GENEReviews

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Emery-Dreifuss Muscular Dystrophy

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Summary

Disease 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. 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.

Diagnosis/testing. The two genes known to be associated with EDMD are *EMD*, encoding emerin and causing X-linked EDMD (XL-EDMD), and *LMNA*, encoding lamins A and C and causing autosomal dominant EDMD (AD-EDMD) and autosomal recessive EDMD (AR-EDMD). The diagnosis of X-linked EDMD is based on immunodetection of emerin in various

tissues and molecular genetic testing of *EMD*. The diagnosis of AD-EDMD and AR-EDMD is based on clinical findings, family history, and molecular genetic testing of *LMNA*.

Management. *Treatment of manifestations:* surgery to release contractures and manage scoliosis as needed; aids (canes, walkers, orthoses, wheelchairs) as needed to help ambulation; treatment for cardiac arrhythmias, AV conduction disorders, congestive heart failure, including antiarrhythmic drugs, cardiac pacemaker, implantable cardioverter defibrillator (ICD); heart transplantation for the end stages of heart failure as appropriate; respiratory aids (respiratory muscle training, assisted coughing techniques, mechanical ventilation) as needed. *Prevention of primary manifestations:* physical therapy and stretching to prevent contractures; implantation of cardiac defibrillators to reduce risk of sudden death. *Prevention of secondary complications:* antithromboembolic drugs to prevent cerebral thromboembolism of cardiac origin in those with decreased left ventricular function or atrial arrhythmias. *Surveillance:* 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. *Testing of relatives at risk:* cardiac evaluation for relatives at risk for AD-EDMD and female carriers of XL-EDMD.

Genetic counseling. EDMD is inherited in an X-linked, autosomal dominant, or autosomal recessive manner. If the mother of a proband with XL-EDMD has a disease-causing mutation, the chance of transmitting it in each pregnancy is 50%. Males who inherit the mutation will be affected; females who inherit the mutation will be carriers. Female carriers are usually asymptomatic, but they are at risk of developing a cardiac disease, progressive muscular dystrophy, and/or an EDMD phenotype. In AD-EDMD, 76% of probands have a *de novo* mutation. Each child of an individual with AD-EDMD has a 50% chance of inheriting the mutation. At conception, each sib of an individual with AR-EDMD 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. Prenatal testing is possible for pregnancies of women who are carriers if the *EMD* mutation has been identified in a family member. Prenatal testing is possible for pregnancies at increased risk for EDMD caused by *LMNA* mutations if the mutation(s) has/have been identified in an affected family member.

Diagnosis

Clinical Diagnosis

The clinical diagnosis of Emery-Dreifuss muscular dystrophy (EDMD) is based on the presence of 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** 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 cardiomyopathy may be detected by the performance of echocardiographic evaluation.

Other clinical findings are nonspecific:

- **Electromyogram (EMG)** usually shows myopathic features with normal nerve conduction studies, but neuropathic patterns have been described for X-linked EDMD (XL-EDMD) [Hopkins et al 1981] and for autosomal dominant EDMD (AD-EDMD) [Witt et al 1988].
- **CT scan of muscle** shows a diffuse pattern of involvement affecting the biceps, soleus, peroneal, external vasti, gluteus, and paravertebral muscles [Graux et al 1993]. Characteristic findings in the calf muscles on MRI have been reported in AD-EDMD [Mercuri et al 2002].

Testing

Other nonspecific laboratory findings:

- **Serum CK concentration** is normal or moderately elevated (2-20 times 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 2002].
- **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. Electronic microscopy may reveal specific alterations in nuclear architecture [Fidzianska et al 1998, Sabatelli et al 2001, Sewry et al 2001, Fidzianska & Hausmanowa-Petrusewicz 2003]. 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 immunoflurescence (IF) and/or by western blot (WB) in various tissues: exfoliative buccal cells (IF), lymphocytes (WB), lymphoblastoid cell lines (WB), skin biopsy (IF, WB), or muscle biopsy (IF, WB) [Manilal et al 1997, Mora et al 1997].
  - In individuals with XL-EDMD, emerin is absent in 95% [Yates & Wenhert 1999].
  - In female carriers of XL-EDMD, emerin is absent in varying proportions in nuclei, but western blot is not reliable in carrier detection because it may show either a normal amount or reduced amount of emerin.
  - In individuals with AD-EDMD, emerin is normally expressed.
- **Immunodetection of lamins A/C.** This test is not reliable for confirmation of the diagnosis of AD-EDMD because lamins A/C are always present, usually in normal amounts, in the nuclei of individuals with AD-EDMD.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Genes. The two genes known to be associated with EDMD are *EMD* and *LMNA*, encoding ubiquitous proteins of the nuclear membrane.

