

The University of Chicago Genetic Services Laboratories



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Lamin A/C (LMNA) Sequencing

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 heterogeneous 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 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 gene sequencing. We will issue a report at the end of testing and bill only for the full gene sequencing. For all other indications, we offer full gene sequencing of the entire coding region and intron/exon boundaries.

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:	\$390
CPT codes:	83891, 83898 x 2, 83894, 83912
Turn-around time:	3-4 weeks

Full gene sequencing

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	\$1000
CPT codes:	83891, 83898 x2, 83904 x4, 83912
Turn-around time:	4-6 weeks

Testing for a known mutation in additional family members

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	\$390
CPT codes:	83891, 83898 x 2, 83894, 83912
Turn-around time:	3-4 weeks

Prenatal testing for a known mutation

Sample specifications:	2 T25 flasks of cultured cells from amnio or CVS or 10ml of amniotic fluid
Cost:	\$590
CPT codes:	83891, 83898 x 2, 83894, 83912, 99051
Turn-around time:	1-2 weeks

Results

You will be informed of the results of your case as soon as it has been completed. Results, along with an interpretive report, will be faxed and mailed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

Laboratory Faculty and Staff:

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References:

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2. Fatkin et al., Missense mutations in the Rod Domain of the Lamin A/C Gene as Causes of Dilated Cardiomyopathy and Conduction-System Disease. (1999) N. Eng. J. Med. 341:1715-1724.
3. Bonne et al., Mutations in the gene encoding lamin A/C cause autosomal dominant Emery-Dreifuss muscular dystrophy (1999) Nat. Genet. 21:285-288.
4. Muchir et al., Identification of mutations in the gene encoding lamins A/C in autosomal dominant limb girdle muscular dystrophy with atrioventricular conduction disturbances (LGMD1B). (2000) Hum. Mol. Genet. 9:1453-1459.
5. Erickson et al. Recurrent *de novo* point mutations in lamin A cause Hutchinson-Gilford progeria syndrome (2003) Nature 423(6937): 293-298.
6. Novelli G, et al. Mandibuloacral Dysplasia Is Caused by a Mutation in *LMNA*-Encoding Lamin A/C. (2002) Am. J. Hum. Genet. 71:426-431.
7. De Sandre-Giovannoli, A. 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. (2002) Am. J. Hum. Genet. 70:726-736.
8. Boguslavsky, RL et al. Nuclear lamin A inhibits adipocyte differentiation: implications for Dunnigan-type familial partial lipodystrophy (2006) Human Molecular Genetics 15(4):653-663.

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