



HAL
open science

Emery-Dreifuss Muscular Dystrophy

Gisèle Bonne, France Leturcq, Rabah Ben Yaou

► **To cite this version:**

Gisèle Bonne, France Leturcq, Rabah Ben Yaou. Emery-Dreifuss Muscular Dystrophy. Gene Reviews, 2019. hal-03292021

HAL Id: hal-03292021

<https://hal.sorbonne-universite.fr/hal-03292021>

Submitted on 20 Jul 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Emery-Dreifuss Muscular Dystrophy

Gisèle Bonne, PhD,¹ France Leturcq, MD,² and Rabah Ben Yaou, MD³

Created: September 29, 2004; Updated: August 15, 2019.

Summary

Clinical characteristics

Emery-Dreifuss muscular dystrophy (EDMD) is characterized by the clinical triad of: joint contractures that begin in early childhood; slowly progressive muscle weakness and wasting initially in a humero-peroneal distribution that later extends to the scapular and pelvic girdle muscles; and cardiac involvement that may manifest as palpitations, presyncope and syncope, poor exercise tolerance, and congestive heart failure along with variable cardiac rhythm disturbances. Age of onset, severity, and progression of muscle and cardiac involvement demonstrate both inter- and intrafamilial variability. Clinical variability ranges from early onset with severe presentation in childhood to late onset with slow progression in adulthood. In general, joint contractures appear during the first two decades, followed by muscle weakness and wasting. Cardiac involvement usually occurs after the second decade and respiratory function may be impaired in some individuals.

Diagnosis/testing

The diagnosis of EDMD is established in a proband with:

- A clearly relevant clinical picture including limb muscle wasting and/or weakness and elbow or neck/spine joint contractures (cardiac disease may be missing in the first decades of life); AND
- A hemizygous pathogenic variant in *EMD* or *FHL1*, a heterozygous pathogenic variant in *LMNA*, or (more rarely) biallelic pathogenic variants in *LMNA* identified by molecular genetic testing.

Author Affiliations: 1 Sorbonne Université, INSERM UMRS_974, Centre de Recherche en Myologie, Paris, France; Email: g.bonne@institut-myologie.org. 2 AP-HP, Laboratoire de Biochimie & Génétique Moléculaire HUPC Cochin, Sorbonne Université, INSERM UMRS_974, Centre de Recherche en Myologie, Paris, France; Email: france.leturcq@inserm.fr. 3 Sorbonne Université, INSERM UMRS_974, Centre de Recherche en Myologie, Cellule Bases de Données, Institut de Myologie, AP-HP, Groupe Hospitalier-Universitaire La Pitié-Salpêtrière, Centre de Référence des Maladies Neuromusculaires Nord/Est/Ile-de-France, Paris, France; Email: r.benyaou@institut-myologie.org.

Management

Treatment of manifestations: Treatment for cardiac arrhythmias, AV conduction disorders, congestive heart failure, including antiarrhythmic drugs, cardiac pacemaker, implantable cardioverter defibrillator; heart transplantation for the end stages of heart failure as appropriate; respiratory aids (respiratory muscle training, assisted coughing techniques, mechanical ventilation) as needed. Surgery to release contractures and manage scoliosis as needed; aids (canes, walkers, orthoses, wheelchairs) as needed to help ambulation; physical therapy and stretching to prevent contractures.

Surveillance: At a minimum, annual cardiac assessment (ECG, Holter monitoring, echocardiography); monitoring of respiratory function.

Agents/circumstances to avoid: Triggering agents for malignant hyperthermia, such as depolarizing muscle relaxants (succinylcholine) and volatile anesthetic drugs (halothane, isoflurane); obesity.

Evaluation of relatives at risk: Molecular genetic testing if the pathogenic variant(s) in the family are known; clinical evaluation, including at least muscular and cardiac assessments if the pathogenic variant(s) in the family are not known.

Genetic counseling

EDMD is inherited in an X-linked, autosomal dominant, or, rarely, autosomal recessive manner.

- **XL-EDMD.** If the mother of a proband has a pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygous. Heterozygous females are usually asymptomatic but are at risk of developing a cardiac disease, progressive muscular dystrophy, and/or an EDMD phenotype.
- **AD-EDMD.** 65% of probands with AD-EDMD have a *de novo* LMNA pathogenic variant. Each child of an individual with AD-EDMD has a 50% chance of inheriting the pathogenic variant.
- **AR-EDMD.** At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being neither affected nor a carrier.

Once the pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for EDMD are possible.

Diagnosis

Suggestive Findings

Emery-Dreifuss muscular dystrophy (EDMD) **should be suspected** in individuals with the following triad [Emery 2000]:

- **Early contractures** of the elbow flexors, Achilles tendons (heels), and neck extensors resulting in limitation of neck flexion, followed by limitation of extension of the entire spine
- **Slowly progressive wasting and weakness** typically of the humero-peroneal/scapulo-peroneal muscles in the early stages
- **Cardiac disease with conduction defects and arrhythmias**
 - Atrial fibrillation, flutter and standstill, supraventricular and ventricular arrhythmias, and atrio-ventricular and bundle-branch blocks may be identified on resting electrocardiography (ECG) or by 24-hour ambulatory ECG.
 - Dilated or hypertrophic cardiomyopathy may be detected by the performance of echocardiographic evaluation.

Age of onset. Onset usually occurs between age five and ten years, rarely before age five years.

Family history. May be positive (autosomal dominant, X-linked, or, rarely, autosomal recessive). However, simplex cases due to *de novo* genetic events are not rare.

Note: Diagnosis guidelines have been published [Emery 1997, Bonne et al 2002b, Madej-Pilarczyk 2018].

Establishing the Diagnosis

The diagnosis of EDMD is **established** in a proband with a clearly relevant clinical picture including limb muscle wasting and/or weakness and elbow or neck/spine joint contractures (cardiac disease may be missing in the first decades of life) and a hemizygous pathogenic variant in *EMD* or *FHL1*, a heterozygous pathogenic variant in *LMNA*, or (more rarely) biallelic pathogenic variants in *LMNA* identified by molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of EDMD is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with atypical features in whom the diagnosis of EDMD has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of EDMD, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

Single-gene testing. Sequence analysis detects small intragenic deletions/insertions and missense, nonsense, and splice site variants. If no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications. Note: Lack of amplification by PCR prior to sequence analysis can suggest a putative (multi)exon or whole-gene deletion on the X chromosome in affected males; confirmation requires additional testing by gene-targeted deletion/duplication analysis.

The likelihood of identifying a causative variant in *EMD*, *FHL1*, or *LMNA* is dependent on known or suspected mode of inheritance.

- In cases of X-linked inheritance, *EMD*-related disease is most likely, followed by *FHL1*.
- In cases of autosomal dominant or recessive inheritance, *LMNA*-related disease is most likely.
- In the absence of a clear inheritance pattern, *LMNA*-related disease is most likely followed by *EMD*- and then *FHL1*-related disease.

In an affected female who represents a simplex case (i.e., a single occurrence in a family) *LMNA*-related disease is more likely than an X-linked disorder. Carrier females rarely manifest X-linked EDMD (XL-EDMD); thus, affected females are much more likely to have AD-EDMD.

A multigene panel that includes *EMD*, *FHL1*, *LMNA*, and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include

a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

For an introduction to multigene panels click [here](#). More detailed information for clinicians ordering genetic tests can be found [here](#).

Option 2

When the diagnosis of EDMD is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

Exome array (when clinically available) may be considered if exome sequencing is not diagnostic.

For an introduction to comprehensive genomic testing click [here](#). More detailed information for clinicians ordering genomic testing can be found [here](#).

Table 1. Molecular Genetic Testing Used in Emery-Dreifuss Muscular Dystrophy (EDMD)

Gene ^{1, 2}	Proportion of EDMD Attributed to Pathogenic Variants in Gene ³	Proportion of Pathogenic Variants ⁴ Detectable by This Method	
		Sequence analysis ⁵	Gene-targeted deletion/duplication analysis ⁶
<i>EMD</i>	8.5%	99% ⁷	Rare ^{8, 9}
<i>FHL1</i>	1.2%	99% ¹⁰	Rare ^{7, 11}
<i>LMNA</i>	26.5%	99% ¹²	None reported ¹³
Unknown	63.4%	NA	

1. Genes are listed in alphabetic order.

2. See Table A. Genes and Databases for chromosome locus and protein.

3. Gueneau et al [2009]

4. See Molecular Genetics for information on allelic variants detected in this gene.

5. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click [here](#).

6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

7. [UMD-EMD Database](#)

8. Lack of amplification by PCR prior to sequence analysis can suggest a putative (multi)exon or whole-gene deletion on the X chromosome in affected males; confirmation requires additional testing by deletion/duplication analysis.

9. Manilal et al [1998], Small & Warren [1998], Fujimoto et al [1999], Ankala et al [2012], Askree et al [2013]

10. Gueneau et al [2009], Knoblauch et al [2010]

11. Gueneau et al [2009], Tiffin et al [2013]

12. [UMD-LMNA Database](#)

13. Intragenic *LMNA* deletions and duplications have been associated with cardiomyopathy.

Clinical Characteristics

Clinical Description

AD-EDMD and XL-EDMD

Autosomal dominant Emery-Dreifuss muscular dystrophy (AD-EDMD) and X-linked EDMD (XL-EDMD) have similar but not identical neuromuscular and cardiac involvement [Yates et al 1999, Bonne et al 2000, Bonne et al 2002b, Boriani et al 2003, Astejada et al 2007, Gueneau et al 2009, Cowling et al 2011, Carboni et al 2012b, Madej-Pilarczyk 2018].

EDMD is characterized by the presence of the following clinical triad:

- **Joint contractures** that begin in early childhood in both XL-EDMD and AD-EDMD. In XL-EDMD, joint contractures are usually the first sign, whereas in AD-EDMD, joint contractures may appear after the onset of muscle weakness. Joint contractures predominate in the elbows, ankles, and posterior cervical muscles (responsible for limitation of neck flexion followed by limitation in movement of the entire spine). The degree and the progression of contractures are variable and not always age related [Bonne et al 2000]. Severe contractures may lead to loss of ambulation by limitation of movement of the spine and lower limbs.
- **Slowly progressive muscle weakness and wasting** that are initially in a humero-peroneal distribution and can later extend to the scapular and pelvic girdle muscles. The progression of muscle wasting is usually slow in the first three decades of life, after which it becomes more rapid. Loss of ambulation due to muscle weakness can occur in AD-EDMD but is rare in XL-EDMD [Bonne et al 2000].
- **Cardiac involvement** usually appears within the end of the second to third decades of life and may include palpitations, presyncope and syncope, poor exercise tolerance, congestive heart failure, and a variable combination of supraventricular arrhythmias, disorders of atrioventricular conduction, ventricular arrhythmias, dilated cardiomyopathy, and sudden death despite pacemaker implantation [Bécane et al 2000, Boriani et al 2003, Sanna et al 2003, Sakata et al 2005, Astejada et al 2007, Carboni et al 2012b].
 - Cardiac conduction defects can include sinus bradycardia, first-degree atrioventricular block, bundle-branch blocks, Wenckebach phenomenon, and third-degree atrioventricular block requiring pacemaker implantation.
 - Atrial arrhythmias (extrasystoles, atrial fibrillation, flutter) and ventricular arrhythmias (extrasystoles, ventricular tachycardia) are frequent.
 - The risk for ventricular tachyarrhythmia and dilated cardiomyopathy manifested by left ventricular dilation and dysfunction is higher in AD-EDMD than in XL-EDMD.
 - In both XL- and AD/AR-EDMD, affected individuals are at risk for cerebral emboli and sudden death [Boriani et al 2003, Redondo-Vergé et al 2011, Homma et al 2018].
 - A generalized dilated (in *LMNA*- or *EMD*-related EDMD) or hypertrophic cardiomyopathy (in *FHL1*-related EDMD) often occurs.

Other clinical findings may be nonspecific:

- **Electromyogram** usually shows myopathic features with normal nerve conduction studies, but neuropathic patterns have been described for both XL-EDMD [Hopkins et al 1981] and AD-EDMD [Witt et al 1988].
- **CT scan of muscle.** Characteristic findings in the calf and posterior thigh muscles on MRI or CT scan have been reported in AD-EDMD [Mercuri et al 2002, Deconinck et al 2010, Carboni et al 2012a]. A similar pattern of muscle fatty infiltration was reported and mainly involves paravertebral, gluteal,

quadriceps, biceps, semitendinosus, semimembranosus, adductor major, soleus, and gastrocnemius muscles [Díaz-Manera et al 2016].