- ***EMD*,** encoding emerin [Bione et al 1994] and causing XL-EDMD

- ***LMNA*,** encoding lamins A and C [Bonne et al 1999] and causing AD-EDMD and AR-EDMD

Other loci. About 45% of individuals with EDMD who have emerin detected on immunocytochemistry and/or immunoblotting have no mutation identified in *EMD* or *LMNA*, suggesting that these individuals are either misdiagnosed or that other as yet unidentified genes are involved in EDMD.

Clinical uses

- Diagnostic testing
- Confirmatory diagnostic testing
- Carrier testing
- Prenatal diagnosis
- Preimplantation genetic diagnosis

Note: It is the policy of *GeneReviews* to include clinical uses of testing available from laboratories listed in the GeneTests Laboratory Directory; inclusion does not necessarily reflect the endorsement of such uses by the author(s), editor(s), or reviewer(s).

Clinical testing

- **Sequence analysis or mutation scanning**

  Sequencing of genomic *EMD* (six exons, five short introns, and promoter region) detects an *EMD* mutation in more than 99% of individuals with established X-linked inheritance and/or with no emerin detected by immunodetection methods [Manilal et al 1998].

  Sequence analysis of the coding regions of *LMNA* (12 exons and their flanking intronic regions) detects mutations in 100% of individuals with *LMNA* point mutations; however, this represents only about 45% of individuals with AD-EDMD because large deletions and duplications involving one or several exons are not detected [Bonne et al 2000, Brown et al 2001, Bonne et al 2003, Vytopil et al 2003]. Complementary DNA sequencing may be necessary to identify splice-site mutations.

- **Deletion/duplication analysis.** Deletion/duplication analysis detects large deletions and duplications involving one or several exons. Such deletions/duplications are very rare.

Table 1 summarizes molecular genetic testing for this disorder.

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

Test Method	Mutations Detected	Mutation Detection Frequency [1]	Test Availability
Sequence analysis	*EMD* sequence variants	>99% XL-EDMD [2]	Clinical Testing
Sequence analysis or mutation scanning	*LMNA* sequence variants	~45% AD-EDMD [3]	Clinical Testing
Deletion/duplication analysis	*LMNA* deletions/duplications	Unknown % AD-EDMD	

1. Proportion of affected individuals with a mutation(s) as classified by test method, gene, and mode of inheritance
2. Males with an established X-linked inheritance or individuals with no emerin expression as determined by immunodetection studies of muscle tissue
3. AR-EDMD is very rare. To date only one *LMNA* mutation in a homozygous state leading to AR-EDMD has been reported [Raffaele di Barletta et al 2000].

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

- Family history may help distinguish between XL-EDMD and AD/AR-EDMD.
- In the absence of an informative family history, emerin immunodetection studies help to distinguish between XL- and AD-EDMD and thus determine the appropriate gene for molecular genetic testing.

Genetically Related (Allelic) Disorders

***EMD*.** No other phenotypes are associated with mutations in *EMD*.

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

- **Disorders of striated muscle**
  - **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 atrio-ventricular block [Forissier et al 2003] or early atrial fibrillation [Sebillon et al 2003] or left ventricular non-compaction [Hermida-Prieto et al 2004].
  - Autosomal dominant quadriceps myopathy associated with dilated cardiomyopathy and cardiac conduction defects [Charniot et al 2003]
  - Neurogenic variant of EDMD [Walter et al 2005]

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 founder mutation p.Arg298Cys [De Sandre-Giovannoli et al 2002] (see Charcot-Marie-Tooth type 2)
  - Autosomal dominant CMT2 associated to 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 mutations affecting codon Arg482, leading to several amino acid substitutions [Bonne et al 2003].
- **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 mutations are reported in MAD (p.Arg527His) [De Sandre-Giovannoli et al 2002, 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). Mutations 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 dermopathies such as a lethal neonatal laminopathy [Navarro et al 2004]
- Progeria, arthropathy, and calcinosis of tendons [Van Esch et al 2006]

- **Silent polymorphisms of *LMNA*.** Some silent polymorphisms of *LMNA* are also reported to be related to susceptibility to obesity and to insulin resistance [Hegele, Ban et al 2001; Hegele, Huff et al 2001; Murase et al 2002].

