THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Laminopathy testing: Mutation Analysis of *LMNA*

Clinical Features, Molecular Genetics, and Inheritance:

- Dilated cardiomyopathy (DCM) is a severe disease of heart muscle characterized by progressive ventricular dilation and impaired systolic function and is a major cause of congestive heart failure. The prevalence of DCM is estimated at 1 in 2,500 individuals, with inherited forms accounting for 30-50%. Inherited forms of DCM show clinical variability and are a genetically heterogeneous group. Mutations of the Lamin A/C gene (*LMNA*) have been identified in ~8% of all DCM patients (1). Of the subset of inherited DCM patients with accompanying conduction disease, *LMNA* mutations are present in 40-50% of cases (2). *LMNA*-associated DCM is inherited in an autosomal dominant fashion.

- Emery-Dreifuss Muscular Dystrophy (EDMD) is characterized by early contractures of the elbows and Achilles tendons, slowly progressive muscle wasting and weakness, and late onset cardiomyopathy and arrhythmia. EDMD can be either X-linked or autosomal dominant in inheritance, and the vast majority of autosomal dominant cases are due to mutations in the *LMNA* gene (3).

- The Limb Girdle Muscular Dystrophies (LGMD) are a genetically heterogenous group of disorders. One form, LGMD1B, is autosomal dominant with slowly progressive limb girdle muscular dystrophy, age-related atrioventricular cardiac conduction disturbances, and the absence of early contractures. Mutations of the *LMNA* gene are the basis of LGMD1B (4).

- Hutchinson-Gilford progeria syndrome (HGPS) is a rare autosomal dominant genetic disorder, estimated to affect 1 in 4 million individuals, that causes clinical features in childhood that are associated with premature aging. Such features may include hair loss, growth retardation, joint degeneration, and atherosclerosis. Children with HGPS tend to appear normal at birth and usually have normal motor and mental development, but severe growth retardation is observed by 2 years of age. A vast majority of patients with HGPS have a *LMNA* G608G mutation, but other mutations in *LMNA* have been reported (5).

- Mandibuloacral dysplasia (MAD) is a rare autosomal recessive disorder caused by *LMNA* mutations, which results in post-natal growth retardation, craniofacial and skeletal anomalies, and mottled cutaneous pigmentation. Symptoms become evident after 4 years of life and first present with growth retardation (6).

- Charcot-Marie-Tooth type 2B1 is an axonal autosomal recessive laminopathy and neuropathy, characterized predominantly by symmetrical distal muscle weakness and atrophy. Individuals initially present with depressed or absent tendon reflexes with weakness of foot dorsiflexion at the ankle. The average age of onset is 14 years (7).

- Familial partial lipodystrophy (FLPD), Dunnigan type, is an autosomal dominant disease characterized by the progressive loss of subcutaneous fat from the extremities. A muscular appearance with prominent superficial veins results, and excess fat accumulates on the face and neck. Prior to puberty, patients have a normal fat distribution (8).

Additional Resources:

The Progeria Research Foundation
Phone: 978-535-2594
Fax: 978-535-5849
Email: info@progeriaresearch.org
www.progeriaresearch.org

The American Heart Association
Phone: 1-800-242-8721
www.americanheart.org

Test methods:

For Hutchinson-Gilford progeria, we offer targeted mutation analysis for the common mutation (G608G). If this testing is positive, we will issue a report and bill only for the targeted analysis. If this testing is negative, we will perform full mutation analysis. We will issue a report at the end of testing and bill only for the full mutation analysis.

For all other indications, we offer comprehensive sequence coverage of the coding regions and splice junctions of the *LMNA* gene. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp. Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

Please be clear about the suspected diagnosis or indication on the requisition form.

Targeted mutation analysis (*for Hutchinson-Gilford progeria only*)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$500
CPT codes:	81403
Turn-around time:	3 weeks

LMNA sequencing and deletion/duplication analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81405, 81406
Turn-around time:	4 weeks

Results:

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References:

1. Taylor MR, Fain PR, Sinagra G et al. Natural history of dilated cardiomyopathy due to lamin A/C gene mutations. J Am Coll Cardiol 2003: 41: 771-780.
2. Fatkin D, MacRae C, Sasaki T et al. Missense mutations in the rod domain of the lamin A/C gene as causes of dilated cardiomyopathy and conduction-system disease. N Engl J Med 1999: 341: 1715-1724.
3. Bonne G, Di Barletta MR, Varnous S et al. Mutations in the gene encoding lamin A/C cause autosomal dominant Emery-Dreifuss muscular dystrophy. Nat Genet 1999: 21: 285-288.
4. Muchir A, Bonne G, van der Kooi AJ et al. Identification of mutations in the gene encoding lamins A/C in autosomal dominant limb girdle muscular dystrophy with atrioventricular conduction disturbances (LGMD1B). Hum Mol Genet 2000: 9: 1453-1459.
5. Eriksson M, Brown WT, Gordon LB et al. Recurrent de novo point mutations in lamin A cause Hutchinson-Gilford progeria syndrome. Nature 2003: 423: 293-298.
6. Novelli G, Muchir A, Sangiuolo F et al. Mandibuloacral dysplasia is caused by a mutation in LMNA-encoding lamin A/C. Am J Hum Genet 2002: 71: 426-431.
7. De Sandre-Giovannoli A, Chaouch M, Kozlov S et al. Homozygous defects in LMNA, encoding lamin A/C nuclear-envelope proteins, cause autosomal recessive axonal neuropathy in human (Charcot-Marie-Tooth disorder type 2) and mouse. Am J Hum Genet 2002: 70: 726-736.
8. Boguslavsky RL, Stewart CL, Worman HJ. Nuclear lamin A inhibits adipocyte differentiation: implications for Dunnigan-type familial partial lipodystrophy. Hum Mol Genet 2006: 15: 653-663.