GENEReviews

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Multiminicore Disease

[*Minicore Disease, Minicore Myopathy, Multicore Disease, Multicore Myopathy, Multiminicore Myopathy. Includes: RYR1-Related Multiminicore Disease, SEPN1-Related Multiminicore Disease*]

Alan H Beggs, PhD
Department of Pediatrics
School of Medicine
Harvard University
Program in Genomics and Genetics Division
Children's Hospital Boston
beggs@enders.tch.harvard.edu

Pankaj B Agrawal, MD, MMSc
Department of Pediatrics
School of Medicine
Harvard University
Program in Genomics and Genetics Division
Children's Hospital Boston
pankaj.agrawal@tch.harvard.edu

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Summary

Disease characteristics. Multiminicore disease (MmD) is broadly classified into four groups: classic form (75% of individuals); moderate form, with hand involvement (<10%); antenatal form, with arthrogryposis multiplex congenita (<10%); and ophthalmoplegic form (<10%). Onset of the classic form is usually congenital or early in childhood with neonatal hypotonia, delayed motor development, axial muscle weakness, scoliosis, and significant respiratory involvement (often with secondary cardiac impairment). Spinal rigidity of varying severity is present.

Diagnosis/testing. The diagnosis of MmD is based on the presence of multiple "minicores" visible on muscle biopsy using oxidative stains, clinical findings of static or slowly progressive weakness, and absence of findings diagnostic of other neuromuscular disorders. Mutations in *SEPN1* and *RYR1* account for approximately 50% of MmD cases reported; further genetic heterogeneity is suggested, but no other candidate region or gene has been identified to date. *SEPN1* mutations inherited in an autosomal recessive manner account for approximately 30% of MmD and approximately 50% of classic MmD. Some forms of MmD are associated with *RYR1* mutations inherited in an autosomal recessive manner.

Management. *Treatment of manifestations:* respiratory support as needed; aggressive treatment of lower respiratory infections; nasogastric feeding and high-caloric density formulas as needed; physical and occupational therapy to improve/maintain gross and fine motor function and reduce joint contractures; speech therapy as needed; orthopedic treatment of scoliosis. *Prevention of secondary complications:* yearly influenza and other respiratory infection-related immunizations. *Surveillance:* routine evaluations of neuromuscular status to assess disease progression, respiratory function re the risk of insidious nocturnal hypoxia and sudden respiratory failure, cardiac status re the risk of cardiac impairment secondary to respiratory involvement, the spine for scoliosis particularly during childhood and adolescence.

Agents/circumstances to avoid: depolarizing muscle relaxants and inhalational agents during surgery or childbirth, as they can trigger malignant hyperthermia.

Genetic counseling. MmD is inherited in an autosomal recessive manner, although occurrence in two generations in a few families has been reported. Assuming autosomal recessive inheritance, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrierf. Carrier testing for at-risk relatives and prenatal testing for pregnancies at increased risk are possible if the disease-causing mutations in the family have been identified.

Diagnosis

Clinical Diagnosis

Multiminicore disease (MmD) has a wide clinical spectrum with four distinct phenotypes (see Clinical Description). Clinical findings that may support the diagnosis of MmD include the following:

- **Weakness** (predominantly axial and proximal) and hypotonia; scoliosis and respiratory difficulty occur in approximately two-thirds of affected individuals.
- **Onset** typically at birth or during infancy; sometimes in childhood

Testing

Muscle Biopsy—The diagnosis of MmD is based on the presence of multiple "minicores," small zones of sarcomeric disorganization and/or diminished oxidative activity that correlate with lack of mitochondria in muscle fibers. Unlike the cores typical of central core disease, minicores affect both type I and type II fibers and are short in length, spanning only a few sarcomeres in the fiber longitudinal axis.

Note: Because minicores are not specific to MmD, the diagnosis of MmD is based on the presence of minicores in a large proportion of muscle fibers associated with static or slowly progressive weakness and absence of findings diagnostic of other disorders.

H&E staining reveals moderate to marked variability in fiber size; the number of internal nuclei may be increased. Fat and/or connective tissue is normal or mildly increased. Myofibrillar ATPase staining may be normal, but frequently shows type I fiber predominance. Relative hypotrophy of type I fibers is often observed, with mean diameter of type I fibers smaller than that of type II fibers in many cases.