Clinical Description

Natural History

Autosomal dominant Emery-Dreifuss muscular dystrophy (AD-EDMD) and XL-EDMD have similar, but not identical, neuromuscular and cardiac involvement [Wulff et al 1997, Manilal et al 1998, Yates et al 1999, Bécane et al 2000, Bonne et al 2000, Felice et al 2000, Raffaele di Barletta et al 2000, Brown et al 2001, Boriani et al 2003, Vytopil et al 2003].

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. However, 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 postcervical 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 can occur in AD-EDMD, but is rare in XL-EDMD [Bonne et al 2000].
- Cardiac involvement that 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 [Sanna et al 2003]. Cardiac conduction defects can include sinus bradycardia, first-degree atrioventricular block, Wenckebach phenomenon, third-degree atrioventricular block, and bundle-branch block. Atrial arrhythmias

(extrasystoles, atrial fibrillation, flutter) and ventricular arrhythmias (extrasystoles, ventricular tachycardia) are frequent. In AD-EDMD, the risk of ventricular tachyarrhythmia and dilated cardiomyopathy manifested by left ventricular dilation and dysfunction is higher than in XL-EDMD [Bécane et al 2000, Bonne et al 2003, Boriani et al 2003, Draminska et al 2005]. Individuals are at risk for cerebral emboli and sudden death [Boriani et al 2003]. A generalized dilated cardiomyopathy often occurs in the latter stages of the disease.

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]. 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. Cardiac involvement usually arises after the second decade of life. Respiratory function can be impaired in some individuals [Emery 2000, Mercuri et al 2000, Ben Yaou et al 2002, Talkop et al 2002, Mercuri et al 2004]. On occasion, sudden cardiac death is the first manifestation of the disorder [Bécane et al 2000, Karkkainen et al 2004].

Autosomal recessive EDMD. Only one individual with genetically proven AR-EDMD (i.e., homozygous for a *LMNA* mutation) has been reported [Raffaele di Barletta et al 2000]. He had severe muscular dystrophy. He experienced difficulties when he started walking at age 14 months; at age five years, contractures prevented him from standing. By age 40 years, he had severe and diffuse muscle wasting and was confined to a wheelchair. Cardiac evaluation revealed no abnormalities [Raffaele di Barletta et al 2000].

Genotype-Phenotype Correlations

- ***EMD*.** The majority of *EMD* mutations are null mutations that result in complete absence of emerin expression in nuclei; however, intra- and interfamilial variability in the severity of the phenotype associated with null mutations may be observed [Muntoni et al 1998, Hoeltzenbein et al 1999, Canki-Klain et al 2000, Ellis et al 2000]. The few missense mutations that have been identified are associated with decreased or normal amounts of emerin and result in a milder phenotype [Yates et al 1999].
- ***LMNA*.** *LMNA* mutations do not show a clear correlation between genotype and phenotype [Bonne et al 2000, Genschel & Schmidt 2000, Bonne et al 2003].
  - Marked intra- and interfamilial variability is observed for the same *LMNA* mutation [Bécane et al 2000, Bonne et al 2000, Mercuri et al 2005]. For example, within the same family the same mutation can lead to AD-EDMD, LGMD1B, or isolated DCM-CD, i.e., laminopathies involving striated muscle [Bécane et al 2000, Brodsky et al 2000].
  - Because only one individual with AR-EDMD and a homozygous p.His222Tyr mutation of *LMNA* has been reported [Raffaele di Barletta et al 2000], no genotype-phenotype correlations can be made.
- Severe EDMD has been reported in individuals with mutations in both *EMD* and *LMNA* [Muntoni et al 2006]. A range of clinical presentations (i.e. CMT2, CMT2-EDMD, and isolated cardiomyopathy) were found in a large family in which mutations in both *EMD* and *LMNA* genes cosegregate [Ben Yaou et al 2007].