Other laboratory findings:

- **Serum CK concentration** is normal or moderately elevated (2-20x upper normal level). Increases in serum CK concentration are more often seen at the beginning of the disease than in later stages [Bonne et al 2000, Bonne et al 2002a].
- **Muscle histopathology** shows nonspecific myopathic or dystrophic changes, including variation in fiber size, increase in internal nuclei, increase in endomysial connective tissue, and necrotic fibers. Electron microscopy may reveal specific alterations in nuclear architecture [Fidziańska et al 1998, Sabatelli et al 2001, Sewry et al 2001, Fidziańska & Hausmanowa-Petrusewicz 2003, Fidziańska & Glinka 2007]. Inflammatory changes may also be found in *LMNA*-related myopathies including EDMD [Komaki et al 2011]. Muscle biopsy is now rarely performed for diagnostic purposes because of the lack of specificity of the dystrophic changes observed.
- **Immunodetection of emerin.** In normal individuals, the protein emerin is ubiquitously expressed on the nuclear membrane. Emerin can be detected by immunofluorescence and/or by western blot in various tissues: exfoliative buccal cells, lymphocytes, lymphoblastoid cell lines, skin biopsy, or muscle biopsy [Manilal et al 1997, Mora et al 1997].
 - In individuals with XL-EDMD, emerin is absent in 95% [Yates & Wehnert 1999].
 - In female carriers of XL-EDMD, emerin is absent in varying proportions in nuclei, as demonstrated by immunofluorescence. However, western blot is not reliable in carrier detection because it may show either a normal or a reduced amount of emerin, depending on the proportion of nuclei expressing emerin.
 - In individuals with AD-EDMD, emerin is normally expressed.
- **Immunodetection of FHL1.** In controls, the three FHL1 isoforms (A, B, and C) are ubiquitously expressed in the cytoplasm as well as in the nucleus. The isoforms can be detected by immunofluorescence and/or western blot in fresh muscle biopsy or myoblasts, fibroblasts, and cardiomyocytes [Sheikh et al 2008, Gueneau et al 2009].
 - In individuals with *FHL1*-related XL-EDMD, FHL1 is absent or significantly decreased [Gueneau et al 2009].
 - In female carriers of *FHL1*-related XL-EDMD, FHL1 is expected to be variably expressed.
- **Immunodetection of lamins A/C.** Lamins A/C are expressed at the nuclear rim (i.e., nuclear membrane) and within the nucleoplasm (i.e., nuclear matrix). Depending on the antibody used, lamins A/C can be localized to both the nuclear membrane and matrix or to the nuclear matrix only. However, this test is not reliable for confirmation of the diagnosis of AD-EDMD because in AD-EDMD lamins A/C are always present due to expression of the wild type allele at the nuclear membrane and in the nuclear matrix. Western blot analysis for lamin A/C may contribute to the diagnosis, but yields normal results in many affected individuals [Menezes et al 2012].

Variability. Age of onset, severity, and progression of the muscle and cardiac involvement demonstrate both inter- and intrafamilial variability [Mercuri et al 2000, Mercuri et al 2004, Carboni et al 2010]. Clinical variability ranges from early and severe presentation in childhood to late onset and a slowly progressive course. In general, joint contractures appear during the first two decades, followed by muscle weakness and wasting. In a large published series of affected individuals, Astejada et al [2007] found a range of onset of 10.1 ± 9.5 and 3.3 ± 2.9 years respectively in 20 individuals with pathogenic variants in *EMD* and 27 individuals with pathogenic variants in *LMNA*.

Progression. Cardiac involvement usually arises after the second decade of life. Respiratory function can be impaired in some individuals [Emery 2000, Mercuri et al 2000, Talkop et al 2002, Mercuri et al 2004, Ben Yaou et

al 2007, Gueneau et al 2009]. On occasion, sudden cardiac death is the first manifestation of the disorder [Bécane et al 2000, Kärkkäinen et al 2004, De Backer et al 2010].

AR-EDMD

Nine individuals with genetically confirmed isolated autosomal recessive EDMD (i.e., homozygous or compound heterozygous for a *LMNA* pathogenic variant) have been reported [Raffaele Di Barletta et al 2000, Brown et al 2001, Vytopil et al 2002, Mittelbronn et al 2006, Scharner et al 2011, Jimenez-Escrig et al 2012, Sframeli et al 2017] (see Table 2). When reported, heterozygous relatives were asymptomatic.

Table 2. Clinical Characteristics in Ten Reported Individuals with Biallelic *LMNA* Pathogenic Variants

Reference	# of Reported Individuals	Onset		Last Muscular Assessment		Heart Involvement
		Age	Symptoms	Age	Findings	
Raffaele Di Barletta et al [2000]	1	14 mos	Walking difficulties	40 yrs	Initial wheelchair use at age 4 yrs; severe & diffuse muscle wasting, wheelchair bound	None
Brown et al [2001]	1	3 yrs	Not reported	12 yrs	Proximal upper & distal lower limb weakness; ankle, elbow, & knee contractures	None
Vytopil et al [2002]	1	Childhood	Stumbled frequently; slower than peers	16 yrs	Head flexion & scapulo-humero-peroneal weakness; stiff neck; ankle, hip, & elbow contractures	Polymorphic ventricular premature beats; salvos of atrial premature beats
Scharner et al [2011]	1	<1 yr	Not reported	6 yrs	Proximal upper & limb-girdle weakness; stiff neck; elbow, ankle, & knee contractures	Cardiomyopathy from age 3 yrs
Jimenez-Escrig et al [2012]	4	14 yrs	Difficulty in running	50 yrs	Initial wheelchair use at age 35 yrs; stiff neck; ankle & elbow contractures	Supraventricular premature beats
		12 yrs	Clumsy gait	46 yrs	Still ambulant; elbow & ankle contractures	Supraventricular & ventricular premature beats
		4 yrs	Difficulty rising from the floor	43 yrs	Wheelchair use at age 25 yrs; elbow, hip, & ankle contractures	Supraventricular & ventricular premature beats
		3rd decade	Not reported	41 yrs	Still ambulant w/cane; lower- & upper-limb proximal weakness; no contractures	Supraventricular premature beats
Sframeli et al [2017]	1	Early childhood	Mobility difficulties	Child	Upper- & lower-limb weakness; elbow & ankle contractures	None

Genotype-Phenotype Correlations

EMD. Intra- and interfamilial variability in the severity of clinical features are observed. However,

- Null variants, the majority of *EMD* pathogenic variants that result in complete absence of emerin expression, tend to have a more severe phenotype [Muntoni et al 1998, Hoeltzenbein et al 1999, Canki-Klain et al 2000, Ellis et al 2000].
- Missense variants associated with decreased or normal amounts of emerin and result in a milder phenotype [Yates et al 1999].

LMNA. Marked intra- and interfamilial variability is observed for the same *LMNA* pathogenic variant [Bécane et al 2000, Bonne et al 2000, Mercuri et al 2005, Carboni et al 2010]. For example, within the same family the same pathogenic variant can lead to AD-EDMD, LGMD1B, or isolated DCM-CD (i.e., laminopathies involving striated muscle) [Bécane et al 2000, Brodsky et al 2000, Granger et al 2011]. However,

- Missense variants have been associated with early skeletal muscle involvement and joint contractures (i.e., EDMD type) while frameshift variants have been associated with later-onset muscle symptoms of limb girdle type [Benedetti et al 2007].
- Homozygous and compound heterozygous pathogenic variants appear to lead to a more severe muscular phenotype [Raffaele Di Barletta et al 2000, Brown et al 2001, Scharner et al 2011, Jimenez-Escrig et al 2012].
- Pathogenic variants destabilizing the 3D structure of the C-terminal domain of lamin A/C lead to EDMD [Krimm et al 2002].

EMD and LMNA. Severe EDMD has been reported in individuals with pathogenic variants in both *EMD* and *LMNA* [Muntoni et al 2006, Meinke et al 2011]. A range of clinical presentations (i.e., CMT2, CMT2-EDMD, and isolated cardiomyopathy) were found in a large family in which pathogenic variants in *EMD* and *LMNA* cosegregate [Ben Yaou et al 2007, Meinke et al 2011].

FHL. No definite genotype-phenotype correlations for *FHL1* have been identified.

Penetrance

Five *LMNA* pathogenic variants were reported with reduced penetrance in families with AD-EDMD or other *LMNA*-related disorders [Vytopil et al 2002, Rankin et al 2008].

Prevalence

The prevalence of XL-EDMD has been estimated at 0.13:100,000-0.2:100,000 [Norwood et al 2009]. This form of EDMD accounts for approximately 10% of the total cases of EDMD (see Table 1). Therefore, the prevalence of EDMD of all types is estimated to be 1.3:100,000-2:100,000.

Genetically Related (Allelic) Disorders

EMD

The disorders caused by pathogenic variants in *EMD* are called "emerinopathies" and affect striated muscles:

- X-linked limb-girdle muscular dystrophy (LGMD) phenotype caused by pathogenic variants in *EMD*; rarely reported [Ura et al 2007, Fanin et al 2009]
- X-linked isolated cardiac disease with prominent sinus node disease and atrial fibrillation [Ben Yaou et al 2007, Karst et al 2008]

FHL1

FHL1-related diseases include three allelic disorders characterized by the presence of reducing bodies detected on histopathology:

- Reducing body myopathy [Schessler et al 2008]
- X-linked scapuloperoneal myopathy [Quinzii et al 2008]
- Some cases of rigid spine syndrome [Shalaby et al 2008]

Other allelic *FHL1*-related diseases:

- X-linked myopathy with postural muscle atrophy (X-MPMA) and generalized muscle hypertrophy or X-MPMA in which reducing bodies are absent and FHL1 protein is reduced on immunodetection (making this disorder similar to *FHL1*-related EDMD) [Windpassinger et al 2008]
- X-linked hypertrophic cardiomyopathy [Gueneau et al 2009, Friedrich et al 2012]

LMNA

The disorders caused by pathogenic variants in *LMNA* are called "laminopathies."

Disorders of striated muscle (see Note)

- LGMD1B, an autosomal dominant form of limb-girdle muscular dystrophy associated with atrioventricular conduction defect [van der Kooi et al 1996, Muchir et al 2000]
- CMD1A or DCM-CD, an autosomal dominant form of dilated cardiomyopathy with cardiac conduction defects [Fatkin et al 1999, Bécane et al 2000]
- [Autosomal dominant dilated cardiomyopathy](#) (DCM) with apical left ventricular aneurysm without atrioventricular block [Forissier et al 2003]; DCM with early atrial fibrillation [Sébillon et al 2003]; DCM with left ventricular non-compaction [Hermida-Prieto et al 2004]
- [Arrhythmogenic right ventricular cardiomyopathy](#) [Quarta et al 2012]
- Autosomal dominant quadriceps myopathy associated with dilated cardiomyopathy and cardiac conduction defects [Charniot et al 2003]
- Neurogenic variant of EDMD [Walter et al 2005]
- *LMNA*-related congenital muscular dystrophy (L-CMD) [Quijano-Roy et al 2008]

Note: (1) These may not truly be allelic disorders because the phenotype overlaps with EDMD. See comments in Genotype-Phenotype Correlations. (2) Laminopathies affecting striated muscles are important to recognize because of the severity of the dilated cardiomyopathy associated with conduction/rhythm (DCM-CD) disorders, and the high frequency of sudden death [van Berlo et al 2005]. (3) See also [Dilated Cardiomyopathy Overview](#).

Disorders of peripheral nerve

- CMT2B1, an autosomal recessive form of axonal Charcot-Marie-Tooth disease with the pathogenic founder variant p.Arg298Cys [De Sandre-Giovannoli et al 2002] (see [Charcot-Marie-Tooth Hereditary Neuropathy Overview](#))
- Autosomal dominant CMT2 associated with muscular dystrophy, cardiomyopathy, and leukonychia [Goizet et al 2004].
- Autosomal dominant CMT2 associated with myopathy [Benedetti et al 2005].

Disorders of fatty tissues. Autosomal dominant Dunnigan-type familial partial lipodystrophy (FPLD) [Shackleton et al 2000]. The majority of FPLD cases are caused by *LMNA* pathogenic variants affecting arginine codon 482, leading to several amino acid substitutions [Bonne et al 2003]. Isolated metabolic manifestations without lipodystrophy have been also reported [Young et al 2005, Decaudoain et al 2007].