Oxidative stains (NADH-TR, succinate dehydrogenase, cytochrome oxidase) reveal multiple small focal lesions ("minicores") of sarcomeric disorganization and/or reduced or absent oxidative activity in 60%-90% of fibers. These focal lesions are generally round, small, variable in size, multiple, and randomly distributed with poorly defined boundaries. The cores are often oriented transversely to the fibers and may span up to 15 to 20 sarcomeres [Ferreiro et al 2000, Jungbluth et al 2000]. While cytochrome oxidase staining is specific for lack of mitochondria, NADH-TR staining reveals both the lack of mitochondria and the myofibrillar disruption characteristic of "unstructured cores."

Immunohistochemistry. Reliable (but nonspecific) markers for MmD [Fischer et al 2002, Bonnemann et al 2003] include the following:

- **Anti-titin antibodies** reveal disorganization of the normal striated pattern in unstructured cores.
- **Anti-desmin antibodies** show increased reactivity in the core lesions.

- **AlphaB-crystallin, heat shock protein 27, and filamin C** have shown increased immunoreactivity in core lesions (minicore, central core, and target fibers).

Anti-alpha-actinin and anti-actin antibodies do not reveal any abnormalities [Ferreiro et al 2000].

Electron microscopy. Cores are typically unstructured and often circular. Their appearance ranges from focal areas of Z line streaming and reduced or absent mitochondria to severe focal disorganization of myofibrillar structure [Ferreiro et al 2000, Jungbluth et al 2000]. "Structured" minicores, exhibiting intact sarcomeres and only absence of mitochondria, may be more difficult to detect [Ferreiro & Fardeau 2002].

Biochemical and Electrophysiologic Studies —Studies may suggest a myopathic process but have a limited role in making the diagnosis.

Serum creatine kinase concentration is normal or slightly elevated.

EMG ranges from normal to nonspecifically abnormal, with findings such as low-amplitude polyphasic potentials of short duration. The absence of a neurogenic pattern eliminates the possibility of denervation, which may also lead to presence of core lesions.

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. Mutations in two genes account for MmD in approximately 50% of affected individuals:

- ***SEPN1*.** Autosomal recessive *SEPN1* mutations account for approximately 30% of all MmD and approximately 50% of classic MmD [Ferreiro, Quijano-Roy et al 2002]. An estimated 40% of individuals with *SEPN1* mutations are compound heterozygotes. Up to two-thirds of mutations cause premature termination of translation; the remaining mutations are missense changes. Mutations appear to be distributed throughout the gene.
- ***RYR1*.** Some forms of MmD are associated with *RYR1* mutations inherited in an autosomal recessive manner.

Other loci. Further genetic heterogeneity is suggested; no other candidate region or gene has been identified to date.

Clinical testing

- **Sequence analysis** to identify mutations in *SEPN1* and *RYR1* is available clinically.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Multiminicore Disease

Gene Symbol	Proportion of MmD Attributed to Mutations in This Gene	Test Method	Mutation Detection Frequency by Test Method	Test Availability
SEPN1	30%-54%	Sequence analysis	>90%	Clinical Testing
RYR1	Unknown	Sequence analysis	Unknown	Clinical Testing

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

Testing Strategy

Establishing the diagnosis. MmD is a clinicopathologic entity that requires histopathologic examination of a muscle biopsy for the diagnosis to be made.

Clinical evaluation includes the following:

- Personal medical history and physical examination, with particular attention to features of congenital myopathy or muscular dystrophy (e.g., weakness, hypotonia, failure to thrive, scoliosis)
- Family history, with particular attention to features of congenital myopathy or muscular dystrophy

Genetic diagnosis requires molecular genetic testing of *SEPN1* and *RYR1*.

- Because the majority of individuals with MmD have a mutation in *SEPN1*, this testing should be done first.
- If no *SEPN1* mutations are identified, testing of *RYR1* should be considered, particularly for those individuals with non-classic forms of MmD.

Carrier testing for at-risk relatives requires prior identification of the disease-causing mutations in the family.

Note: Carriers are heterozygotes for an autosomal recessive disorder and are not at risk of developing the disorder.