Penetrance

Four relatively rare *LMNA* mutations were reported with incomplete penetrance in families with AD-EDMD [Vytopil et al 2002].

Anticipation

Anticipation has not been observed to date.

Prevalence

The overall prevalence of EDMD is not known. The prevalence of XL-EDMD is estimated to be 1:100,000. Heterozygous *LMNA* mutations causing AD-EDMD are more common than *EMD* mutations causing XL-EDMD.

Hopkins and Warren (1992) estimated EDMD to be the third most prevalent muscular dystrophy, with the two dystrophinopathies, Duchenne muscular dystrophy and Becker muscular dystrophy, being the two most prevalent.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Some neuromuscular disorders result in a similar pattern of muscle involvement, joint contractures, or cardiac disease, but none associates the triad observed in Emery-Dreifuss muscular dystrophy (EDMD).

Scapulo-peroneal syndromes without contractures or cardiac disease

- Facioscapulohumeral muscular dystrophy (FSHD)
- Adult-onset scapulo-peroneal myopathy
- Scapulo-peroneal muscular dystrophy linked to chromosome 12 [Wilhelmsen et al 1996]
- Scapulo-peroneal spinal muscle atrophy linked to chromosome 12 [Isozumi et al 1996]
- Spinal muscle atrophy of Stark-Kaeser type [Kaeser 1965]
- Some forms of hyaline body myopathy [Masuzugawa et al 1997, Onengut et al 2004]

Other myopathies with or without contractures and/or cardiac disease that can resemble AD-EDMD but have distinguishing features

- Rigid spine syndrome [Moghadaszadeh et al 1999], especially selenopathies [Moghadaszadeh et al 2001, Ferreiro et al 2002]
- *FKRP* gene-related disorders [Poppe et al 2003]
- Bethlem myopathy caused by collagen VI gene mutations [Bertini & Pepe 2002] (see Collagen Type VI-Related Disorders)
- Myotonic dystrophy type 1
- Dystrophinopathies
- Limb-girdle muscular dystrophies with cardiac involvement [Muntoni 2003] (see Limb-Girdle Muscular Dystrophy Overview)
- Desmin-related myopathies [Goldfarb et al 2004] (see Myofibrillar Myopathy)
- X-linked vacuolar myopathies with cardiomyopathy or Danon disease [Danon et al 1981]

- Myotonic dystrophy type 2 [**pro**ximal **m**yotonic **m**yopathy (PROMM)] [Udd et al 2003]

Other disorders with distinguishing features

- Ankylosing spondylitis [Goncu et al 2003]

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with Emery-Dreifuss muscular dystrophy (EDMD), the following evaluations are recommended:

- ECG, Holter-ECG monitoring, echocardiography, radionucleotide angiography, and cardiac MRI. Electrophysiologic study is often advisable in EDMD; however, it is performed in selected individuals on the basis of the clinical presentation and the results of noninvasive studies and not as an "evaluation at initial diagnosis" in all individuals.
- Evaluation of respiratory function (vital capacity measurement and other pulmonary volume measurements)
- Evaluation of metabolic functions (glycemia, insulinemia, trigylceridemia)

Treatment of Manifestations

- Orthopedic surgeries to release Achilles tendons and other contractures or scoliosis as needed
- Use of mechanical aids (canes, walkers, orthoses, wheelchairs) as needed to help ambulation
- Specific treatments for cardiac features (arrhythmias, AV conduction disorders, and congestive heart failure), including antiarrhythmic drugs, cardiac pacemaker, implantable cardioverter defibrillator (ICD), and both pharmacologic and non-pharmacologic therapy for heart failure [Bécane et al 2000, Bonne et al 2003, Boriani et al 2003]. Heart transplantation may be necessary in the end stages of heart failure, but some individuals may not be candidates for heart transplantation based upon associated severe skeletal muscle and respiratory involvement.
- Use of respiratory aids (respiratory muscle training and assisted coughing techniques, mechanical ventilation) if indicated in late stages

Prevention of Primary Manifestations

Physical therapy and stretching exercises promote mobility and help prevent contractures.

When indicated, implantation of cardiac defibrillators can considerably reduce the risk of sudden death [Meune et al 2006].