Disorders involving several tissues

- Autosomal dominant muscular dystrophy, dilated cardiomyopathy, and partial lipodystrophy [Garg et al 2002, van der Kooi et al 2002]
- Mandibuloacral dysplasia (MAD) (autosomal recessive). Founder pathogenic variants are reported in MAD (p.Arg527His) [Novelli et al 2002].
- Generalized lipotrophy, insulin-resistant diabetes mellitus, disseminated leukomelanodermic papules, liver steatosis, and cardiomyopathy (LDHCP) [Caux et al 2003]
- [Hutchinson-Gilford progeria syndrome](#) (HGPS) (autosomal dominant). Pathogenic variants in codon 608 are associated with HGPS [De Sandre-Giovannoli et al 2003, Eriksson et al 2003].

- Atypical Werner syndrome (autosomal dominant) [Chen et al 2003]
- Restrictive dermopathy [Navarro et al 2004]
- Progeria, arthropathy, and calcinosis of tendons [Van Esch et al 2006]
- Heart-hand syndrome, Slovenian type [Renou et al 2008]

Differential Diagnosis

Some neuromuscular disorders result in a similar pattern of muscle involvement, joint contractures, or cardiac disease, but most do not feature the complete triad observed in Emery-Dreifuss muscular dystrophy (EDMD).

Table 3. Disorders to Consider in the Differential Diagnosis of Emery-Dreifuss Muscular Dystrophy

Disorder Name	Gene(s)	MOI ¹	Clinical Findings			
			Muscle involvement	Joint contractures	Cardiac disease	Distinguishing feature(s)
Facioscapulohumeral muscular dystrophy	<i>DNMT3B</i> <i>DUX4L1</i> <i>SMCHD1</i>	AD	+++ (scapulo-peroneal)	–	–	No joint contractures or cardiac disease
Other scapulo-peroneal syndromes (neurogenic & myopathic types) (OMIM 181400, 181405, 181430, 608358, 255160)	<i>DES</i> <i>MYH7</i> <i>TRPV4</i>	AD AR	+++	– (<i>DES</i> , <i>MYH</i>)	++ (<i>DES</i> , <i>MYH</i>)	<ul style="list-style-type: none"> • No joint contractures (<i>DES</i>, <i>MYH</i>) • No cardiac disease (<i>TRPV4</i>)
<i>SYNE1</i> -related disorders (OMIM 612998)	<i>SYNE1</i>	AD	±	++	±	Unavailable (pending description of clear phenotype)
<i>SYNE2</i> -related disorders (OMIM 612999)	<i>SYNE2</i>	AD	±	–	±	No joint contractures
<i>TMEM43</i> -related myopathies (OMIM 614302)	<i>TMEM43</i>	AD	+++	±	±	Unavailable (pending description of clear phenotype)
<i>SUN1</i> -related disorders (OMIM 613569)	<i>SUN1</i>	AD	++	++	–	No cardiac disease
Multiminicore disease (rigid spine syndrome) (OMIM 602771)	<i>SELENON</i> (<i>SEPN1</i>)	AR	+++	++	–	<ul style="list-style-type: none"> • No cardiac disease • Early & severe respiratory failure
<i>TTN</i> -related myopathies (see Salih Myopathy, Hereditary Myopathy w/Early Respiratory Failure, Udd Distal Myopathy)	<i>TTN</i>	AD AR	+++	+++	±	<ul style="list-style-type: none"> • Variably present cardiac disease • Severe respiratory involvement • Specific muscle pathology
<i>LAMA2</i> -related muscular dystrophy	<i>LAMA2</i>	AR	+++	++	±	Leukodystrophy
<i>FKRP</i> -related muscle diseases (OMIM 606596)	<i>FKRP</i>	AR	+++	±	±	<ul style="list-style-type: none"> • Variably present cardiac disease • Possible CNS involvement

Table 3. continued from previous page.

Disorder Name	Gene(s)	MOI ¹	Clinical Findings			
			Muscle involvement	Joint contractures	Cardiac disease	Distinguishing feature(s)
Collagen type VI-related Bethlem myopathy	<i>COL6A1</i> <i>COL6A2</i> <i>COL6A3</i>	AD	+++	++	–	<ul style="list-style-type: none"> No cardiac disease Specific muscle imaging pattern
Myotonic dystrophy type 1	<i>DMPK</i>	AD	+++	–	++	<ul style="list-style-type: none"> No joint contractures Myotonia
Dystrophinopathies	<i>DMD</i>	XL	+++	–	++	No joint contractures or conduction defects / arrhythmias
Limb-girdle muscular dystrophies w/cardiac involvement	>50 genes ²	AR AD	+++	–	++	No joint contractures
Desmin-related myopathies (OMIM 601419)	<i>DES</i>	AD	+++	–	++	No joint contractures
X-linked vacuolar myopathies w/ cardiomyopathy (OMIM 300257)	<i>LAMP2</i>	XL	+++	–	++	No joint contractures
Myotonic dystrophy type 2	<i>CNBP</i>	AD	+++	–	++	No joint contractures
Myopathy with maltase acid deficiency	<i>GAA</i>	AR	+++	–	++ (rare cases)	<ul style="list-style-type: none"> No joint contractures Peculiar muscle pathology
<i>BAG3</i> -related myofibrillar myopathy (OMIM 612954)	<i>BAG3</i>	AD	+++	++	++	<ul style="list-style-type: none"> Peculiar muscle pathology Peripheral neuropathy
Ankylosing spondylitis	Acquired disease		–	++ (spine)	±	No overt muscle involvement or limb joint contractures

AD = autosomal dominant; AR = autosomal recessive; CNS = central nervous system; MOI = mode of inheritance; XL = X-linked

1. Typical MOI; exceptions occur

2. See [Autosomal Recessive Limb-Girdle Muscular Dystrophy: Phenotypic Series](#) and [Autosomal Dominant Limb-Girdle Muscular Dystrophy: Phenotypic Series](#) to view genes associated with these phenotypes in OMIM.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Emery-Dreifuss muscular dystrophy (EDMD), the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Emery-Dreifuss Muscular Dystrophy

System/Concern	Evaluation	Comment
Cardiac	<ul style="list-style-type: none"> • ECG • Holter-ECG monitoring • Echocardiography • Cardiac MRI • Electrophysiologic study 	
Respiratory	Eval of respiratory function (vital capacity measurement & other pulmonary volume measurements)	
Musculoskeletal	Eval of joints by PT or orthopedist to determine need for therapies	Therapies may incl physiotherapy, mechanical aids, orthopedic surgeries.
Metabolic functions	Eval of metabolic functions (glycemia, insulinemia, cholesterolemia, triglyceridemia)	Rarely, a person w/ <i>LMNA</i> EDMD has overlapping <i>LMNA</i> phenotype & partial lipodystrophy features, requiring careful metabolic assessment [Garg et al 2002, van der Kooi et al 2002].
Other	Consultation w/clinical geneticist &/or genetic counselor	

PT = physical therapist

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with Emery-Dreifuss Muscular Dystrophy

Manifestation/Concern	Treatment	Considerations/Other
Cardiac	Specific for cardiac issue in the individual; can incl antiarrhythmic drugs, cardiac pacemaker, implantable cardioverter defibrillator, & both pharmacologic & non-pharmacologic therapy for heart failure	Heart transplantation may be necessary in end stages of heart failure; some persons may not be candidates for transplantation due to assoc severe skeletal muscle & respiratory involvement.
Respiratory	Use of respiratory aids (respiratory muscle training & assisted coughing techniques, mechanical ventilation) if indicated in late stages	
Musculoskeletal	<ul style="list-style-type: none"> • Orthopedic surgeries to release Achilles tendons & other contractures or scoliosis as needed • Mechanical aids (canes, walkers, orthoses, wheelchairs) as needed to help ambulation • PT & stretching exercises to promote mobility & help prevent contractures 	

PT = physical therapy

Surveillance

Table 6. Recommended Surveillance for Individuals with Emery-Dreifuss Muscular Dystrophy

System/Concern	Evaluation	Frequency
Cardiac	<ul style="list-style-type: none"> • ECG, Holter monitoring, & echocardiography to detect asymptomatic cardiac disease • More advanced & invasive cardiac assessment may be required for those w/ cardiac disease. 	Annual
Respiratory	Pulmonary function tests	If normal, every 2-3 yrs; if abnormal, annually

Agents/Circumstances to Avoid

Although **malignant hyperthermia susceptibility** has not been described in EDMD, it is appropriate to anticipate a possible malignant hyperthermia reaction and to avoid triggering agents such as depolarizing muscle relaxants (succinylcholine) and volatile anesthetic drugs (halothane, isoflurane). Other anesthetic precautions must be considered [Aldwinckle & Carr 2002].

Body weight should be monitored, as affected individuals may be predisposed to obesity.

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic at-risk sibs, parents, and relatives of individuals with EDMD because of the high risk for cardiac complications (including sudden death) associated with EDMD. Evaluation may allow early identification of family members who would benefit from initiation of treatment and preventive measures [Manilal et al 1998, Bécane et al 2000, Boriani et al 2003, Maioli et al 2007, Gueneau et al 2009, Scharner et al 2011, Jimenez-Escrig et al 2012, Stallmeyer et al 2012, Madej-Pilarczyk et al 2018].

Evaluations can include:

- Molecular genetic testing if the pathogenic variant(s) in the family are known;
- Clinical evaluation, including at least muscular and cardiac assessments if the pathogenic variant(s) in the family are not known.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

In a woman with EDMD, pregnancy complications may include the development of cardiomyopathy or progression of preexisting cardiomyopathy, preterm delivery, respiratory involvement, cephalopelvic disproportion, and delivery of a low birth-weight infant. Pregnancy management is challenging, with very limited literature addressing the issue. Caesarean section delivery may be required. Referral of an affected pregnant woman to a specialized obstetric unit in close collaboration with a cardiologist is recommended for optimal pregnancy outcome.

Therapies Under Investigation

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://clinicaltrialsregister.eu) in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Emery-Dreifuss muscular dystrophy (EDMD) is inherited in an X-linked (XL-EDMD), an autosomal dominant (AD-EDMD), or, rarely, an autosomal recessive (AR-EDMD) manner.

X-Linked Inheritance – Risk to Family Members

Parents of a male proband

- The father of an affected male will not have the disease nor will he be hemizygous for the *EMD* or *FHL1* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote (carrier). Note: If a woman has more than one affected son and no other affected relatives and if the *EMD* or *FHL1* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism. One instance of germline mosaicism in XL-EDMD has been reported [Manilal et al 1998].
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote or the affected male may have a *de novo* *EMD* or *FHL1* pathogenic variant, in which case the mother is not a heterozygote. The frequency of *de novo* pathogenic variants is thought to be less than 1/3, although no published data from large series are available [Wulff et al 1997, Yates & Wehnert 1999].
- Female heterozygotes are usually asymptomatic, but they are at risk of developing a cardiac disease, a progressive muscular dystrophy, or an EDMD phenotype [Gueneau et al 2009, Knoblauch et al 2010]. (See Management, Evaluation of Relatives at Risk.)

Sibs of a male proband. The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband has an *EMD* or *FHL1* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected. Females who inherit the pathogenic variant are usually asymptomatic but are at risk of developing a cardiac disease, a progressive muscular dystrophy, or an EDMD phenotype [Gueneau et al 2009, Knoblauch et al 2010]. (See Evaluation of Relatives at Risk.)
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *EMD* or *FHL1* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is low but greater than that of the general population because of the possibility of maternal germline mosaicism. Germline mosaicism has been reported in XL-EDMD [Manilal et al 1998].

Offspring of a proband. Affected males transmit the *EMD* or *FHL1* pathogenic variant to:

- All of their daughters, who will be heterozygotes. Female heterozygotes are usually asymptomatic, but they are at risk of developing a cardiac disease, a progressive muscular dystrophy, or an EDMD phenotype [Gueneau et al 2009, Knoblauch et al 2010]. (See Evaluation of Relatives at Risk.)
- None of their sons.

Other family members. The proband's maternal aunts may be at risk of being carriers and the aunt's offspring, depending on their gender, may be at risk of being heterozygotes or of being affected.

Heterozygote Detection

Molecular genetic testing of at-risk female relatives to determine their genetic status is most informative if the *EMD* or *FHL1* pathogenic variant has been identified in the proband.

Note: Females heterozygous for an *EMD* or *FHL1* pathogenic variant are usually asymptomatic, but they are at risk of developing a cardiac disease, a progressive muscular dystrophy, or an EDMD phenotype [Gueneau et al 2009, Knoblauch et al 2010]. (See Evaluation of Relatives at Risk.)