Prenatal diagnosis for at-risk pregnancies requires prior identification of the disease-causing mutations in the family.

Genetically Related (Allelic) Disorders

SEPN1

Congenital fiber-type disproportion (CFTD) is a type of congenital myopathy characterized by hypotonia and mild-to-severe generalized muscle weakness at birth or within the first year of life. The diagnosis is made on muscle biopsy showing type 1 fibers that are at least 12% smaller than the mean diameter of type 2A and/or type 2B fibers in the absence of other significant pathologic findings (e.g., nemaline bodies, cores, or central nuclei).

In a recent study [Clarke et al 2006]:

- Two sibs with CFTD homozygous for a c.943G>A mutation in *SEPN1* had clinical findings similar to those of *SEPN1*-related myopathy.

- Three women in one family who were homozygous for the c.943G>A mutation had similar clinical findings. Only one had a muscle biopsy; it revealed type 1 fibers to be 10.5% smaller than type 2 fibers (for the diagnosis of CFTD, the type 1 fibers should be >12% smaller), consistent with nonspecific myopathy. No histopathologic features of MmD, RSMD, or desmin-related myopathy were found.

It is important to remember that a few cases of CFTD and centronuclear myopathy may show features consistent with MmD on ultrastructural examination [Nadaj-Pakleza et al 2007].

Desminopathy. *SEPN1* mutations have been identified in individuals with desmin-related myopathy with Mallory body-like inclusions [Ferreiro et al 2004] (see Myofibrillar Myopathy). The clinical presentation is similar to that of MmD/RSMD; on muscle biopsy, hyaline plaques that are devoid of any NADH/SDH activity are seen in up to 10% of fibers under light microscopy. Ultrastructurally, these represent intramyofibrillar inclusions arranged in bundles composed of helical filaments 10-12 nm in diameter and surrounded by electron-dense amorphous material.

RYR1

Heterozygous mutations cause two different dominantly inherited conditions:

- **Central core disease** (CCD) is most often caused by mutations in *RYR1*. The majority of CCD-causing mutations are located in the C-terminal region (last 15 exons), which contributes to the formation of the Ca^{2+} (calcium)-conducting pore [Monnier et al 2001, Wu et al 2006]. Rarely, CCD caused by *RYR1* mutations may exhibit minicore lesions resulting in clinical and pathologic overlap between CCD and MmD:
  - One family in whom muscle fibers showed coexistence of minicores, central cores, and a few rod-like structures had a homozygous *RYR1* mutation in exon 101 [Jungbluth et al 2002].
  - Another family homozygous for an *RYR1* mutation in exon 71 had three affected children with a moderate form of minicore disease with hand involvement. Initial biopsy results for this family were consistent with MmD but subsequent biopsy showed progression to lesions typical of CCD [Ferreiro, Monnier et al 2002].
- **Malignant hyperthermia susceptibility** (MHS) is caused by *RYR1* mutations predominantly in the N-terminal region of the gene, affecting the cytoplasmic domain of the protein that possibly interacts with dihydropyridine receptor. Approximately 50% of all reported MHS is caused by *RYR1* mutations. Malignant hyperthermia is also associated with mutations affecting the central domain and more recently the *RYR1* C-terminal region [Galli et al 2002]. Multiple minicores have been described in a small proportion of individuals with MHS (2.6%; n=534) [Guis et al 2004]. This study also reported a large family of 17 people with MHS, 16 of whom had multiminicores in muscle fiber and two missense mutations of *RYR1* on the same allele in exons 50 and 53.
- A missense *RYR1* mutation was reported with dominant congenital myopathy in a family with both nemaline bodies and cores [Scacheri et al 2000].

Clinical Description

Natural History

Multiminicore disease (MmD) is characterized by axial and proximal muscle weakness. It is usually slowly progressive; however, fatal cases have been described. High-arched palate and chest deformities are common.

MmD is broadly classified into four forms [Ferreiro et al 2000, Jungbluth et al 2000, Ferreiro & Fardeau 2002, Nadaj-Pakleza et al 2007]:

- Classic form
- Moderate form, with hand involvement
- Antenatal form, with arthrogryposis multiplex congenita
- Ophthalmoplegic form

In all forms, males and females are equally affected.