Prevention of Secondary Complications

Antithromboembolic drugs (vitamin K antagonists, warfarin, heparin) are probably required to prevent cerebral thromboembolism of cardiac origin in those individuals with either decreased left ventricular function or atrial arrhythmias [Boriani et al 2003].

Surveillance

- A cardiac assessment consisting of ECG, Holter monitoring, and echocardiography once a year in order to detect asymptomatic cardiac disease. More advanced and invasive cardiac assessment may be required.
- Monitoring of respiratory function

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 have to be considered [Aldwinckle & Carr 2002].

Body weight should be controlled to prevent obesity.

Testing of Relatives at Risk

Because of the high risk of cardiac complications (including sudden death) observed in individuals with *LMNA* mutations, cardiac evaluation for relatives is recommended [Bécane et al 2000, Boriani et al 2003, Taylor et al 2003]; however, in families with AD-EDMD and incomplete penetrance, no cardiac complications were reported in asymptomatic relatives [Vytopil et al 2002].

Cardiac evaluation is recommended for female carriers of an *EMD* mutation as they are at increased risk of developing cardiac complications [Manilal et al 1998, Canki-Klain et al 2000].

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

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

Risk to Family Members — XL-EDMD

Parents of a proband

- The father of an affected male will not have the disease nor will he be a carrier of the mutation.
- In a family with more than one affected individual, the mother of an affected male is an obligate carrier.
- If pedigree analysis reveals that the proband is the only affected family member, the mother may be a carrier or the affected male may have a *de novo* gene mutation and, thus, the mother is not a carrier. The frequency of *de novo* mutations is thought to be less than 1/3, as expected in lethal diseases, although no large published data are available [Wulff et al 1997, Yates & Wehnert 1999].
- If a woman has more than one affected son and the disease-causing mutation cannot be detected in her DNA, she has germline mosaicism.
- Female carriers are usually asymptomatic, but they are at risk of developing a cardiac disease, a progressive muscular dystrophy, or an EDMD phenotype [Manilal et al 1998, Canki-Klain et al 2000].

Sibs of a proband

- The risk to sibs depends upon the carrier status of the mother and the presence or absence of other affected sibs.
- If the mother of the proband has a disease-causing mutation, the chance of transmitting it in each pregnancy is 50%.
  - Male sibs who inherit the mutation will be affected; female sibs who inherit the mutation will be carriers.
  - Female carriers are usually asymptomatic, but they are at risk of developing a cardiac disease, a progressive muscular dystrophy, or an EDMD phenotype [Manilal et al 1998, Canki-Klain et al 2000].
- Germline mosaicism has been demonstrated in XL-EDMD [Manilal et al 1998]. Thus, even if the disease-causing mutation has not been identified in DNA extracted from the mother's leukocytes, sibs of a proband who represents a simplex case (i.e., the only affected individual in the family) are still at increased risk of inheriting the disease-causing mutation.

Offspring of a proband

- Males will pass the disease-causing mutation to all of their daughters and none of their sons.
- Female carriers are usually asymptomatic, but they are at risk of developing a cardiac disease, a progressive muscular dystrophy, or an EDMD phenotype [Manilal et al 1998, Canki-Klain et al 2000].

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

Carrier Detection

Carrier testing of at-risk female relatives is available on a clinical basis if the mutation has been identified in the proband.

Risk to Family Members — AD-EDMD

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* mutation. Bonne et al (2000) reported that 76% of mutations were *de novo*.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include clinical evaluation — in particular, cardiac investigations and molecular genetic testing.

Note: Although some individuals diagnosed with AD-EDMD have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent.

Sibs of a proband

- The risk to the sibs of the proband depends upon the genetic status of the proband's parents.
- If a parent of the proband is affected, the risk to the sibs is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.
- If a disease-causing mutation cannot be detected in the DNA extracted from leukocytes of either parent, two possible explanations are a *de novo* mutation in the proband or germline mosaicism in a parent. Germline mosaicism has been reported; its incidence is not known [Bonne et al 1999].

Offspring of a proband. Each child of an individual with AD-EDMD has a 50% chance of inheriting the mutation.

Other family members of a proband. The risk to other family members depends upon the genetic status of the proband's parents. If a parent is found to be affected, his or her family members are at risk.

