mutation analysis.

Indications for testing

Patients with X-linked, autosomal, or sporadic Emery-Dreifuss muscular dystrophy may consider, with genetic counseling, emerin (EMD) gene or 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. Of particular concern is the identification of those who may be at risk for cardiac arrhythmias, including heterozygous carriers of X-linked EDMD with no skeletal muscle abnormalities.

Methodology

Emerin (EMD): All 6 exons and associated intron junctions of the emerin (EMD) gene are analyzed by direct DNA sequence analysis using an automated fluorescent sequencer. 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. **Prenatal diagnosis is available for a male fetus once carrier status has been established for the mother.**

Lamin A/C (LMNA): All 12 exons and associated intron junctions of the lamin A/C (LMNA) gene are analyzed by direct DNA sequence analysis using an automated fluorescent sequencer. 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

Sequencing of emerin detects ~98% of mutations in individuals diagnosed with X-linked Emery Dreifus Muscular Dystrophy². Once a mutation is found, the sensitivity and specificity for carrier detection for

families with identified emerin gene mutations are both estimated to be greater than 99%. Sequence analysis of the coding regions of *LMNA* detects mutations in only about 45% of individuals with AD-EDMD. If a point mutation or small deletion/insertion is present within the regions of the emerin or lamin genes that are sequenced, the sensitivity of mutation detection is approximately 99%.

Limitations

The mutation analysis will not detect mutations located in regions of the EMD or LMNA genes 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 (in females for EMD). 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.

| Order Codes | CPT Codes | TAT |
|---|---|------------|
| EMD-SEQ (Emerin gene, full gene sequencing) | 83890, 83898(x5), 83904(x6), 83894, 83912 | 4 wks |
| EMD-CAS (Emerin gene, targeted mutation analysis, known mutation) | 83890, 83898, 83904, 83894, 83912 | 3 wks |
| EMD-PD (Emerin gene, known mutation detection, prenatal) | 83890, 83898, 83894, 83904, 83912 | 2 wks |
| 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

1. Bione, S. et al. (1994) Nat. Genet. 8:323-327.
2. Manilal, S. et al. (1998) Hum. Mol. Genet. 7:855-864.
3. Muntoni, F. et al. (1998) Neuromuscul. Disord. 8:72-76.
4. Hoeltzenbein, M. et al. (1999) Neuromuscul. Disord. 9:166-170.
5. Canki-Klain, N. et al. (2000) Croat. Med. J. 41:389-395.
6. Yates, J.R. et al. (1999) Neuromuscul. Disord. 9:159-65.
7. LeBonne, G. et al. (1999) Nat. Genet. 21: 285-288.
8. Genschel, J. and Schmidt, H.H.-J. (2000) Hum. Mut. 16: 451-459.
9. DiBarletta, M.R. et al. (2000) Am.J.Hum.Genet. 66: 1407-1412.

10. Brown, C.A. et al. (2001) Am. J. Med. Genet. 102: 359-367.

11. Raffaele Di Barletta, M. et al. (2000) Am. J. Hum. Genet. 66:1407-1412.

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