Classic MmD (75%)

- **Characteristic features**
  - Onset is usually congenital or occurs in early childhood with neonatal hypotonia and delayed motor development including head lag, a common and early sign.
  - Axial muscle weakness leads to development of scoliosis and major respiratory involvement in approximately two-thirds of individuals. Scoliosis develops at a mean age of 8.5 years and is generally cervicodorsal and progressive [Ferreiro et al 2000]. Varying severity of spinal rigidity is present.
  - Rigid spine muscular dystrophy (RSMD), characterized by limited flexion of dorsolumbar and cervical spine (caused by contractures of spinal extensor muscles) is now considered a form of classic MmD. The majority of individuals with these findings have *SEPN1* mutations and minicores on muscle biopsy [Moghadaszadeh et al 2001; Ferreiro, Quijano-Roy et al 2002].
  - Strength of trunk and neck flexors is usually scored 1 to 2 out of 5, pelvic and shoulder girdle muscles 3 to 4, and distal muscles normal or only moderately weak (3+ to 5). Individuals are usually ambulatory, as limb muscle strength is relatively preserved.
  - Facial muscle strength ranges from normal to severe weakness; extraocular muscles are spared.
- **Cardiac.** Cardiac involvement (right ventricular failure, cardiomyopathy) secondary to respiratory impairment is common. Mitral valve prolapse is occasionally seen.
- **Other features.** Most individuals have short stature and failure to thrive. Some individuals are slender and have a marfanoid habitus but no other features of Marfan syndrome.
- **Course.** Scoliosis is progressive and associated with loss of respiratory function in mid-later childhood, after which the course is often static.

Individuals may walk well into adulthood despite severe scoliosis and need for ventilatory support. In a few severe cases the disease may progress slowly through adolescence and adulthood, eventually leading to loss of ambulation.

Death often occurs as a result of respiratory infection in a setting of severe respiratory insufficiency.

Late onset of the disease is usually associated with better prognosis.

Moderate form with hand involvement (<10%). The characteristic feature is distal weakness of the upper limbs with joint hyperlaxity. Distal lower limbs are relatively normal. Scoliosis and respiratory involvement are mild or absent.

Antenatal form with arthrogryposis multiplex congenita (AMC) (<10%). The characteristic feature is generalized joint contractures at birth as a result of poor fetal movement. Associated distinctive features are dolicocephaly, prominent nasal root, oblique palpebral fissues, high-arched palate, low-set ears, short neck, and clinodactyly.

Ophthalmoplegic form (<10%) usually presents in the neonatal period or early infancy with marked generalized hypotonia and weakness. Failure to thrive and pronounced weakness of the axial and proximal muscles are common. External ophthalmoplegia predominantly affects upward and lateral gaze. Ligaments are universally lax. Respiratory function is moderately impaired but nocturnal hypoventilation is usually not a finding [Jungbluth et al 2000, Jungbluth et al 2005].

Genotype-Phenotype Correlations

***SEPN1*.** Individuals with *SEPN1* mutations have classic MmD. May develop early and severe scoliosis resulting in respiratory insufficiency requiring respiratory assistance [Ferreiro, Quijano-Roy et al 2002].

***RYR1*.** The disease is usually milder than that caused by mutations in *SEPN1*. The forms of MmD associated with *RYR1* mutations include the moderate form with hand involvement [Ferreiro, Monnier et al 2002] and the ophthalmoplegic form [Monnier et al 2003, Jungbluth et al 2005].

Nomenclature

Rigid spine muscular dystrophy or rigid spine syndrome are now considered the same entity as severe classic MmD.

Prevalence

MmD is thought to be rare. Actual prevalence figures are unknown.

The disease occurs in diverse ethnic and racial groups.

Differential Diagnosis

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

All forms of congenital myopathy have a number of common clinical features: generalized proximal weakness, hypotonia, hyporeflexia, poor muscle bulk, and features secondary to myopathy (e.g., elongated facies, high arched palate, pectus carinatum, scoliosis, foot deformities). Presence of severe rapidly progressive scoliosis favors a diagnosis of classic multiminicor disease (MmD); however, marked clinical overlap exists among MmD and

congenital myopathies as well as other neuromuscular disorders including congenital muscular dystrophy. Therefore, the diagnosis of MmD rests on the presence of typical structural changes on muscle biopsy.