Related Genetic Counseling Issues

DNA banking. 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, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%, and it is useful for searching for modifier genes that would explain the wide clinical variability observed in EDMD. See 

for a list of laboratories offering DNA banking.

Prenatal Testing

Prenatal testing is possible for pregnancies of women who are carriers if the *EMD* mutation has been identified in a family member. The usual procedure is to determine the sex by performing chromosome analysis on fetal cells obtained by chorionic villus sampling (CVS)

at about ten to 12 weeks' gestation or by amniocentesis usually performed at about 15-18 weeks' gestation. If the karyotype is 46,XY, DNA from fetal cells can be analyzed for the known disease-causing mutation.

Prenatal diagnosis for pregnancies at increased risk for EDMD because of the presence of a *LMNA* mutation(s) is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or CVS at about ten to 12 weeks' gestation. The disease-causing allele(s) of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified. For laboratories offering PGD, see Testing.

Note: It is the policy of GeneReviews to include information on preimplantation genetic diagnosis available from laboratories listed in the GeneTests Laboratory Directory; inclusion does not necessarily reflect the endorsement of such uses by the author(s), editor(s), or reviewer (s).

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Emery-Dreifuss Muscular Dystrophy

Gene Symbol	Chromosomal Locus	Protein Name
EMD	Xq28	Emerin
LMNA	1q21.2	Lamin-A/C

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Emery-Dreifuss Muscular Dystrophy

150330	LAMIN A/C; LMNA
181350	EMERY-DREIFUSS MUSCULAR DYSTROPHY, AUTOSOMAL DOMINANT; EDMD2
300384	EMERIN; EMD
310300	EMERY-DREIFUSS MUSCULAR DYSTROPHY, X-LINKED; EDMD
604929	EMERY-DREIFUSS MUSCULAR DYSTROPHY, AUTOSOMAL RECESSIVE; EDMD3

Table C. Genomic Databases for Emery-Dreifuss Muscular Dystrophy

Gene Symbol	Locus Specific	Entrez Gene	HGMD
EMD	EMD	2010 (MIM No. 300384)	EMD
LMNA	LMNA	4000 (MIM No. 150330)	LMNA

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

Elucidation of the pathophysiology of Emery-Dreifuss muscular dystrophy (EDMD), caused by mutations in *EMD* and *LMNA*, still requires deciphering of the role of the proteins that they encode in the functional organization of the nuclear envelope.

EMD mutations cause, in most cases, absence of emerin [Manilal et al 1998]; a few missense or in-frame deletions or insertions lead to aberrant targeting at the inner nuclear membrane and binding of emerin to lamins [Fairley et al 1999]. Missense *LMNA* mutations lead to expression of abnormal lamins A/C [Muchir et al 2004], whereas nonsense *LMNA* mutations act as haploinsufficiency with decreased amount of normal lamins A/C [Bonne et al 1999, Bécane et al 2000]. Analysis of cells or tissues from affected individuals demonstrates an abnormal nuclear envelope with increased fragility [Manilal et al 1999; Muchir et al 2004; Reichart et al 2004] as well as chromatin alterations [Ognibene et al 1999, Sabatelli et al 2001, Sewry et al 2001, Fidzianska & Hausmanowa-Petrusewicz 2003].

Although some hypotheses such as an increased susceptibility to apoptosis [Morris 2000] of muscle cell nuclei cannot be completely ruled out, two mechanisms, not necessarily mutually exclusive, could be involved in EDMD pathogenesis: (1) structural mechanisms caused by mechanical stress present in skeletal muscle and cardiac muscle and (2) modification of gene expression relative to abnormal chromatin organization associated with alteration of proliferation/differentiation of muscle cells [Broers et al 2006, Worman & Bonne 2007].

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 might be impaired in the disease [Maraldi et al 2002]. Numerous other interactions have been analyzed resulting in identification of transcription factors such as c-fos, pRb, Lco1, as binding partners of Lamin A/C. This points toward possible deregulation of signaling pathways and alteration of proliferation/differentiation of muscle cells [Broers et al 2006, Vlcek & Foisner 2006, Worman & Bonne 2007].

