Emery-Dreifuss Muscular Dystrophy Panel, Sequencing

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Emery-Dreifuss muscular dystrophy (EDMD) is characterized by a clinical triad of early onset joint contractures (commonly involving elbows, ankles, and neck), slowly progressive limb muscle weakness and wasting, and cardiac disease. Age of onset, severity, and disease progression are variable, although penetrance is high. Typical presentation includes joint contractures in the first two decades of life, followed by muscle weakness and wasting, with cardiac involvement occurring in the second to third decades. Muscle histopathology may show myopathic or dystrophic changes, and serum creatine kinase may be normal or moderately elevated. Inheritance may be X-linked (XL) (*EMD* or *FHL1*), autosomal dominant (AD) (*LMNA*), and rarely autosomal recessive (AR) (*LMNA*). Carrier females of XL-EDMD are usually asymptomatic but are at risk for developing cardiac disease and, less commonly, mild muscle disease.

Featured ARUP Testing

Emery-Dreifuss Muscular Dystrophy Panel, Sequencing 3001839

Method: Massively Parallel Sequencing

Use to assess for EDMD in individuals with clinical findings or family history of EDMD.

If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information.

Disease Overview

Symptoms

EDMD has inter- and intrafamilial variability in age of onset and disease severity, but typical disease presentation includes:

- Early joint contractures (typically the first sign in XL-EDMD and present in the first decade, but may appear after muscle weakness in AD-EDMD):
  - Elbow flexors
  - Achilles tendon
  - Neck extensors resulting in limited neck flexion and later limitation of extension of the entire spine
- Slowly progressive muscle wasting and weakness:
  - Initially of the humeroperoneal muscles, with progression to scapular and pelvic girdle muscles
  - Loss of ability to walk due to progressive muscle weakness (more common in AD-EDMD but rare in XL-EDMD)
  - Severe muscular disease may result from biallelic LMNA variants
- Cardiac disease:
  - Cardiac symptoms (eg, palpitations, presyncope/syncope, poor exercise tolerance, or sudden death)
  - Atrial or ventricular arrhythmias
  - Dilated or hypertrophic cardiomyopathy
  - Cardiac conduction defects
    - Includes sinus bradycardia and atrioventricular and bundle-branch blocks
    - 20% of female carriers of EDMD1 develop conduction defects[1]

Prevalence

1-2/100,000[2]

Genetics

Etiology

EDMD is caused by pathogenic germline variants in *EMD*, *FHL1*, or *LMNA*, with each gene accounting for the following amount of cases[2]:

- *LMNA*: 26.5% of cases
- *EMD*: 8.5% of cases
- *FHL1*: 1.2% of cases

Inheritance

Gene	Inheritance Pattern
EMD	XL
FHL1	XL
LMNA	Typically AD De novo variants common (up to 65% of cases) AR (biallelic variation) is rare

Genotype-Phenotype Correlations

The majority of causative variants in *EMD* are null variants, resulting in absence of emerin expression, which often result in more severe disease compared with missense variants associated with decreased expression.

LMNA missense variants are typically associated with EDMD2, whereas truncating variants have been associated with a later onset limb-girdle muscular dystrophy phenotype.

Test Interpretation

Clinical Sensitivity

Estimated at 36% for EDMD[2]

Analytic Sensitivity

For massively parallel sequencing:

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%)	Analytic Sensitivity (PPA) 95% Credibility Region[a] (%)
SNVs	99.2	96.9-99.4
Deletions 1-10 bp	93.8	84.3-98.2
Deletions 11-44 bp	99.9	87.8-100
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	99.9	62.1-100

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

Limitations

- A negative result does not exclude a diagnosis of Emery-Dreifuss muscular dystrophy.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of targeted genes

- Regulatory region and deep intronic variants
- Large deletions/duplications in any of the tested genes (putative large deletions in *EMD* or *FHL1* identified in males using massively parallel sequencing should be confirmed by a validated method)
- Noncoding transcripts

- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Low-level somatic variants

Genes Tested

Gene	MIM #	Disorder	Inheritance
EMD	300384	EDMD1	XL
FHL1	300163	EDMD6 Myopathy with postural muscle atrophy Reducing body myopathy 1a, severe infantile or early childhood onset Reducing body myopathy 1b, with late childhood or adult onset Scapuloperoneal myopathy Uruguay faciocardiomuscular syndrome	XL
LMNA	613205	EDMD2 Dilated cardiomyopathy 1A Congenital muscular dystrophy	AD
		EDMD3	AR

References

1. Madej-Pilarczyk A. Clinical aspects of Emery-Dreifuss muscular dystrophy. *Nucleus*. 2018;9(1):268-274.

2. Bonne G, Leturcq F, Ben Yaou R. Emery-Dreifuss muscular dystrophy. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews*. University of Washington, Seattle.

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