Minicore lesions can coexist with central cores, rods or centrally located nuclei, and variable fibrosis. The differential diagnosis in those cases can include central core disease, nemaline myopathy, centronuclear myopathy, or one of the muscular dystrophies. Of these conditions, central core disease is most difficult to differentiate because minicores may be the predominant histopathologic finding in central core disease. In this situation, presence of pronounced hip girdle weakness, only mild facial involvement, lack of significant respiratory impairment, and myalgias or muscle cramps may support a diagnosis of central core disease. Central cores in central core disease have sharply defined boundaries, involve exclusively type I fibers, and extend throughout the entire fiber length, often centrally. However, it is important to remember that the differentiation between minicores and central cores is not always straightforward, and a continuum of histopathologic changes may be present in individuals.

Dominant mutations in the *ACTA1* have been described in individuals with congenital myopathy with atypical cores (not typical of central cores or multiple minicores) and those with coexisting cores and nemaline rods [Jungbluth et al 2001, Kaindl et al 2004]. Nemaline bodies with cores have been described in a family with recessive *CFL2* mutation [Agrawal et al 2007]. Similarly, a locus on chromosome 15q21-q23 has been linked to a dominantly inherited nemaline myopathy with core-like lesions [Gommans et al 2003].

Secondary MmD. Multiple minicore lesions can also be secondary to other conditions including SCAD (short chain acyl-COA dehydrogenase) deficiency, multiple pterygium syndrome with hypertrophic cardiomyopathy, other cardiomyopathies, hypohidrotic ectodermal dysplasia, Marfan syndrome, anesthetic reaction, and neurogenic conditions including denervation.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with multiminicore disease (MmD), the following evaluations are recommended:

- Comprehensive respiratory evaluation including assessment of breathing rate, signs of respiratory distress, ability to maintain oxygen saturations, pulmonary function studies, and sleep studies to rule out nocturnal hypoxia
- Assessment of feeding abilities including suck, swallow, gastroesophageal reflux, and maintenance of airway while feeding; evaluation of growth parameters to identify failure to thrive and determine need for interventions including gavage feeds and gastrostomy tube insertion
- Spinal x-rays to evaluate for presence of scoliosis; physical examination for joint contractures
- Cardiac evaluation for cardiomyopathy/cardiac involvement secondary to respiratory complications
- Physical and occupational therapy evaluation to develop interventions based on the distribution and extent of weakness
- Speech evaluation, especially if dysarthria or hypernasal speech is present
- Orthodontic evaluation for palatal anomalies

Treatment of Manifestations

Treatment is aimed at prevention of disease manifestations, early diagnosis by regular screening, and aggressive management of complications that may develop. Effective treatment requires a multidisciplinary approach that can improve both quality of life and survival for the affected individual.

Ongoing careful assessment of the potential need for part-time or permanent respiratory support is absolutely critical, as affected individuals may rapidly enter respiratory crisis or may unknowingly suffer from potentially fatal nocturnal hypoventilation.

Feeding support with tube/gavage feeds is needed if oral intake is poor. Failure to thrive may need to be overcome with high-caloric density formulas/feeds. Gastroesophageal reflux (if present) is treated in the usual manner.

Physical and occupational therapy may help to improve/maintain gross motor and fine motor functions.

Speech therapy should be provided for individuals with dysarthria/hypernasal speech.

Prevention of Secondary Complications

Annual influenza and other respiratory infection-related immunizations are advised.

Aggressive treatment of lower respiratory infections is critical.

Surveillance

Monitoring for potential complications that can influence the prognosis of MmD includes the following:

- Frequent and regular monitoring of the spine particularly during childhood and adolescence when scoliosis can rapidly progress during the adolescent growth spurt
- Careful monitoring of respiratory function from an early stage because of the risk of insidious nocturnal hypoxia and sudden respiratory failure. Monitoring of respiratory function should include: close attention to nocturnal hypoventilation symptoms including early morning headaches, daytime drowsiness, loss of appetite, and deteriorating school performance; lung function tests (FEV1 and FVC); sleep studies; and assessment of the need for intermittent or permanent ventilation. Nocturnal ventilation, when indicated, may significantly improve the prognosis.
- Assessment of cardiac status because of the risk of cardiac impairment secondary to respiratory involvement

Growth should be assessed regularly.

