

# LMNA-Related Disorders (*LMNA*) Sequencing

*TO CONFIRM A CLINICAL DIAGNOSIS OF A LAMINOPATHY*

## Disease Overview

- Mutations in the *LMNA* gene cause a broad range of clinical diseases collectively termed laminopathies.
- *LMNA*-related disorders include:
  - Hutchinson-Gilford progeria syndrome (HGPS)
  - Emery-Dreifuss muscular dystrophy type 2 (EDMD2)
  - Limb Girdle muscular dystrophy 1B (LGMD1B)
  - Charcot-Marie-Tooth 2B1 (CMT2B1)
  - Familial partial lipodystrophy (FLPD) Dunnigan type
  - Dilated cardiomyopathy (DCM)
  - Mandibulo-acral dysplasia (MAD)
  - Atypical Werner syndrome (WS)
  - Restrictive dermopathy (RD)
- Clinical findings are highly variable.

Disease	Clinical Features	Inheritance
HGPS	Accelerated aging, profound failure to thrive, characteristic facies, alopecia, joint degeneration, growth retardation; average life span is 13 years.	All affected individuals carry a de novo, dominant p.Gly608Gly mutation in <i>LMNA</i> exon 11.
EDMD2	Joint contractures, progressive muscle weakness and wasting, cardiac disease with conduction defects and arrhythmias; age of onset is variable.	Typically autosomal dominant; autosomal recessive cases are very rare.
LGMD1B	Progressive proximal lower limb weakness and atrioventricular cardiac conduction complications.	Autosomal dominant.
CMT2B1	Symmetrical distal muscle weakness and atrophy, depressed or absent tendon reflexes; approximate age of onset is 14 years.	Autosomal recessive; very rare.
FLPD	Post-pubescent progressive loss of subcutaneous fat from the extremities and excess fat accumulation on the face and neck.	Autosomal dominant.

Disease	Clinical Features	Inheritance
DCM	Progressive ventricular dilation and impaired systolic function leading to congestive heart failure.	Autosomal dominant.
MAD	Post-natal growth retardation, craniofacial and skeletal anomalies, mottled cutaneous pigmentation; symptoms are evident at approximately 4 years of age.	Autosomal dominant.
Atypical WS	Progeroid syndrome with features of partial alopecia, premature aging, short stature, hypogonadism, osteoporosis, premature atherosclerosis, weak voice, cataracts; approximate age of onset is 13 years.	Autosomal dominant.
RD	Skin tightness causes fetal akinesia or hypokinesia deformation sequence; lethal.	All reported cases are de novo, caused by an autosomal dominant mutation.

## Incidence

- The birth incidence of HGPS is approximately one in eight million.
- DCM occurs in approximately one in 2,500 births and is familial in 30–60 percent of cases, of which approximately 8 percent are caused by *LMNA* gene mutations.
- The incidence of other *LMNA*-associated disorders is unknown.

## 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.

- The G608G mutation in exon 11 of the *LMNA* gene is present in all individuals with HGPS.

### Indication for Ordering

To confirm a clinical diagnosis of HGPS, non-X-linked EDMD2, LGMD1B, CMT2B1, FLPD, Inherited DCM, MAD, atypical Werner syndrome, or RD.

### Contraindication for Ordering

To determine carrier or affected status in relatives of an individual with a previously identified *LMNA* mutation, order Familial Mutation, Targeted Sequencing (ARUP test #2001961).

### Interpretation

- Positive:
  - Detection of a single pathogenic *LMNA* mutation is consistent with diagnosis of an autosomal dominant laminopathy or may indicate carrier status for an autosomal recessive *LMNA*-related disorder.
  - Detection of two pathogenic *LMNA* mutations is consistent with diagnosis of an autosomal recessive laminopathy.
- Negative: Lack of detection of an *LMNA* mutation decreases, but does not exclude, the possibility of a laminopathy.
- Gene variants of uncertain significance may be detected by *LMNA* sequencing.

### Methodology

- Bidirectional sequencing of the entire *LMNA* coding region and intron-exon boundaries.
- Analytical sensitivity and specificity are 99 percent.
- Clinical sensitivity is dependant upon the specific *LMNA*-related disorder.

### Limitations

- Some regulatory region mutations and all deep intronic mutations of *LMNA* will not be detected.
- Rare diagnostic errors may occur due to primer-site mutations.

### Related Tests

- *LMNA*-Related Disorders (*LMNA*) Deletions/Duplications (2004539)
- Familial Mutation, Targeted Sequencing (2001961)

### References

1. Eriksson M, et al. Recurrent de novo point mutations in lamin A cause Hutchinson-Gilford progeria syndrome. *Nature* 2003;423:293–8.
2. Worman HJ, Bonne G. Laminopathies: a wide spectrum of human diseases. *Exp Cell Res* 2007;313(10):2121–33.
3. Genschel J and Schmidt HH-J. Mutations in the LMNA gene encoding lamin A/C. *Human Mutat* 2000;16:451–9.
4. Online Mendelian Inheritance in Man. [www.ncbi.nlm.nih.gov](http://www.ncbi.nlm.nih.gov) (accessed on November 1, 2010).
5. Online GeneTests. [www.genetests.org](http://www.genetests.org) (accessed on November 1, 2010).

## Test Information

2004543

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For specific collection, transport, and testing information, refer to the ARUP website at [www.aruplab.com](http://www.aruplab.com).

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at [www.arupconsult.com](http://www.arupconsult.com).