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Some individuals diagnosed with AD-EDMD have an affected parent.
- A proband with AD-EDMD often has the disorder as the result of a *de novo* *LMNA* pathogenic variant. Current unpublished data indicate that 65% of pathogenic variants are *de novo* [Author, personal observation].
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include molecular genetic testing and clinical evaluation – in particular, cardiac investigations.
- If the pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Germline mosaicism has been reported; its incidence is not known [Bonne et al 1999, Makri et al 2009].
- The family history of some individuals diagnosed with AD-EDMD may appear to be negative because of failure to recognize the disorder in family members, reduced penetrance, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless appropriate evaluations (e.g., molecular genetic testing and cardiac evaluation) have been performed on the parents of the proband. (See Evaluation of Relatives at Risk.)
- If the parent is the individual in whom the pathogenic variant first occurred, s/he may have somatic mosaicism for the variant and may be mildly/minimally affected.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs is 50%.
- If the *LMNA* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is low but slightly greater than that of the general population because of the possibility of parental germline mosaicism.
- If the parents have not been tested for the *LMNA* pathogenic variant identified in the proband but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for AD-EDMD because of the possibility of reduced penetrance in a heterozygous parent or parental germline mosaicism.

Offspring of a proband. Each child of an individual with AD-EDMD has a 50% chance of inheriting the *LMNA* pathogenic variant.

Other family members of a proband. The risk to other family members depends on the genetic status of the proband's parents: if a parent is affected and/or has the pathogenic variant, his or her family members are at risk.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an affected individual are typically obligate heterozygotes (i.e., carriers of one *LMNA* pathogenic variant).
- Heterozygotes are usually asymptomatic and are not at risk of developing the disorder. In rare cases, late-onset cardiac disease may occur [Jimenez-Escrig et al 2012]. (See Evaluation of Relatives at Risk.)

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes are usually asymptomatic and are not at risk of developing the disorder. In rare cases, late-onset cardiac disease may occur [Jimenez-Escrig et al 2012]. (See Evaluation of Relatives at Risk.)

Offspring of a proband. The offspring of an individual with AR-EDMD are obligate heterozygotes for a pathogenic variant in *LMNA*.

Other family members. Each sib of the proband's parents is at a 50% risk of being heterozygous for an *LMNA* pathogenic variant.

Heterozygote Detection

Molecular genetic testing for at-risk relatives requires prior identification of the *LMNA* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with AD-EDMD has the *LMNA* pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are heterozygotes, or are at risk of being heterozygotes.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for EDMD are possible.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click [here](#).

- **National Library of Medicine Genetics Home Reference**
[Emery-Dreifuss muscular dystrophy](#)
- **Association Francaise contre les Myopathies (AFM)**
1 Rue de l'International
BP59
Evry cedex 91002
France
Phone: +33 01 69 47 28 28

Email: dmc@afm.genethon.fr
www.afm-telethon.fr

- **European Neuromuscular Centre (ENMC)**
 Lt Gen van Heutszlaan 6
 3743 JN Baarn
 Netherlands
Phone: 31 35 5480481
Fax: 31 35 5480499
Email: enmc@enmc.org
www.enmc.org
- **Japan Muscular Dystrophy Association**
 3-43-11 Fukushi Zaidan Bldg
 Tokyo 170-0005
 Japan
Phone: 81-3-6907-3521
www.jmda.or.jp
- **Muscular Dystrophy Association (MDA) - USA**
 161 North Clark
 Suite 3550
 Chicago IL 60601
Phone: 800-572-1717
Email: ResourceCenter@mdausa.org
www.mda.org
- **Muscular Dystrophy UK**
 61A Great Suffolk Street
 London SE1 0BU
 United Kingdom
Phone: 0800 652 6352 (toll-free); 020 7803 4800
Email: info@muscular dystrophyuk.org
www.muscular dystrophyuk.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Emery-Dreifuss Muscular Dystrophy: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
<i>EMD</i>	Xq28	Emerin	The UMD-EMD mutations database EMD homepage - Leiden Muscular Dystrophy pages	EMD	EMD
<i>FHL1</i>	Xq26.3	Four and a half LIM domains protein 1	FHL1 homepage - Leiden Muscular Dystrophy pages	FHL1	FHL1

Table A. continued from previous page.

LMNA	1q22	Prelamin-A/C	Human Intermediate Filament Database LMNA (lamin C1) Human Intermediate Filament Database LMNA (lamin A) Human Intermediate Filament Database LMNA (lamin C2) IPN Mutations, LMNA The UMD-LMNA mutations database LMNA homepage - Leiden Muscular Dystrophy pages	LMNA	LMNA
------	------	--------------	---	------	------

Data are compiled from the following standard references: gene from [HGNC](#); chromosome locus from [OMIM](#); protein from [UniProt](#). For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click [here](#).

Table B. OMIM Entries for Emery-Dreifuss Muscular Dystrophy (View All in OMIM)

150330	LAMIN A/C; LMNA
181350	EMERY-DREIFUSS MUSCULAR DYSTROPHY 2, AUTOSOMAL DOMINANT; EDMD2
300163	FOUR-AND-A-HALF LIM DOMAINS 1; FHL1
300384	EMERIN; EMD
300696	MYOPATHY, X-LINKED, WITH POSTURAL MUSCLE ATROPHY; XMPMA
310300	EMERY-DREIFUSS MUSCULAR DYSTROPHY 1, X-LINKED; EDMD1

Molecular Pathogenesis

The genes *EMD*, *LMNA*, and *FHL1* – pathogenic variants in which cause Emery-Dreifuss muscular dystrophy (EDMD) – encode proteins critical for the organization of the nuclear envelope. Although not entirely elucidated, two main mechanisms (not necessarily mutually exclusive) are thought to be involved in EDMD pathogenesis [Broers et al 2006, Worman & Bonne 2007, Worman et al 2009]:

- Structural strain caused by mechanical stress present in skeletal muscle and cardiac muscle
- Modification of gene expression caused by abnormal chromatin organization associated with alteration of proliferation/differentiation and/or signaling pathways of muscle cells

Interactions of these nuclear envelope proteins with chromatin- and nuclear matrix-associated proteins are of particular interest. Both emerin and lamin A/C interact with nuclear actin, a component of the chromatin remodeling complex associated with the nuclear matrix, suggesting that either chromatin arrangement or gene transcription or both could be impaired in the disease [Maraldi et al 2002].

EMD

Gene structure. The gene has six exons. For a detailed summary of gene and protein information, see Table A, [Gene](#).

Pathogenic variants. More than 130 different pathogenic variants have been reported to date (see the [UMD-EMD Database](#)). The majority of pathogenic variants (95%) are null variants: nonsense variants, deletions/insertions, and splice site variants. A few reported missense variants and in-frame deletions lead to decreased expression of emerin or to normal expression of a nonfunctional protein [Ellis et al 1998, Yates et al 1999, Yates & Wehnert 1999, Ellis et al 2000]. Most pathogenic variants are unique to a single family. On occasion, two or three families have the same pathogenic variant. No "hot spot" for pathogenic variants is observed in *EMD*; pathogenic variants are nearly randomly spread out along the gene. (For more information, see Table A.)

Normal gene product. Emerin is a 254-amino-acid serine-rich protein expressed in most tissues. It belongs to a family of type II integral membrane proteins, including lamina-associated protein 2 (LP2; β -thymopoietin) and lamin B receptor. The hydrophobic tail anchors the protein to the inner nuclear membrane and the hydrophilic remainder of the molecule projects into the nucleoplasm, where it interacts with the nuclear lamina [Manilal et al 1996, Yorifuji et al 1997].

Emerin binds directly to lamins A/C and to BAF (OMIM 603811), a DNA-bridging protein. This binding requires conserved residues in a central lamin A-binding domain and the N-terminal LEM domain of emerin, respectively [Clements et al 2000, Lee et al 2001]. BAF is required for the assembly of emerin and A-type lamins at the reforming nuclear envelope during telophase of mitosis and may mediate their stability in the subsequent interphase [Haraguchi et al 2001].

Abnormal gene product. Most pathogenic variants result in no emerin production. In the rare cases in which protein is expressed, either the gene product is lacking the transmembrane domain (in-frame distal deletions) resulting in mislocalization of the protein in the nucleoplasm or cytoplasm, or the abnormal protein is present at the nuclear rim (missense variants) but has weakened interactions with the lamina components [Ellis et al 1999, Fairley et al 1999, Ellis et al 2000].

FHL1

Gene structure. The gene has eight exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Of the more than 40 disease-associated variants reported in *FHL1*, seven have been associated with EDMD [Gueneau et al 2009, Knoblauch et al 2010]. EDMD-associated variants are localized in the distal exons (5-8) of *FHL1*: two missense variants affecting highly conserved cysteines, one abolishing the termination codon, and four out-of-frame insertions or deletions [Gueneau et al 2009]. (For more information, see Table A.)

Normal gene product. Three FHL1 isoforms are produced by alternative splicing of *FHL1*.

FHL1 proteins belong to a protein family containing LIM domains (Lin-11, Isl-1, Mec3), which are highly conserved sequences comprising two zinc fingers in tandem, implicated in numerous interactions. Each of the two zinc fingers contains four highly conserved cysteines linking together one zinc ion [Kadrmas & Beckerle 2004].

The main isoform, FHL1A, is predominantly expressed in striated muscles [Lee et al 1998, Taniguchi et al 1998]. FHL1A can be localized to the sarcolemma, sarcomere, and nucleus of muscle cells [Brown et al 1999, Ng et al 2001]. It has been implicated in sarcomere assembly by interacting with myosin-binding protein C [McGrath et al 2006].

The two other (less abundant) isoforms, FHL1B and FHL1C, are expressed in striated muscles [Brown et al 1999, Ng et al 2001]. FHL1A, FHL1B, and FHL1C are, respectively, composed of 4.5, 3.5, and 2.5 LIM domains. FHL1B and FHL1C have different C-terminal domains, which correspond to nuclear import and export signals in FHL1B and to the RBP-J binding domain in FHL1B and FHL1C [Brown et al 1999, Ng et al 2001].

Abnormal gene product. Pathogenic variants in *FHL1* affect FHL1 isoforms differently since they are located in alternatively spliced exons:

- Missense variants affect highly conserved cysteine residues important for the zinc finger conformation and lead to variable expression level of mutated protein in muscles of affected individuals.
- Loss-of-function variants are expressed at a very low level. In myoblasts from affected individuals myotube formation was severely delayed [Gueneau et al 2009].

LMNA

Gene structure. *LMNA* encodes four transcripts via alternative splicing – two major transcripts: the full-length lamin A (exon 1-12) and a shorter transcript lamin C (exon 1-10); and two minor transcripts: lamin A-delta-10, which lacks exon 10, and lamin C2, which has a different N-terminal start (alternative exon 1) from lamin C. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. More than 450 *LMNA* pathogenic variants are reported to date. See the [UMD-LMNA Database](#) [Bonne et al 2003] and [Leiden Muscular Dystrophy pages](#)[©]. The majority (85%) of pathogenic variants are missense variants. Nonsense variants, small deletions/insertions in-frame or with frameshift, and splice site variants also occur. Pathogenic variants are distributed along the length of the gene [Bonne et al 2000, Brown et al 2001]. A few recurrent pathogenic variants exist [Broers et al 2006]. (For more information, see Table A.)

Pathogenic variants associated with autosomal recessive (AR) disease generally occur at different residues from those responsible for autosomal dominant (AD) disease. As yet, variants cannot be predicted to cause AR or AD disease.

Table 7. Selected *LMNA* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.664C>T	p.His222Tyr ¹	NM_005572.3
c.674G>A	p.Arg225Gln	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See [Quick Reference](#) for an explanation of nomenclature.

1. See Genotype-Phenotype Correlations.

Normal gene product. Four A-type lamins (A, AΔ10, C, and C2) are produced by *LMNA* alternative splicing. Lamin A and lamin C are the two main isoforms. They are initially expressed in muscle of the trunk, head, and appendages. Later, they are ubiquitously expressed. A few myeloid and lymphoid cell lines have no lamins.

The promoter 1C2 located in the first intron of *LMNA* allows transcription of lamin C2. The fourth lamin is lamin AΔ10 (missing exon 10) described in cancer cells [Alsheimer & Benavente 1996, Machiels et al 1996]. Lamins are type V intermediate filaments that form the nuclear lamina, a fibrous network underlying the inner face of the internal nuclear membrane.

Transcription factors such as c-fos, pRb, and Lco1 have been identified as binding partners of Lamin A/C, suggesting possible deregulation of signaling pathways and alteration of proliferation/differentiation of muscle cells [Broers et al 2006, Vlcek & Foisner 2007, Worman & Bonne 2007, Azibani et al 2014].