Regular neuromuscular evaluation to assess disease progress is indicated.

Agents/Circumstances to Avoid

Risk for malignant hyperthermia. Depolarizing muscle relaxants (e.g., succinylcholine) and inhalational agents (e.g., halothane, isoflurane, desflurane) can cause malignant hyperthermia and therefore need to be avoided during surgical procedures/childbirth, as *RYR1* mutations are associated with both malignant hyperthermia susceptibility and MmD.

Testing of Relatives at Risk

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

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

Multiminicore disease (MmD) is inherited in an autosomal recessive manner [Ferreiro et al 2000, Jungbluth et al 2002].

Note: Monoallelic expression of just the mutant allelle in skeletal muscle has been seen in some persons heterozygous at the genomic DNA level for recessive *RYR1* mutations [Zhou et al 2006].

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes and therefore carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic.

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.
- Once an at-risk sib is known to be unaffected, the chance of his/her being a carrier is 2/3.
- Carriers (heterozygotes) are asymptomatic.

Offspring of a proband. The offspring of a proband with MmD are obligate carriers (heterozygotes) for the mutant allele causing MmD.

Other family members of a proband. Each sib of the proband's parents is at a 50% risk of being a carrier.

Carrier Detection

Carrier testing for at-risk family members is available on a clinical basis once the disease-causing mutations in the family have been identified.

Related Genetic Counseling Issues

Occurrence in more than one generation. In a few families, occurrence in two generations has been reported. Whether this situation represents autosomal dominant inheritance or "pseudodominant inheritance" of an autosomal recessive disorder is unclear. To establish that a disorder is inherited in an autosomal dominant manner, transmission through a minimum of three generations and/or the presence of heterozygous disease-causing mutations is required; it is not clear that MmD has met these criteria.

Note: Pseudodominant inheritance is more likely to occur in autosomal recessive disorders with a high carrier frequency, for example in inbred populations and in cases of consanguinity.

A further complication is the uncertainty of the diagnosis of MmD in the cases reported by Paljarvi et al (1987). The affected individuals may have either autosomal dominant central core disease, with coexisting minicores, or secondary minicores possibly caused by denervation.

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal 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 or at risk of being carriers.

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 when the sensitivity of currently available testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk for *RYR1*-related and *SEPN1*-related MmD is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. Both disease-causing alleles 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.

Molecular Genetics

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

Table A. Molecular Genetics of Multiminicore Disease

Gene Symbol	Chromosomal Locus	Protein Name
RYR1	19q13.1	Ryanodine receptor 1
SEPN1	1p36-p35	Selenoprotein N

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 Multiminicore Disease

117000	CENTRAL CORE DISEASE OF MUSCLE
180901	RYANODINE RECEPTOR 1; RYR1
255320	MINICORE MYOPATHY WITH EXTERNAL OPHTHALMOPLEGIA
602771	RIGID SPINE MUSCULAR DYSTROPHY 1; RSMD1
606210	SELENOPROTEIN N, 1; SEPN1
607552	MINICORE MYOPATHY, ANTENATAL ONSET, WITH ARTHROGRYPOSIS

Table C. Genomic Databases for Multiminicore Disease

Gene Symbol	Entrez Gene	HGMD
RYR1	6261 (MIM No. 180901)	RYR1
SEPN1	57190 (MIM No. 606210)	SEPN1

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

Note: HGMD requires registration.

SEPN1

Normal allelic variants: The gene has 13 exons spanning 18.5 kb. The transcription product is 4.5 kb and the open reading frame has 1770 nucleotides. The functional transcript has one in-frame TGA codon in exon 10, which is read as selenocysteine because of the presence of a selenocysteine insertion sequence (SECIS) element in the 3' UTR region. Known non-pathogenic polymorphisms are included in Table 2 (pdf).

Pathologic allelic variants: The pathologic mutations in *SEPN1* associated with MmD are summarized in Table 3 (pdf) [Ferreiro, Monnier et al 2002; Ferreiro, Quijano-Roy et al 2002; Tajsharghi et al 2005; Zorzato et al 2007].

