LMNA-Related Disorders

Indications for Ordering

To confirm a clinical diagnosis of a *LMNA*-related disorder
- 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, Dunnigan type (FPLD)
- *LMNA*-related dilated cardiomyopathy (DCM)
- Mandibulo-acral dysplasia (MAD)
- Atypical Werner syndrome (WS)
- Restrictive dermopathy (RD)
- Other, intermediate phenotypes

Test Description

- Polymerase chain reaction (PCR) followed by bidirectional sequencing of all coding regions and intron/exon boundaries of the *LMNA* gene
- Multiplex ligation-dependent probe amplification (MLPA) to detect large *LMNA* deletions/duplications

Tests to Consider

Primary tests

LMNA-Related Disorders (*LMNA*) Sequencing 2004543
- Confirm suspected laminopathy caused by *LMNA* variants, including HGPS, EDMD2, LGMD1B, CMT2B1, FPLD , DCM, MAD, WS, or RD

LMNA-Related Disorders (*LMNA*) Deletion/Duplication 2004539
- Confirm suspected laminopathy caused by *LMNA* variants, including EDMD2, LGMD1B, or DCM

Related test

Familial Mutation, Targeted Sequencing 2001961
- Useful when a pathogenic familial variant identifiable by sequencing is known

Disease Overview

Prevalence and/or incidence
- HGPS – 1/8 million births
- DCM – ~1/2,500 births
  - Familial – 30-60%
    - *LMNA* gene variants cause ~8% of familial cases
- Incidence of other *LMNA*-associated disorders – unknown

Symptoms
- Variants in the *LMNA* gene cause a broad range of clinical diseases collectively termed laminopathies
- Clinical findings are highly variable
- See table

Genetics

Genes – *LMNA*

Inheritance – see table

Penetrance – varies by syndrome

Structure/function
- Composed of 12 exons
- *LMNA* encodes isoforms A and C of the lamin protein
  - Structural component of the nuclear membrane
  - Anchors heterochromatin to the inner nuclear membrane

Variants
- Alternative splicing of the *LMNA* gene produces two proteins (lamin A and C)
- Variants occur throughout the gene
  - Predominantly missense
  - p.G608G variant in exon 11
    - Present in all individuals with HGPS

Test Interpretation

Sensitivity/specificity
- Clinical sensitivity – dependent on the specific *LMNA*-related disorder
- Analytic sensitivity
  - Sequencing – 99%
  - MLPA – 90%
- Analytical specificity
  - Sequencing – 99%
  - MLPA – 98%

Results
- Positive – single pathogenic *LMNA* variant detected
  - Consistent with diagnosis of an autosomal dominant laminopathy
  - May indicate carrier status for an autosomal recessive *LMNA*-related disorder
- Negative – *LMNA* variant not detected
  - Lack of detection decreases the probability of, but does not exclude, the possibility of a laminopathy
- Gene variants of uncertain significance may be detected by *LMNA* sequencing

Limitations

- Diagnostic errors can occur due to rare sequence variations
- Not determined or evaluated
  - Some regulatory region variants
  - Deep intronic variants
  - Breakpoints of large deletions/duplications
  - Variants in genes other than *LMNA*
- Large deletions/duplications in exon 8 may not be detected

***LMNA*-Related Disorders: Clinical Features and Inheritance Patterns**		
Disease	**Clinical Features**	**Inheritance**
HGPS	• Symptoms that resemble accelerated aging, profound failure to thrive, characteristic facies, alopecia, joint degeneration, growth retardation • Age of onset – ~1 year with average life expectancy of 13 years	All affected individuals carry a de novo, dominant p.Gly608Gly variant in *LMNA* exon 11
EDMD2	• Joint contractures, progressive muscle weakness and wasting, cardiac disease with conduction defects and arrhythmias • Age of onset – variable	Autosomal dominant most common; autosomal recessive cases are very rare
LGMD1B	• Progressive proximal lower limb weakness and atrioventricular cardiac conduction complications • Age of onset – birth to adulthood, with 50% in childhood	Autosomal dominant
CMT2B1	• Symmetrical distal muscle weakness and atrophy, depressed or absent tendon reflexes • Age of onset – ~14 years	Autosomal recessive; very rare
FPLD	• Progressive loss of subcutaneous fat from the extremities and excess fat accumulation on the face and neck • Age of onset – postpubescent	Autosomal dominant
DCM	• Progressive ventricular dilation and impaired systolic function leading to congestive heart failure • Age of onset – usually adults between 4^{th} and 6^{th} decade	Autosomal dominant
MAD	• Postnatal growth retardation, craniofacial and skeletal anomalies, mottled cutaneous pigmentation • Age of onset – ~4 years	Autosomal recessive
Atypical WS	• Progeroid syndrome with features of partial alopecia, premature aging, short stature, hypogonadism, osteoporosis, premature atherosclerosis, weak voice, cataracts • Age of onset – ~13 years	Autosomal dominant
RD	• Skin tightness causes fetal akinesia or hypokinesia deformation sequence – lethal • Age of onset – fetal with live born children usually dying in 1^{st} week	Rarely due to variant of *LMNA*; reported cases have a de novo, autosomal dominant variant