Abnormal gene product. Missense variants are reported in the majority of cases. Western blot analysis on fibroblasts of affected individuals demonstrates a normal level of protein expression, strongly suggesting that abnormal proteins are expressed [Muchir et al 2004]. Nonsense variants resulting in approximately 50% of normal protein levels have also been described [Bécane et al 2000, Muchir et al 2003].

References

Literature Cited

Aldwinckle RJ, Carr AS. The anesthetic management of a patient with Emery-Dreifuss muscular dystrophy for orthopedic surgery. *Can J Anaesth.* 2002;49:467–70. PubMed PMID: 11983660.

- Alsheimer M, Benavente R. Change of karyoskeleton during mammalian spermatogenesis: expression pattern of nuclear lamin C2 and its regulation. *Exp Cell Res.* 1996;228:181–8. PubMed PMID: 8912709.
- Ankala A, Kohn JN, Hegde A, Meka A, Ephrem CL, Askree SH, Bhide S, Hegde MR. Aberrant firing of replication origins potentially explains intragenic nonrecurrent rearrangements within genes, including the human DMD gene. *Genome Res.* 2012;22:25–34. PubMed PMID: 22090376.
- Askree SH, Chin EL, Bean LH, Coffee B, Tanner A, Hegde M. Detection limit of intragenic deletions with targeted array comparative genomic hybridization. *BMC Genet.* 2013;14:116. PubMed PMID: 24304607.
- Astejada MN, Goto K, Nagano A, Ura S, Noguchi S, Nonaka I, Nishino I, Hayashi YK. Emerinopathy and laminopathy clinical, pathological and molecular features of muscular dystrophy with nuclear envelopathy in Japan. *Acta Myol.* 2007;26:159–64. PubMed PMID: 18646565.
- Azibani F, Muchir A, Vignier N, Bonne G, Bertrand AT. Striated muscle laminopathies. *Semin Cell Dev Biol.* 2014;29:107–15. PubMed PMID: 24440603.
- Bécane HM, Bonne G, Varnous S, Muchir A, Ortega V, Hammouda EH, Urtizbera JA, Lavergne T, Fardeau M, Eymard B, Weber S, Schwartz K, Duboc D. High incidence of sudden death with conduction system and myocardial disease due to lamins A and C gene mutation. *Pacing Clin Electrophysiol.* 2000;23:1661–6. PubMed PMID: 11138304.
- Ben Yaou R, Toutain A, Arimura T, Demay L, Massart C, Peccate C, Muchir A, Llense S, Deburgrave N, Leturcq F, Litim KE, Rahmoun-Chiali N, Richard P, Babuty D, Recan-Budiartha D, Bonne G. Multitissular involvement in a family with LMNA and EMD mutations: Role of digenic mechanism? *Neurology.* 2007;68:1883–94. PubMed PMID: 17536044.
- Benedetti S, Bertini E, Iannaccone S, Angelini C, Trisciani M, Toniolo D, Sferrazza B, Carrera P, Comi G, Ferrari M, Quattrini A, Previtali SC. Dominant LMNA mutations can cause combined muscular dystrophy and peripheral neuropathy. *J Neurol Neurosurg Psychiatry.* 2005;76:1019–21. PubMed PMID: 15965218.
- Benedetti S, Menditto I, Degano M, Rodolico C, Merlini L, D'Amico A, Palmucci L, Berardinelli A, Pegoraro E, Trevisan CP, Morandi L, Moroni I, Galluzzi G, Bertini E, Toscano A, Olivè M, Bonne G, Mari F, Caldara R, Fazio R, Mammì I, Carrera P, Toniolo D, Comi G, Quattrini A, Ferrari M, Previtali SC. Phenotypic clustering of lamin A/C mutations in neuromuscular patients. *Neurology.* 2007;69:1285–92. PubMed PMID: 17377071.
- Bonne G, Ben Yaou R, Demay L, Richard P, Eymard B, Urtizbera JA, Duboc D. Clinical analysis of 32 patients carrying R453W LMNA mutation. *Neuromuscul Disord.* 2002a;12:721.
- Bonne G, Capeau J, De Visser M, Duboc D, Merlini L, Morris GE, Muntoni F, Recan D, Sewry C, Squarzoni S, Stewart C, Talim B, van der Kooi A, Worman H, Schwartz K. 82nd ENMC international workshop, 5th international Emery-Dreifuss muscular dystrophy (EDMD) workshop, 1st Workshop of the MYO-CLUSTER project EUROMEN (European muscle envelope nucleopathies), 15-16 September 2000, Naarden, The Netherlands. *Neuromuscul Disord.* 2002b;12:187–94. PubMed PMID: 11738362.
- Bonne G, Di Barletta MR, Varnous S, Becane HM, Hammouda EH, Merlini L, Muntoni F, Greenberg CR, Gary F, Urtizbera JA, Duboc D, Fardeau M, Toniolo D, Schwartz K. Mutations in the gene encoding lamin A/C cause autosomal dominant Emery-Dreifuss muscular dystrophy. *Nat Genet.* 1999;21:285–8. PubMed PMID: 10080180.
- Bonne G, Mercuri E, Muchir A, Urtizbera A, Becane HM, Recan D, Merlini L, Wehnert M, Boor R, Reuner U, Vorgerd M, Wicklein EM, Eymard B, Duboc D, Penisson-Besnier I, Cuisset JM, Ferrer X, Desguerre I, Lacombe D, Bushby K, Pollitt C, Toniolo D, Fardeau M, Schwartz K, Muntoni F. Clinical and molecular genetic spectrum of autosomal dominant Emery-Dreifuss muscular dystrophy due to mutations of the lamin A/C gene. *Ann Neurol.* 2000;48:170–80. PubMed PMID: 10939567.
- Bonne G, Yaou RB, Beroud C, Boriani G, Brown S, de Visser M, Duboc D, Ellis J, Hausmanowa-Petrusewicz I, Lattanzi G, Merlini L, Morris G, Muntoni F, Opolski G, Pinto YM, Sangiuolo F, Toniolo D, Trembath R, van Berlo JH, van der Kooi AJ, Wehnert M. 108th ENMC International Workshop, 3rd Workshop of the MYO-

- CLUSTER project: EUROMEN, 7th International Emery-Dreifuss Muscular Dystrophy (EDMD) Workshop, 13-15 September 2002, Naarden, The Netherlands. *Neuromuscul Disord*. 2003;13:508–15. PubMed PMID: 12899879.
- Boriani G, Gallina M, Merlini L, Bonne G, Toniolo D, Amati S, Biffi M, Martignani C, Frabetti L, Bonvicini M, Rapezzi C, Branzi A. Clinical relevance of atrial fibrillation/flutter, stroke, pacemaker implant, and heart failure in Emery-Dreifuss muscular dystrophy: a long-term longitudinal study. *Stroke*. 2003;34:901–8. PubMed PMID: 12649505.
- Brodsky GL, Muntoni F, Miodic S, Sinagra G, Sewry C, Mestroni L. Lamin A/C gene mutation associated with dilated cardiomyopathy with variable skeletal muscle involvement. *Circulation*. 2000;101:473–6. PubMed PMID: 10662742.
- Broers JL, Ramaekers FC, Bonne G, Yaou RB, Hutchison CJ. Nuclear lamins: laminopathies and their role in premature ageing. *Physiol Rev*. 2006;86:967–1008. PubMed PMID: 16816143.
- Brown CA, Lanning RW, McKinney KQ, Salvino AR, Cherniske E, Crowe CA, Darras BT, Gominak S, Greenberg CR, Grosman C, Heydemann P, Mendell JR, Pober BR, Sasaki T, Shapiro F, Simpson DA, Suchowersky O, Spence JE. Novel and recurrent mutations in lamin A/C in patients with Emery-Dreifuss muscular dystrophy. *Am J Med Genet*. 2001;102:359–67. PubMed PMID: 11503164.
- Brown S, McGrath MJ, Ooms LM, Gurung R, Maimone MM, Mitchell CA. Characterization of two isoforms of the skeletal muscle LIM protein 1, SLIM1. Localization of SLIM1 at focal adhesions and the isoform slimmer in the nucleus of myoblasts and cytoplasm of myotubes suggests distinct roles in the cytoskeleton and in nuclear-cytoplasmic communication. *J Biol Chem*. 1999;274:27083–91. PubMed PMID: 10480922.
- Canki-Klain N, Recan D, Milicic D, Llense S, Leturcq F, Deburgrave N, Kaplan JC, Debevec M, Zurak N. Clinical variability and molecular diagnosis in a four-generation family with X-linked Emery-Dreifuss muscular dystrophy. *Croat Med J*. 2000;41:389–95. PubMed PMID: 11063761.
- Carboni N, Mura M, Mercuri E, Marrosu G, Manzi RC, Cocco E, Nissardi V, Isola F, Mateddu A, Solla E, Maioli MA, Oppo V, Piras R, Marini S, Lai C, Politano L, Marrosu MG. Cardiac and muscle imaging findings in a family with X-linked Emery-Dreifuss muscular dystrophy. *Neuromuscul Disord*. 2012a;22:152–8. PubMed PMID: 21993399.
- Carboni N, Porcu M, Mura M, Cocco E, Marrosu G, Maioli MA, Solla E, Tranquilli S, Orrù P, Marrosu MG. Evolution of the phenotype in a family with an LMNA gene mutation presenting with isolated cardiac involvement. *Muscle Nerve*. 2010;41:85–91. PubMed PMID: 19768759.
- Carboni N, Sardu C, Cocco E, Marrosu G, Manzi RC, Nissardi V, Isola F, Mateddu A, Solla E, Maioli MA, Oppo V, Piras R, Coghe G, Lai C, Marrosu MG. Cardiac involvement in patients with lamin A/C gene mutations: a cohort observation. *Muscle Nerve*. 2012b;46:187–92. PubMed PMID: 22806367.
- Caux F, Dubosclard E, Lascols O, Buendia B, Chazouilleres O, Cohen A, Courvalin JC, Laroche L, Capeau J, Vigouroux C, Christin-Maitre S. A new clinical condition linked to a novel mutation in lamins A and C with generalized lipodystrophy, insulin-resistant diabetes, disseminated leukomelanodermic papules, liver steatosis, and cardiomyopathy. *J Clin Endocrinol Metab*. 2003;88:1006–13. PubMed PMID: 12629077.
- Charniot JC, Pascal C, Bouchier C, Sébillon P, Salama J, Duboscq-Bidot L, Peuchmaurd M, Desnos M, Artigou JY, Komajda M. Functional consequences of an LMNA mutation associated with a new cardiac and non-cardiac phenotype. *Hum Mutat*. 2003;21:473–81. PubMed PMID: 12673789.
- Chen L, Lee L, Kudlow BA, Dos Santos HG, Sletvold O, Shafeghati Y, Botha EG, Garg A, Hanson NB, Martin GM, Mian IS, Kennedy BK, Oshima J. LMNA mutations in atypical Werner's syndrome. *Lancet*. 2003;362:440–5. PubMed PMID: 12927431.
- Clements L, Manilal S, Love DR, Morris GE. Direct interaction between emerin and lamin A. *Biochem Biophys Res Commun*. 2000;267:709–14. PubMed PMID: 10673356.