Normal gene product: The gene encodes a 590-amino acid protein called selenoprotein N. The function of selenoprotein N is not known, but it is found in virtually all tissues examined by western blot. The protein is expressed in very low levels and most studies require overexpression. An enzymatic function has been hypothesized for selenoprotein N based on protein structure and analogies with other selenoproteins with known function. Most of the selenoproteins identified to date are catalysts either in redox processes or in thyroid hormone processing.

Selenoprotein N has an EF hand Ca^{2+} binding motif similar to that found in proteins like calmodulin, suggesting that Ca^{2+} may play a role in Ca homeostasis and/or in modulation of selenoprotein N function.

Abnormal gene product: The abnormal gene product either is a truncated protein or may contain a missense amino acid substitution. The functional significance of these abnormal products is unknown. *SEPN1* mRNAs associated with frameshift or nonsense mutations may be resistant to nonsense-mediated decay [Okamoto et al 2006].

RYR1

Normal allelic variants: The *RYR1* gene has 106 exons encompassing a total of 160 kb.

Pathologic allelic variants: More than 25 missense dominant mutations in *RYR1* gene have been associated with malignant hyperthermia susceptibility and/or central core disease [Galli et al 2002]. Mutations in *RYR1* associated with MmD described to date have been homozygous (see Table 4) (pdf) [Ferreiro, Monnier et al 2002; Jungbluth et al 2002; Jungbluth et al 2005; Zhou et al 2007; Zorzato et al 2007].

Zhou et al (2006) found that *RYR1* undergoes polymorphic, tissue-specific, and developmentally regulated allele silencing; and this unveils recessive mutations in individuals with core myopathies.

Normal gene product: *RYR1* encodes ryanodine receptor 1, the calcium release channel of skeletal muscle sarcoplasmic reticulum. With 5038 amino acids, ryanodine receptor 1 is one of the largest known proteins. The functional channel is composed of four identical subunits of 565 kd each and has been shown to interact with a number of regulatory proteins. The first 4000 amino acids comprise the hydrophilic cytoplasmic domain that bridges the gap between the transverse tubules and sarcoplasmic reticulum; the last 1000 amino acids form the hydrophobic membrane-spanning plate containing the pore [Tilgen et al 2001].

Abnormal gene product: Most *RYR1* mutations associated with malignant hyperthermia (MH) and central core disease (CCD) affect calcium homeostasis by either making the calcium channels hypersensitive to activation (associated with MH) or decreasing the amount of calcium released after activation (CCD phenotype) [Dulhunty et al 2006]. Studies on *RYR1* mutations associated with MmD phenotype have shown variable dysregulation of calcium homeostasis. While the Pro3527Ser mutation caused decreased calcium release after stimulation, there was no reduction in the case of the Ser71Tyr mutation, and increased calcium release was noted with the Asn2283His mutation. One hypothesis is that these mutations cause instability of the ryanodine receptor macromolecular complex leading to altered binding of regulatory proteins. In contrast, the mutations Arg109Trp, Met485Val, and the 14646+2.99 kb intronic splicing variant are associated with very low endogenous ryanodine receptor protein levels [Ducreux et al 2006, Zorzato et al 2007].

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.

Muscular Dystrophy Association (MDA)
3300 East Sunrise Drive
Tucson AZ 85718-3208
Phone: 800-572-1717
Fax: 520-529-5300

Email: mda@mdausa.org
www.mdausa.org

Muscular Dystrophy Campaign
61 Southwark Street
London SE1 0HL
United Kingdom
Phone: 0800 652 6352; (+44) 0 020 7803 4800
Fax: (+44) 0 020 7401 3495
Email: info@muscular-dystrophy.org
www.muscular-dystrophy.org

References

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

Author Notes

Web page: www.childrenshospital.org

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Revision History

- 10 April 2008 (me) Comprehensive update posted to live Web site
- 10 January 2006 (cd) Revision: *RYR1* mutation testing clinically available; *SEPN1* mutation testing available through custom laboratories
- 26 July 2005 (me) Comprehensive update posted to live Web site
- 25 March 2003 (me) Review posted to live Web site
- 6 December 2002 (ab) Original submission