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Gisèle Bonne, France Leturcq, Rabah Ben Yaou

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Emery-Dreifuss Muscular Dystrophy

Gisèle Bonne, PhD,[1] France Leturcq, MD,[2] and Rabah Ben Yaou, MD[3]

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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 novoLMNA* 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]
EMD	8.5%	99% [7]	Rare [8, 9]
FHL1	1.2%	99% [10]	Rare [7, 11]
LMNA	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 [Schessl 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, Decaudain 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 lipoatrophy, 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	*DNMT3B* *DUX4L1* *SMCHD1*	AD	+++ (scapulo-peroneal)	–	–	No joint contractures or cardiac disease
Other scapuloperoneal syndromes (neurogenic & myopathic types) (OMIM 181400, 181405, 181430, 608358, 255160)	*DES* *MYH7* *TRPV4*	AD AR	+++	– (*DES*, *MYH*)	++ (*DES*, *MYH*)	• No joint contractures (*DES*, *MYH*) • No cardiac disease (*TRPV4*)
SYNE1-related disorders (OMIM 612998)	*SYNE1*	AD	±	++	±	Unavailable (pending description of clear phenotype)
SYNE2-related disorders (OMIM 612999)	*SYNE2*	AD	±	_	±	No joint contractures
TMEM43-related myopathies (OMIM 614302)	*TMEM43*	AD	+++	±	±	Unavailable (pending description of clear phenotype)
SUN1-related disorders (OMIM 613569)	*SUN1*	AD	++	++	–	No cardiac disease
Multiminicore disease (rigid spine syndrome) (OMIM 602771)	*SELENON* (*SEPN1*)	AR	+++	++	–	• No cardiac disease • Early & severe respiratory failure
TTN-related myopathies (see Salih Myopathy, Hereditary Myopathy w/Early Respiratory Failure, Udd Distal Myopathy)	*TTN*	AD AR	+++	+++	±	• Variably present cardiac disease • Severe respiratory involvement • Specific muscle pathology
LAMA2-related muscular dystrophy	*LAMA2*	AR	+++	++	±	Leukodystrophy
FKRP-related muscle diseases (OMIM 606596)	*FKRP*	AR	+++	±	±	• 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	*COL6A1* *COL6A2* *COL6A3*	AD	+++	++	–	• No cardiac disease • Specific muscle imaging pattern
Myotonic dystrophy type 1	*DMPK*	AD	+++	–	++	• No joint contractures • Myotonia
Dystrophinopathies	*DMD*	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)	*DES*	AD	+++	–	++	No joint contractures
X-linked vacuolar myopathies w/ cardiomyopathy (OMIM 300257)	*LAMP2*	XL	+++	–	++	No joint contractures
Myotonic dystrophy type 2	*CNBP*	AD	+++	–	++	No joint contractures
Myopathy with maltase acid deficiency	*GAA*	AR	+++	–	++ (rare cases)	• No joint contractures • Peculiar muscle pathology
BAG3-related myofibrillar myopathy (OMIM 612954)	*BAG3*	AD	+++	++	++	• 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	• 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, trigylceridemia)	Rarely, a person w/*LMNA* EDMD has overlapping *LMNA* 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	• 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	• 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 in the US and EU Clinical Trials Register 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 novoEMD* 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 novoLMNA* 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@musculardystrophyuk.org
  www.musculardystrophyuk.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
EMD	Xq28	Emerin	The UMD-EMD mutations database EMD homepage - Leiden Muscular Dystrophy pages	EMD	EMD
FHL1	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].

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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)

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