LMNA-Related Disorders (*LMNA*) Deletion/Duplication

TO CONFIRM A CLINICAL DIAGNOSIS OF MUSCULAR DYSTROPHY-RELATED LAMINOPATHY

Disease Overview

- Mutations in the *LMNA* gene cause a broad range of clinical diseases collectively termed laminopathies.
- *LMNA*-related disorders include Emery-Dreifuss muscular dystrophy type 2 (EDMD2) and Limb Girdle muscular dystrophy 1B (LGMD1B).
- Clinical findings are highly variable.

Disease	Clinical Features
EDMD2	Joint contractures, progressive muscle weakness and wasting, cardiac disease with conduction defects and arrhythmias; age of onset is variable.
LGMD1B	Progressive proximal lower limb weakness and atrioventricular cardiac conduction complications.
DCM	Progressive ventricular dilation and impaired systolic function leading to congestive heart failure.

Prevalence

Unknown for laminopathies caused by deletions/duplications.

Genetics

- Lamin A/C codes for isoforms A and C of the protein lamin, a structural component of the nuclear membrane.
- Type A lamins are encoded by the *LMNA* gene, which is composed of 12 exons and is located at 1q21.2-q21.3.
- Alternative splicing of the *LMNA* gene results in the production of multiple proteins, including Lamin A and Lamin C, which have been shown to provide mechanical support to the nucleus and anchor heterochromatin to the inner nuclear membrane.
- Mutations occur throughout the gene and are predominantly missense.

Indication for Ordering

To confirm a clinical diagnosis of non-X-linked EDMD2, LGMD1B, or inherited DCM.

Contraindication for Ordering

Order *LMNA*-Related Disorders (*LMNA*) Sequencing (ARUP test #2004543) to confirm a diagnosis of Hutchinson-Gilford progeria, Charcot-Marie-Tooth 2B1, familial partial lipodystrophy (Dunnigan type), mandibulo-acral dysplasia, atypical Werner syndrome, or restrictive dermopathy.

Interpretation

- Positive: Detection of a single pathogenic *LMNA* mutation is consistent with a diagnosis of an autosomal dominant laminopathy.
- Negative: Lack of detection of an *LMNA* mutation decreases, but does not exclude, the possibility of a laminopathy.

Methodology

- Multiplex ligation-dependent probe amplification (MLPA) of the *LMNA* gene.
- Analytic sensitivity and specificity of MLPA are 90 and 98 percent, respectively.
- Clinical sensitivity is dependant upon the specific *LMNA*-related disorder.

Limitations

Breakpoints of large deletions/duplications detected in *LMNA* will not be determined

Related Test

LMNA-Related Disorders (*LMNA*) Sequencing (2004543)

References

1. Worman HJ and Bonne G. Laminopathies: a wide spectrum of human diseases. *Exp Cell Res* 2007;313(10):2121–33.
2. Genschel J and Schmidt HH-J. Mutations in the LMNA gene encoding lamin A/C. *Human Mutat* 2000;16:451–9.
3. Online Mendelian Inheritance in Man. www.ncbi.ml.nih.gov (accessed on November 1, 2010).
4. Online GeneTests. www.genetests.org (accessed on November 1, 2010).

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ARUP is an enterprise of the University of Utah and its Department of Pathology.

Test Information

2004539 ***LMNA*-Related Disorders (*LMNA*) Deletions/Duplications**

For specific collection, transport, and testing information, refer to the ARUP website at www.aruplab.com.
For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.