- Cowling BS, Cottle DL, Wilding BR, D'Arcy CE, Mitchell CA, McGrath MJ. Four and a half LIM protein 1 gene mutations cause four distinct human myopathies: a comprehensive review of the clinical, histological and pathological features. *Neuromuscul Disord*. 2011;21:237–51. PubMed PMID: 21310615.
- De Backer J, Van Beeumen K, Loeys B, Duytschaever M. Expanding the phenotype of sudden cardiac death-An unusual presentation of a family with a Lamin A/C mutation. *Int J Cardiol*. 2010;138:97–9. PubMed PMID: 18691775.
- De Sandre-Giovannoli A, Bernard R, Cau P, Navarro C, Amiel J, Boccaccio I, Lyonnet S, Stewart CL, Munnich A, Le Merrer M, Lévy N. Lamin a truncation in Hutchinson-Gilford progeria. *Science*. 2003;300:2055. PubMed PMID: 12702809.
- De Sandre-Giovannoli A, Chaouch M, Kozlov S, Vallat JM, Tazir M, Kassouri N, Szepetowski P, Hammadouche T, Vandenberghe A, Stewart CL, Grid D, Levy N. 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;70:726–36. PubMed PMID: 11799477.
- Decaudain A, Vantighem MC, Guerci B, Hécart AC, Auclair M, Reznik Y, Narbonne H, Ducluzeau PH, Donadille B, Lebbé C, Béréziat V, Capeau J, Lascols O, Vigouroux C. New metabolic phenotypes in laminopathies: LMNA mutations in patients with severe metabolic syndrome. *J Clin Endocrinol Metab*. 2007;92:4835–44. PubMed PMID: 17711925.
- Deconinck N, Dion E, Ben Yaou R, Ferreiro A, Eymard B, Briñas L, Payan C, Voit T, Guicheney P, Richard P, Allamand V, Bonne G, Stojkovic T. Differentiating Emery-Dreifuss muscular dystrophy and collagen VI-related myopathies using a specific CT scanner pattern. *Neuromuscul Disord*. 2010;20:517–23. PubMed PMID: 20576434.
- Díaz-Manera J, Alejaldre A, González L, Olivé M, Gómez-Andrés D, Muelas N, Vilchez JJ, Llauger J, Carbonell P, Márquez-Infante C, Fernández-Torrón R, Poza JJ, López de Munáin A, González-Quereda L, Mirabet S, Clarimon J, Gallano P, Rojas-García R, Gallardo E, Illa I. Muscle imaging in muscle dystrophies produced by mutations in the EMD and LMNA genes. *Neuromuscul Disord*. 2016;26:33–40. PubMed PMID: 26573435.
- Ellis JA, Brown CA, Tilley LD, Kendrick-Jones J, Spence JE, Yates JR. Two distal mutations in the gene encoding emerin have profoundly different effects on emerin protein expression. *Neuromuscul Disord*. 2000;10:24–30. PubMed PMID: 10677860.
- Ellis JA, Craxton M, Yates JR, Kendrick-Jones J. Aberrant intracellular targeting and cell cycle-dependent phosphorylation of emerin contribute to the Emery-Dreifuss muscular dystrophy phenotype. *J Cell Sci*. 1998;111:781–92. PubMed PMID: 9472006.
- Ellis JA, Yates JR, Kendrick-Jones J, Brown CA. Changes at P183 of emerin weaken its protein-protein interactions resulting in X-linked Emery-Dreifuss muscular dystrophy. *Hum Genet*. 1999;104:262–8. PubMed PMID: 10323252.
- Emery AE. Emery-Dreifuss muscular dystrophy. *Neuromuscul Disord*. 2000;10:228–32. PubMed PMID: 10838246.
- Emery AEH. *Diagnostic Criteria for Neuromuscular Disorders*. London: Royal Society of Medicine Press; 1997.
- Eriksson M, Brown WT, Gordon LB, Glynn MW, Singer J, Scott L, Erdos MR, Robbins CM, Moses TY, Berglund P, Dutra A, Pak E, Durkin S, Csoka AB, Boehnke M, Glover TW, Collins FS. Recurrent de novo point mutations in lamin A cause Hutchinson-Gilford progeria syndrome. *Nature*. 2003;423:293–8. PubMed PMID: 12714972.
- Fairley EA, Kendrick-Jones J, Ellis JA. The Emery-Dreifuss muscular dystrophy phenotype arises from aberrant targeting and binding of emerin at the inner nuclear membrane. *J Cell Sci*. 1999;112:2571–82. PubMed PMID: 10393813.

- Fanin M, Nascimbeni AC, Aurino S, Tasca E, Pegoraro E, Nigro V, Angelini C. Frequency of LGMD gene mutations in Italian patients with distinct clinical phenotypes. *Neurology*. 2009;72:1432–5. PubMed PMID: 19380703.
- Fatkin D, MacRae C, Sasaki T, Wolff MR, Porcu M, Frenneaux M, Atherton J, Vidaillet HJ Jr, Spudich S, De Girolami U, Seidman JG, Seidman C, Muntoni F, Muehle G, Johnson W, McDonough B. 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;341:1715–24. PubMed PMID: 10580070.
- Fidziańska A, Glinka Z. Nuclear architecture remodelling in envelopopathies. *Folia Neuropathol*. 2007;45:47–55. PubMed PMID: 17594594.
- Fidziańska A, Hausmanowa-Petrusewicz I. Architectural abnormalities in muscle nuclei. Ultrastructural differences between X-linked and autosomal dominant forms of EDMD. *J Neurol Sci*. 2003;210:47–51. PubMed PMID: 12736087.
- Fidziańska A, Toniolo D, Hausmanowa-Petrusewicz I. Ultrastructural abnormality of sarcolemmal nuclei in Emery-Dreifuss muscular dystrophy (EDMD). *J Neurol Sci*. 1998;159:88–93. PubMed PMID: 9700709.
- Forissier JF, Bonne G, Bouchier C, Duboscq-Bidot L, Richard P, Wisniewski C, Briault S, Moraine C, Dubourg O, Schwartz K, Komajda M. Apical left ventricular aneurysm without atrio-ventricular block due to a lamin A/C gene mutation. *Eur J Heart Fail*. 2003;5:821–5. PubMed PMID: 14675861.
- Friedrich FW, Wilding BR, Reischmann S, Crocini C, Lang P, Charron P, Müller OJ, McGrath MJ, Vollert I, Hansen A, Linke WA, Hengstenberg C, Bonne G, Morner S, Wichter T, Madeira H, Arbustini E, Eschenhagen T, Mitchell CA, Isnard R, Carrier L. Evidence for FHL1 as a novel disease gene for isolated hypertrophic cardiomyopathy. *Hum Mol Genet*. 2012;21:3237–54. PubMed PMID: 22523091.
- Fujimoto S, Ishikawa T, Saito M, Wada Y, Wada I, Arahata K, Nonaka I. Early onset of X-linked Emery-Dreifuss muscular dystrophy in a boy with emerin gene deletion. *Neuropediatrics*. 1999;30:161–3. PubMed PMID: 10480214.
- Garg A, Speckman RA, Bowcock AM. Multisystem dystrophy syndrome due to novel missense mutations in the amino-terminal head and alpha-helical rod domains of the lamin A/C gene. *Am J Med*. 2002;112:549–55. PubMed PMID: 12015247.
- Goizet C, Ben Yaou R, Demay L, Richard P, Bouillot S, Rouanet M, Hermosilla E, Le Masson G, Lagueny A, Bonne G, Ferrer X. A new mutation of lamin A/C gene leading to autosomal dominant axonal neuropathy, muscular dystrophy, cardiac disease and leukonychia. *J Med Genet*. 2004;41:e29. PubMed PMID: 14985400.
- Granger B, Gueneau L, Drouin-Garraud V, Pedergrana V, Gagnon F, Ben Yaou R, Tezenas du Montcel S, Bonne G. Modifier locus of the skeletal muscle involvement in Emery-Dreifuss muscular dystrophy. *Hum Genet*. 2011;129:149–59. PubMed PMID: 21063730.
- Gueneau L, Bertrand AT, Jais JP, Salih MA, Stojkovic T, Wehnert M, Hoeltzenbein M, Spuler S, Saitoh S, Verschueren A, Tranchant C, Beuvin M, Lacene E, Romero NB, Heath S, Zelenika D, Voit T, Eymard B, Ben Yaou R, Bonne G. Mutations of the FHL1 gene cause Emery-Dreifuss muscular dystrophy. *Am J Hum Genet*. 2009;85:338–53. PubMed PMID: 19716112.
- Haraguchi T, Koujin T, Segura-Totten M, Lee KK, Matsuoka Y, Yoneda Y, Wilson KL, Hiraoka Y. BAF is required for emerin assembly into the reforming nuclear envelope. *J Cell Sci*. 2001;114:4575–85. PubMed PMID: 11792822.
- Hermida-Prieto M, Monserrat L, Castro-Beiras A, Laredo R, Soler R, Peteiro J, Rodriguez E, Bouzas B, Alvarez N, Muniz J, Crespo-Leiro M. Familial dilated cardiomyopathy and isolated left ventricular noncompaction associated with lamin A/C gene mutations. *Am J Cardiol*. 2004;94:50–4. PubMed PMID: 15219508.

- Hoeltzenbein M, Karow T, Zeller JA, Warzok R, Wulff K, Zschesche M, Herrmann FH, Grosse-Heitmeyer W, Wehnert MS. Severe clinical expression in X-linked Emery-Dreifuss muscular dystrophy. *Neuromuscul Disord.* 1999;9:166–70. PubMed PMID: 10382910.
- Homma K, Nagata E, Hanano H, Uesugi T, Ohnuki Y, Matsuda S, Kazahari S, Takizawa S. A young patient with Emery-Dreifuss muscular dystrophy treated with endovascular therapy for cardioembolic stroke: a case report. *Tokai J Exp Clin Med.* 2018;43:103–5. PubMed PMID: 30191544.
- Hopkins LC, Jackson JA, Elsas LJ. Emery-dreifuss humeroperoneal muscular dystrophy: an x-linked myopathy with unusual contractures and bradycardia. *Ann Neurol.* 1981;10:230–7. PubMed PMID: 7294729.
- Jimenez-Escrig A, Gobernado I, Garcia-Villanueva M, Sanchez-Herranz A. Autosomal recessive Emery-Dreifuss muscular dystrophy caused by a novel mutation (R225Q) in the lamin A/C gene identified by exome sequencing. *Muscle Nerve.* 2012;45:605–10. PubMed PMID: 22431096.
- Kadrmaz JL, Beckerle MC. The LIM domain: from the cytoskeleton to the nucleus. *Nat Rev Mol Cell Biol.* 2004;5:920–31. PubMed PMID: 15520811.
- Kärkkäinen S, Helio T, Miettinen R, Tuomainen P, Peltola P, Rummukainen J, Ylitalo K, Kaartinen M, Kuusisto J, Toivonen L, Nieminen MS, Laakso M, Peuhkurinen K. A novel mutation, Ser143Pro, in the lamin A/C gene is common in finnish patients with familial dilated cardiomyopathy. *Eur Heart J.* 2004;25:885–93. PubMed PMID: 15140538.
- Karst ML, Herron KJ, Olson TM. X-linked non-syndromic sinus node dysfunction and atrial fibrillation caused by emerin mutation. *J Cardiovasc Electrophysiol.* 2008;19:510–5. PubMed PMID: 18266676.
- Knoblauch H, Geier C, Adams S, Budde B, Rudolph A, Zacharias U, Schulz-Menger J, Spuler A, Yaou RB, Nürnberg P, Voit T, Bonne G, Spuler S. Contractures and hypertrophic cardiomyopathy in a novel FHL1 mutation. *Ann Neurol.* 2010;67:136–40. PubMed PMID: 20186852.
- Komaki H, Hayashi YK, Tsuburaya R, Sugie K, Kato M, Nagai T, Imataka G, Suzuki S, Saitoh S, Asahina N, Honke K, Higuchi Y, Sakuma H, Saito Y, Nakagawa E, Sugai K, Sasaki M, Nonaka I, Nishino I. Inflammatory changes in infantile-onset LMNA-associated myopathy. *Neuromuscul Disord.* 2011;21:563–8. PubMed PMID: 21632249.
- Krimm I, Ostlund C, Gilquin B, Couprie J, Hossenlopp P, Mornon JP, Bonne G, Courvalin JC, Worman HJ, Zinn-Justin S. The Ig-like structure of the C-terminal domain of lamin A/C, mutated in muscular dystrophies, cardiomyopathy, and partial lipodystrophy. *Structure.* 2002;10:811–23. PubMed PMID: 12057196.
- Lee KK, Haraguchi T, Lee RS, Koujin T, Hiraoka Y, Wilson KL. Distinct functional domains in emerin bind lamin A and DNA-bridging protein BAF. *J Cell Sci.* 2001;114:4567–73. PubMed PMID: 11792821.
- Lee SM, Tsui SK, Chan KK, Garcia-Barcelo M, Wayne MM, Fung KP, Liew CC, Lee CY. Chromosomal mapping, tissue distribution and cDNA sequence of four-and-a-half LIM domain protein 1 (FHL1). *Gene.* 1998;216:163–70. PubMed PMID: 9714789.
- Machiels BM, Zorenc AH, Endert JM, Kuijpers HJ, van Eys GJ, Ramaekers FC, Broers JL. An alternative splicing product of the lamin A/C gene lacks exon 10. *J Biol Chem.* 1996;271:9249–53. PubMed PMID: 8621584.
- Madej-Pilarczyk A. Clinical aspects of Emery-Dreifuss muscular dystrophy. *Nucleus.* 2018;9:268–74. PubMed PMID: 29633897.
- Madej-Pilarczyk A, Marchel M, Ochman K, Cegielska J, Steckiewicz R. Low-symptomatic skeletal muscle disease in patients with a cardiac disease - Diagnostic approach in skeletal muscle laminopathies. *Neurol Neurochir Pol.* 2018;52:174–80. PubMed PMID: 28987496.
- Maioli MA, Marrosu G, Mateddu A, Solla E, Carboni N, Tacconi P, Lai C, Marrosu MG. A novel mutation in the central rod domain of lamin A/C producing a phenotype resembling the Emery-Dreifuss muscular dystrophy phenotype. *Muscle Nerve.* 2007;36:828–32. PubMed PMID: 17701980.