***EMD*—Normal allelic variants:** The gene has six exons; no polymorphisms have been identified. See Table 2 (pdf).

Pathologic allelic variants: More than 90 mutations have been reported to date [Yates & Wehnert 1999]. See UMD- EMD Database. The majority of mutations (95%) are null mutations: nonsense mutations, deletions/insertions, and splice site mutations that lead to exon skipping, frameshift, and premature arrest of translation and, thus to absence of emerin. A few missense mutations and in-frame deletions also exist, leading 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 mutations are unique to a single family. On occasion, two or three families have the same mutation. No "hot-spot" for mutation is observed in the EMD gene; mutations are nearly randomly spread out along the gene. (For more information, see Genomic Databases table above.)

Normal gene product: Emerin is a 254-amino acid protein, serine-rich, expressed in most tissue. 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 (BANF1; 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: In most cases, null mutations lead to premature arrest of translation with no protein product. In the rare cases in which protein is expressed, either the gene product is lacking the transmembrane domain (in-frame distal deletions) and is not able to target the nuclear membrane and thus is delocalized in the nucleoplasm or cytoplasm, or the mutated protein is present at the nuclear rim (missense mutations) but has weakened interactions with the lamina components [Ellis et al 1999, Fairley et al 1999, Ellis et al 2000].

***LMNA*—Normal allelic variants:** See Table 3 (pdf). An incomplete list of normal allelic variants is available on Leiden Muscular Dystrophy pages© (www.dmd.nl).

Pathologic allelic variants: More than 237 mutations are reported to date. See UMD-*LMNA* database (www.umd.be:2000) [Bonne et al 2003] and Leiden Muscular Dystrophy pages© (www.dmd.nl). The majority of mutations (85%) are missense mutations. Nonsense mutations, small deletions/insertions in-frame or with frameshift, and splice-site mutations also exist.

Mutations are spread all along the gene [Bonne et al 2000, Brown et al 2001]. A few recurrent mutations exist [Broers et al 2006]. (For more information, see Genomic Databases table above.)

Normal gene product: Four A-type lamins (A, AΔ10, C, and C2) exist and are products of the *LMNA* gene by 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. However, a few myeloid and lymphoid cell lines have no lamins. Lamin C2 was described in murine and human germ cells [Alsheimer & Benavente 1996]. 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 [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.

Abnormal gene product: Missense mutation (majority of cases) leads to mutant protein of normal size carrying one modified amino acid. Western blot analysis of fibroblasts of affected individuals demonstrates a normal level of protein expression, strongly suggesting that mutant proteins are expressed [Muchir et al 2004]. Nonsense mutations lead to haploinsufficency with expression of only the normal allele (50% of normal amount); the mutant allele is either not translated (because of degradation of abnormal mRNA) or is translated and degraded [Bécane et al 2000, Muchir et al 2003].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

National Library of Medicine Genetics Home Reference
Emery-Dreifuss muscular dystrophy

Association Francaise contre les Myopathies (AFM)
AFM 1
rue de l'Internationale
Evry
France
Phone: 01 69 47 28 28
Fax: 01 69 47 29 56
Email: decouvrir@afm.genethon.fr
www.afm-france.org

European Neuromuscular Centre (ENMC)
Lt. Gen. van Heutszlaan 6
3743 JN Baarn
Netherlands
Phone: 035 54 80 481
Fax: 035 54 80 499
Email: info@enmc.org
www.enmc.org

Muscular Dystrophy Association (MDA)
3300 East Sunrise Drive
Tucson AZ 85718-3208
Phone: 800-FIGHT-MD (800-344-4863); 520-529-2000
Fax: 520-529-5300
Email: mda@mdausa.org
www.mdausa.org

Muscular Dystrophy Campaign
7-11 Prescott Place
SW4 6BS
United Kingdom
Phone: (+44) 0 020 7720 8055
Fax: (+44) 0 020 7498 0670
Email: info@muscular-dystrophy.org
www.muscular-dystrophy.org

World Muscle Society (WMS)
ICSM Hammersmith Campus
Du Cane Road
London W12 ONN
United Kingdom
Email: j.miller@ic.ac.uk
www.worldmusclesociety.org

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

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- 21 November 2007 (cd) Revision: *LMNA* deletion/duplication testing available clinically
- 26 April 2007 (me) Comprehensive update posted to live Web site
- 29 September 2004 (me) Review posted to live Web site
- 27 January 2004 (gb) Original submission