- Makri S, Clarke NF, Richard P, Maugendre S, Demay L, Bonne G, Guicheney P. Germinal mosaicism for LMNA mimics autosomal recessive congenital muscular dystrophy. *Neuromuscul Disord.* 2009;19:26–8. PubMed PMID: 19084400.
- Manilal S, Nguyen TM, Sewry CA, Morris GE. The Emery-Dreifuss muscular dystrophy protein, emerin, is a nuclear membrane protein. *Hum Mol Genet.* 1996;5:801–8. PubMed PMID: 8776595.
- Manilal S, Recan D, Sewry CA, Hoeltzenbein M, Llense S, Leturcq F, Deburgrave N, Barbot J, Man N, Muntoni F, Wehnert M, Kaplan J, Morris GE. Mutations in Emery-Dreifuss muscular dystrophy and their effects on emerin protein expression. *Hum Mol Genet.* 1998;7:855–64. PubMed PMID: 9536090.
- Manilal S, Sewry CA, Man N, Muntoni F, Morris GE. Diagnosis of X-linked Emery-Dreifuss muscular dystrophy by protein analysis of leucocytes and skin with monoclonal antibodies. *Neuromuscul Disord.* 1997;7:63–6. PubMed PMID: 9132142.
- Maraldi NM, Lattanzi G, Sabatelli P, Ognibene A, Squarzoni S. Functional domains of the nucleus: implications for Emery-Dreifuss muscular dystrophy. *Neuromuscul Disord.* 2002;12:815–23. PubMed PMID: 12398831.
- McGrath MJ, Cottle DL, Nguyen MA, Dyson JM, Coghill ID, Robinson PA, Holdsworth M, Cowling BS, Hardeman EC, Mitchell CA, Brown S. Four and a half LIM protein 1 binds myosin-binding protein C and regulates myosin filament formation and sarcomere assembly. *J Biol Chem.* 2006;281:7666–83. PubMed PMID: 16407297.
- Meinke P, Nguyen TD, Wehnert MS. The LINC complex and human disease. *Biochem Soc Trans.* 2011;39:1693–7. PubMed PMID: 22103509.
- Menezes MP, Waddell LB, Evesson FJ, Cooper S, Webster R, Jones K, Mowat D, Kiernan MC, Johnston HM, Corbett A, Harbord M, North KN, Clarke NF. Importance and challenge of making an early diagnosis in LMNA-related muscular dystrophy. *Neurology.* 2012;78:1258–63. PubMed PMID: 22491857.
- Mercuri E, Brown SC, Nihoyannopoulos P, Poulton J, Kinali M, Richard P, Piercy RJ, Messina S, Sewry C, Burke MM, McKenna W, Bonne G, Muntoni F. Extreme variability of skeletal and cardiac muscle involvement in patients with mutations in exon 11 of the lamin A/C gene. *Muscle Nerve.* 2005;31:602–9. PubMed PMID: 15770669.
- Mercuri E, Counsell S, Allsop J, Jungbluth H, Kinali M, Bonne G, Schwartz K, Bydder G, Dubowitz V, Muntoni F. Selective muscle involvement on magnetic resonance imaging in autosomal dominant Emery-Dreifuss muscular dystrophy. *Neuropediatrics.* 2002;33:10–4. PubMed PMID: 11930270.
- Mercuri E, Manzur AY, Jungbluth H, Bonne G, Muchir A, Sewry C, Schwartz K, Muntoni F. Early and severe presentation of autosomal dominant Emery-Dreifuss muscular dystrophy (EMD2). *Neurology.* 2000;54:1704–5. PubMed PMID: 10762524.
- Mercuri E, Poppe M, Quinlivan R, Messina S, Kinali M, Demay L, Bourke J, Richard P, Sewry C, Pike M, Bonne G, Muntoni F, Bushby K. Extreme variability of phenotype in patients with an identical missense mutation in the lamin A/C gene: from congenital onset with severe phenotype to milder classic Emery-Dreifuss variant. *Arch Neurol.* 2004;61:690–4. PubMed PMID: 15148145.
- Mittelbronn M, Hanisch F, Gleichmann M, Stötter M, Korinthenberg R, Wehnert M, Bonne G, Rudnik-Schöneborn S, Bornemann A. Myofiber degeneration in autosomal dominant Emery-Dreifuss muscular dystrophy (AD-EDMD) (LGMD1B). *Brain Pathol.* 2006; 2006;16:266–72. PubMed PMID: 17107595.
- Mora M, Cartegni L, Di Blasi C, Barresi R, Bione S, Raffaele di Barletta M, Morandi L, Merlini L, Nigro V, Politano L, Donati MA, Cornelio F, Cobianchi F, Toniolo D. X-linked Emery-Dreifuss muscular dystrophy can be diagnosed from skin biopsy or blood sample. *Ann Neurol.* 1997;42:249–53. PubMed PMID: 9266737.
- Muchir A, Bonne G, van der Kooi AJ, van Meegen M, Baas F, Bolhuis PA, de Visser M, Schwartz K. 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;9:1453–9. PubMed PMID: 10814726.
- Muchir A, Medioni J, Laluc M, Massart C, Arimura T, Kooi AJ, Desguerre I, Mayer M, Ferrer X, Briault S, Hirano M, Worman HJ, Mallet A, Wehnert M, Schwartz K, Bonne G. Nuclear envelope alterations in fibroblasts from patients with muscular dystrophy, cardiomyopathy, and partial lipodystrophy carrying lamin A/C gene mutations. *Muscle Nerve.* 2004;30:444. PubMed PMID: 15372542.
- Muchir A, van Engelen BG, Lammens M, Mislou JM, McNally E, Schwartz K, Bonne G. Nuclear envelope alterations in fibroblasts from LGMD1B patients carrying nonsense Y259X heterozygous or homozygous mutation in lamin A/C gene. *Exp Cell Res.* 2003;291:352–62. PubMed PMID: 14644157.
- Muntoni F, Bonne G, Goldfarb LG, Mercuri E, Piercy RJ, Burke M, Yaou RB, Richard P, Recan D, Shatunov A, Sewry CA, Brown SC. Disease severity in dominant Emery Dreifuss is increased by mutations in both emerin and desmin proteins. *Brain.* 2006;129:1260–8. PubMed PMID: 16585054.
- Muntoni F, Lichtarowicz-Krynska EJ, Sewry CA, Manilal S, Recan D, Llense S, Taylor J, Morris GE, Dubowitz V. Early presentation of X-linked Emery-Dreifuss muscular dystrophy resembling limb-girdle muscular dystrophy. *Neuromuscul Disord.* 1998;8:72–6. PubMed PMID: 9608559.
- Navarro CL, De Sandre-Giovannoli A, Bernard R, Boccaccio I, Boyer A, Geneviève D, Hadj-Rabia S, Gaudy-Marqueste C, Smitt HS, Vabres P, Faivre L, Verloes A, Van Essen T, Flori E, Hennekam R, Beemer FA, Laurent N, Le Merrer M, Cau P, Lévy N. Lamin A and ZMPSTE24 (FACE-1) defects cause nuclear disorganization and identify restrictive dermopathy as a lethal neonatal laminopathy. *Hum Mol Genet.* 2004;13:2493–503. PubMed PMID: 15317753.
- Ng EK, Lee SM, Li HY, Ngai SM, Tsui SK, Waye MM, Lee CY, Fung KP. Characterization of tissuespecific.LIM domain protein (FHL1C) which is an alternatively.spliced isoform of a human LIM-only protein (FHL1). *J Cell Biochem.* 2001;82:1–10. PubMed PMID: 11400158.
- Norwood FL, Harling C, Chinnery PF, Eagle M, Bushby K, Straub V. Prevalence of genetic muscle disease in Northern England: in-depth analysis of a muscle clinic population. *Brain.* 2009;132:3175–86. PubMed PMID: 19767415.
- Novelli G, Muchir A, Sangiuolo F, Helbling-Leclerc A, D'Apice MR, Massart C, Capon F, Sbraccia P, Federici M, Lauro R, Tudisco C, Pallotta R, Scarano G, Dallapiccola B, Merlini L, Bonne G. Mandibuloacral dysplasia is caused by a mutation in LMNA-encoding lamin A/C. *Am J Hum Genet.* 2002;71:426–31. PubMed PMID: 12075506.
- Quarta G, Syrris P, Ashworth M, Jenkins S, Zuborne Alapi K, Morgan J, Muir A, Pantazis A, McKenna WJ, Elliott PM. Mutations in the Lamin A/C gene mimic arrhythmogenic right ventricular cardiomyopathy. *Eur Heart J.* 2012;33:1128–36. PubMed PMID: 22199124.
- Quijano-Roy S, Mbieleu B, Bönnemann CG, Jeannot PY, Colomer J, Clarke NF, Cuisset JM, Roper H, De Meirleir L, D'Amico A, Ben Yaou R, Nascimento A, Barois A, Demay L, Bertini E, Ferreiro A, Sewry CA, Romero NB, Ryan M, Muntoni F, Guicheney P, Richard P, Bonne G, Estournet B. De novo LMNA mutations cause a new form of Congenital Muscular Dystrophy (L-CMD). *Ann Neurol.* 2008;64:177–86. PubMed PMID: 18551513.
- Quinzii CM, Vu TH, Min KC, Tanji K, Barral S, Grewal RP, Kattah A, Camaño P, Otaegui D, Kunimatsu T, Blake DM, Wilhelmsen KC, Rowland LP, Hays AP, Bonilla E, Hirano M. X-linked dominant scapuloperoneal myopathy is due to a mutation in the gene encoding four-and-a-half-LIM protein 1. *Am J Hum Genet.* 2008;82:208–13. PubMed PMID: 18179901.
- Raffaele Di Barletta M, Ricci E, Galluzzi G, Tonali P, Mora M, Morandi L, Romorini A, Voit T, Orstavik KH, Merlini L, Trevisan C, Biancalana V, Housmanowa-Petrusewicz I, Bione S, Ricotti R, Schwartz K, Bonne G, Toniolo D. Different mutations in the LMNA gene cause autosomal dominant and autosomal recessive Emery-Dreifuss muscular dystrophy. *Am J Hum Genet.* 2000;66:1407–12. PubMed PMID: 10739764.

- Rankin J, Auer-Grumbach M, Bagg W, Colclough K, Nguyen TD, Fenton-May J, Hattersley A, Hudson J, Jardine P, Josifova D, Longman C, McWilliam R, Owen K, Walker M, Wehnert M, Ellard S. Extreme phenotypic diversity and onpenetrance in families with the LMNA gene mutation R644C. *Am J Med Genet A*. 2008;146A:1530–42. PubMed PMID: 18478590.
- Redondo-Vergé L, Yaou RB, Fernández-Recio M, Dinca L, Richard P, Bonne G. Cardioembolic stroke prompting diagnosis of LMNA-associated Emery-Dreifuss muscular dystrophy. *Muscle Nerve*. 2011;44:587–9. PubMed PMID: 21922471.
- Renou L, Stora S, Yaou RB, Volk M, Sinkovec M, Demay L, Richard P, Peterlin B, Bonne G. Heart-hand syndrome of Slovenian type: a new kind of laminopathy. *J Med Genet*. 2008;45:666–71. PubMed PMID: 18611980.
- Sabatelli P, Lattanzi G, Ognibene A, Columbaro M, Capanni C, Merlini L, Maraldi NM, Squarzoni S. Nuclear alterations in autosomal-dominant Emery-Dreifuss muscular dystrophy. *Muscle Nerve*. 2001;24:826–9. PubMed PMID: 11360268.
- Sakata K, Shimizu M, Ino H, Yamaguchi M, Terai H, Fujino N, Hayashi K, Kaneda T, Inoue M, Oda Y, Fujita T, Kaku B, Kanaya H, Mabuchi H. High incidence of sudden cardiac death with conduction disturbances and atrial cardiomyopathy caused by a nonsense mutation in the STA gene. *Circulation*. 2005;111:3352–8. PubMed PMID: 15967842.
- Sanna T, Dello Russo A, Toniolo D, Vytopil M, Pelargonio G, De Martino G, Ricci E, Silvestri G, Giglio V, Messano L, Zachara E, Bellocchi F. Cardiac features of Emery-Dreifuss muscular dystrophy caused by lamin A/C gene mutations. *Eur Heart J*. 2003;24:2227–36. PubMed PMID: 14659775.
- Scharner J, Brown CA, Bower M, Iannaccone ST, Khatiri IA, Escolar D, Gordon E, Felice K, Crowe CA, Grosmann C, Meriggioli MN, Asamoah A, Gordon O, Gnocchi VF, Ellis JA, Mendell JR, Zammit PS. Novel LMNA mutations in patients with Emery-Dreifuss muscular dystrophy and functional characterization of four LMNA mutations. *Hum Mutat*. 2011;32:152–67. PubMed PMID: 20848652.
- Schessl J, Zou Y, McGrath MJ, Cowling BS, Maiti B, Chin SS, Sewry C, Battini R, Hu Y, Cottle DL, Rosenblatt M, Spruce L, Ganguly A, Kirschner J, Judkins AR, Golden JA, Goebel HH, Muntoni F, Flanigan KM, Mitchell CA, Bönnemann CG. Proteomic identification of FHL1 as the protein mutated in human reducing body myopathy. *J Clin Invest*. 2008;118:904–12. PubMed PMID: 18274675.
- Sébillon P, Bouchier C, Bidot LD, Bonne G, Ahamed K, Charron P, Drouin-Garraud V, Millaire A, Desrumeaux G, Benaiche A, Charniot JC, Schwartz K, Villard E, Komajda M. Expanding the phenotype of LMNA mutations in dilated cardiomyopathy and functional consequences of these mutations. *J Med Genet*. 2003;40:560–7. PubMed PMID: 12920062.
- Sewry CA, Brown SC, Mercuri E, Bonne G, Feng L, Camici G, Morris GE, Muntoni F. Skeletal muscle pathology in autosomal dominant Emery-Dreifuss muscular dystrophy with lamin A/C mutations. *Neuropathol Appl Neurobiol*. 2001;27:281–90. PubMed PMID: 11532159.
- Sframeli M, Sarkozy A, Bertoli M, Astrea G, Hudson J, Scoto M, Mein R, Yau M, Phadke R, Feng L, Sewry C, Fen ANS, Longman C, McCullagh G, Straub V, Robb S, Manzur A, Bushby K, Muntoni F. Congenital muscular dystrophies in the UK population: Clinical and molecular spectrum of a large cohort diagnosed over a 12-year period. *Neuromuscul Disord*. 2017;27:793–803. PubMed PMID: 28688748.
- Shackleton S, Lloyd DJ, Jackson SN, Evans R, Niermeijer MF, Singh BM, Schmidt H, Brabant G, Kumar S, Durrington PN, Gregory S, O'Rahilly S, Trembath RC. LMNA, encoding lamin A/C, is mutated in partial lipodystrophy. *Nat Genet*. 2000;24:153–6. PubMed PMID: 10655060.
- Shalaby S, Hayashi YK, Goto K, Ogawa M, Nonaka I, Noguchi S, Nishino I. Rigid spine syndrome caused by a novel mutation in four-and-a-half LIM domain 1 gene (FHL1). *Neuromuscul. Disord*. 2008;18:959–61. PubMed PMID: 18952429.

- Sheikh F, Raskin A, Chu PH, Lange S, Domenighetti AA, Zheng M, Liang X, Zhang T, Yajima T, Gu Y, Dalton ND, Mahata SK, Dorn GW 2nd, Brown JH, Peterson KL, Omens JH, McCulloch AD, Chen J. An FHL1-containing complex within the cardiomyocyte sarcomere mediates hypertrophic biomechanical stress responses in mice. *J. Clin. Invest.* 2008;118:3870–80. PubMed PMID: 19033658.
- Small K, Warren ST. Emerin deletions occurring on both Xq28 inversion backgrounds. *Hum Mol Genet.* 1998;7:135–9. PubMed PMID: 9384614.
- Stallmeyer B, Koopmann M, Schulze-Bahr E. Identification of novel mutations in LMNA associated with familial forms of dilated cardiomyopathy. *Genet Test Mol Biomarkers.* 2012;16:543–9. PubMed PMID: 22224630.
- Talkop UA, Talvik I, Sonajalg M, Sibul H, Kolk A, Pirsoo A, Warzok R, Wulff K, Wehnert MS, Talvik T. Early onset of cardiomyopathy in two brothers with X-linked Emery-Dreifuss muscular dystrophy. *Neuromuscul Disord.* 2002;12:878–81. PubMed PMID: 12398842.
- Taniguchi Y, Furukawa T, Tun T, Han H, Honjo T. LIM protein KyoT2 negatively regulates transcription by association with the RBP-J DNA-binding protein. *Mol Cell Biol.* 1998;18:644–54. PubMed PMID: 9418910.
- Tiffin HR, Jenkins ZA, Gray MJ, Cameron-Christie SR, Eaton J, Aftimos S, Markie D, Robertson SP. Dysregulation of FHL1 spliceforms due to an indel mutation produces an Emery-Dreifuss muscular dystrophy plus phenotype. *Neurogenetics.* 2013;14:113–21. PubMed PMID: 23456229.
- Ura S, Hayashi YK, Goto K, Atejada MN, Murakami T, Nagato M, Ohta S, Daimon Y, Takekawa H, Hirata K, Nonaka I, Noguchi S, Nishino I. Limb-girdle muscular dystrophy due to emerin gene mutations. *Arch Neurol.* 2007;64:1038–41. PubMed PMID: 17620497.
- van Berlo JH, de Voogt WG, van der Kooi AJ, van Tintelen JP, Bonne G, Yaou RB, Duboc D, Rossenbacker T, Heidbuchel H, de Visser M, Crijns HJ, Pinto YM. Meta-analysis of clinical characteristics of 299 carriers of LMNA gene mutations: do lamin A/C mutations portend a high risk of sudden death? *J Mol Med.* 2005;83:79–83. PubMed PMID: 15551023.
- van der Kooi AJ, Bonne G, Eymard B, Duboc D, Talim B, Van der Valk M, Reiss P, Richard P, Demay L, Merlini L, Schwartz K, Busch HF, de Visser M. Lamin A/C mutations with lipodystrophy, cardiac abnormalities, and muscular dystrophy. *Neurology.* 2002;59:620–3. PubMed PMID: 12196663.
- van der Kooi AJ, Ledderhof TM, de Voogt WG, Res CJ, Bouwsma G, Troost D, Busch HF, Becker AE, de Visser M. A newly recognized autosomal dominant limb girdle muscular dystrophy with cardiac involvement. *Ann Neurol.* 1996;39:636–42. PubMed PMID: 8619549.
- Van Esch H, Agarwal AK, Debeer P, Fryns JP, Garg A. A homozygous mutation in the lamin A/C gene associated with a novel syndrome of arthropathy, tendinous calcinosis, and progeroid features. *J Clin Endocrinol Metab.* 2006;91:517–21. PubMed PMID: 16278265.
- Vlcek S, Foisner R. A-type lamin networks in light of laminopathic diseases. *Biochim Biophys Acta.* 2007;1773:661–74. PubMed PMID: 16934891.
- Vytopil M, Ricci E, Dello Russo A, Hanisch F, Neudecker S, Zierz S, Ricotti R, Demay L, Richard P, Wehnert M, Bonne G, Merlini L, Toniolo D. Frequent low penetrance mutations in the Lamin A/C gene, causing Emery Dreifuss muscular dystrophy. *Neuromuscul Disord.* 2002;12:958–63. PubMed PMID: 12467752.
- Walter MC, Witt TN, Weigel BS, Reilich P, Richard P, Pongratz D, Bonne G, Wehnert MS, Lochmuller H. Deletion of the LMNA initiator codon leading to a neurogenic variant of autosomal dominant Emery-Dreifuss muscular dystrophy. *Neuromuscul Disord.* 2005;15:40–4. PubMed PMID: 15639119.
- Windpassinger C, Schoser B, Straub V, Hochmeister S, Noor A, Lohberger B, Farra N, Petek E, Schwarzbraun T, Ofner L. An X-linked myopathy with postural muscle atrophy and generalized hypertrophy, termed XMPMA, is caused by mutations in FHL1. *Am J Hum Genet.* 2008;82:88–99. PubMed PMID: 18179888.

- Witt TN, Garner CG, Pongratz D, Baur X. Autosomal dominant Emery-Dreifuss syndrome: evidence of a neurogenic variant of the disease. *Eur Arch Psychiatry Neurol Sci.* 1988;237:230–6. PubMed PMID: 3203701.
- Worman HJ, Bonne G. "Laminopathies": a wide spectrum of human diseases. *Exp Cell Res.* 2007;313:2121–33. PubMed PMID: 17467691.
- Worman HJ, Fong LG, Muchir A, Young SG. Laminopathies and the long strange trip from basic cell biology to therapy. *J Clin Invest.* 2009;119:1825–36. PubMed PMID: 19587457.
- Wulff K, Parrish JE, Herrmann FH, Wehnert M. Six novel mutations in the emerin gene causing X-linked Emery-Dreifuss muscular dystrophy. *Hum Mutat.* 1997;9:526–30. PubMed PMID: 9195226.
- Yates JR, Bagshaw J, Aksmanovic VM, Coomber E, McMahon R, Whittaker JL, Morrison PJ, Kendrick-Jones J, Ellis JA. Genotype-phenotype analysis in X-linked Emery-Dreifuss muscular dystrophy and identification of a missense mutation associated with a milder phenotype. *Neuromuscul Disord.* 1999;9:159–65. PubMed PMID: 10382909.
- Yates JR, Wehnert M. The Emery-Dreifuss Muscular Dystrophy Mutation Database. *Neuromuscul Disord.* 1999;9:199. PubMed PMID: 10382916.
- Yorifuji H, Tadano Y, Tsuchiya Y, Ogawa M, Goto K, Umetani A, Asaka Y, Arahata K. Emerin, deficiency of which causes Emery-Dreifuss muscular dystrophy, is localized at the inner nuclear membrane. *Neurogenetics.* 1997;1:135–40. PubMed PMID: 10732816.
- Young J, Morbois-Trabut L, Couzinet B, Lascols O, Dion E, Béréziat V, Fève B, Richard I, Capeau J, Chanson P, Vigouroux C. Type A insulin resistance syndrome revealing a novel lamin A mutation. *Diabetes.* 2005;54:1873–8. PubMed PMID: 15919811.

Chapter Notes

Acknowledgments

Authors are coordinators (GB, FL, RBY) of the French networks for rare diseases on "EDMD and other nuclear envelope pathologies," network supported by AFM (Association Française contre les Myopathies, grant #10722 and #12325). GB and RBY have been members of the European consortium "Euro-Laminopathies" supported by an EU-FP7 grant (#018690) and are currently members of SOLVE-RD, an European Union's Horizon 2020 research and innovation programme under grant agreement No. 779257. GB, FL, RBY are supported by the Institut National de la Santé et de la Recherche Médicale, Sorbonne Université, the Assistance Publique des Hôpitaux de Paris.

Author History

Rabah Ben Yaou, MD (2004-present)
Gisèle Bonne, PhD (2004-present)
France Leturcq, MD (2004-present)
Dominique Récan-Budiartha, MD; Hôpital Cochin (2004-2010)

Revision History

- 15 August 2019 (ha) Comprehensive update posted live
- 25 November 2015 (me) Comprehensive update posted live
- 17 January 2013 (me) Comprehensive update posted live
- 24 August 2010 (cd) Revision: sequence analysis and prenatal testing for *FHL1* mutations available clinically
- 15 June 2010 (me) Comprehensive update posted live
- 21 November 2007 (cd) Revision: LMNA deletion/duplication testing available clinically

- 26 April 2007 (me) Comprehensive update posted live
- 29 September 2004 (me) Review posted live
- 27 January 2004 (gb) Original submission

License

GeneReviews® chapters are owned by the University of Washington. Permission is hereby granted to reproduce, distribute, and translate copies of content materials for noncommercial research purposes only, provided that (i) credit for source (<http://www.genereviews.org/>) and copyright (© 1993-2021 University of Washington) are included with each copy; (ii) a link to the original material is provided whenever the material is published elsewhere on the Web; and (iii) reproducers, distributors, and/or translators comply with the [GeneReviews® Copyright Notice and Usage Disclaimer](#). No further modifications are allowed. For clarity, excerpts of GeneReviews chapters for use in lab reports and clinic notes are a permitted use.

For more information, see the [GeneReviews® Copyright Notice and Usage Disclaimer](#).

For questions regarding permissions or whether a specified use is allowed, contact: admasst@uw.edu.