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Multiminicore Disease – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

Synonyms: Minicore Disease, Minicore Myopathy, Multicore Disease, Multicore Myopathy, Multiminicore Myopathy

Alan H Beggs, PhD[1] and Pankaj B Agrawal, MD, MMSc[1]

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Summary

NOTE: THIS PUBLICATION HAS BEEN RETIRED. THIS ARCHIVAL VERSION IS FOR HISTORICAL REFERENCE ONLY, AND THE INFORMATION MAY BE OUT OF DATE.

Clinical 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%)
- 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. Pathogenic variants in *SELENON* (*SEPN1*) and *RYR1* are known to cause 50% of MmD cases reported; further genetic heterogeneity is suggested, but no other candidate region or gene has been identified to date.

Author Affiliation: 1 Program in Genomics and Division of Genetics, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts; Email: beggs@enders.tch.harvard.edu; Email: pankaj.agrawal@tch.harvard.edu.

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 most often inherited in an autosomal recessive manner. The occurrence of MMD in two generations in a few families has been reported, suggestive of autosomal dominant inheritance. 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 carrier. Carrier testing for at-risk relatives and prenatal testing for pregnancies at increased risk are possible if the pathogenic variants 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, Bönnemann 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

Genes. Pathogenic variants in two genes are known to cause MmD in approximately 50% of affected individuals.

Evidence for locus heterogeneity. Further genetic heterogeneity is suggested: a family with dilated cardiomyopathy and multiple minicores and another family with overlapping features of Laing distal myopathy and MmD have been described, both with heterozygous *MYH7* pathogenic variants [Cullup et al 2012].

Table 1. Molecular Genetic Testing Used in Multiminicore Disease

Gene [1]	Proportion of MmD Attributed to Mutation of This Gene	Method	Variants Detected [2]
SELENON (*SEPN1*)	30%-54% [3]	Sequence analysis [4]	Sequence variants
	Unknown	Deletion/duplication analysis [5]	Unknown; none reported [6]

Table 1. continued from previous page.

Gene [1]	Proportion of MmD Attributed to Mutation of This Gene	Method	Variants Detected [2]
RYR1	Unknown	Sequence analysis [4]	Sequence variants
	Unknown	Sequence analysis of select exons [4, 7]	Sequence variants in select exons
	Unknown	Deletion/duplication analysis [5]	Unknown; none reported [5]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants.
3. Autosomal recessive *SELENON* pathogenic variants account for approximately 30% of all MmD and approximately 50% of classic MmD [Ferreiro et al 2002b]. An estimated 40% of individuals with *SELENON* pathogenic variants are compound heterozygotes.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. 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.
5. Testing that identifies deletions/duplications not readily detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.
6. No deletions or duplications involving *SELENON* or *RYR1* have been reported to cause multiminicore disease.
7. Exons sequenced may vary by laboratory.

Testing Strategy

To confirm/establish the diagnosis in a proband. 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 *SELENON* and *RYR1*.

- Because the majority of individuals with MmD have a pathogenic variant in *SELENON*, sequence analysis should be done first.
- If no *SELENON* pathogenic variants are identified, sequence analysis of *RYR1* should be considered, particularly for those individuals with non-classic forms of MmD.
- Although no deletions or duplications of either *SELENON* or *RYR1* have been reported to date to cause MmD, deletion/duplication analysis of each of these genes could be considered in an individual with features of MmD in whom causative variants in *SELENON* and *RYR1* have not been identified through sequence analysis.

Clinical Characteristics

Clinical Description

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 *SELENON* pathogenic variants and minicores on muscle biopsy [Moghadaszadeh et al 2001, Ferreiro et al 2002b].
  - 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

***SELENON* (*SEPN1*).** Individuals with *SELENON* pathogenic variants have classic MmD. May develop early and severe scoliosis resulting in respiratory insufficiency requiring respiratory assistance [Ferreiro et al 2002b].

***RYR1*.** The disease is usually milder than that caused by mutation of *SELENON*. The forms of MmD associated with *RYR1* pathogenic variants include the moderate form with hand involvement [Ferreiro et al 2002a] 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.

Genetically Related (Allelic) Disorders

SELENON (*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 pathogenic variant in *SELENON* had clinical findings similar to those of *SELENON*-related myopathy.
- Three women in one family who were homozygous for the c.943G>A pathogenic variant 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. *SELENON* pathogenic variants have been identified in individuals with desmin-related myopathy with Mallory body-like inclusions [Ferreiro et al 2004]. 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

Central core disease (CCD) is most often caused by autosomal dominant pathogenic variants in *RYR1*. The majority of CCD-causing variants 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]. Significant clinical and

pathologic overlap between CCD and MmD has been identified in individuals who have homozygous or compound heterozygous pathogenic variants in *RYR1*:

- One family in whom muscle fibers showed coexistence of minicores, central cores, and a few rod-like structures had a homozygous *RYR1* pathogenic variant in exon 101 [Jungbluth et al 2002].
- Another family homozygous for an *RYR1* pathogenic variant 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 et al 2002a].
- Ten individuals in whom muscle biopsy revealed significant overlap between central cores and minicores were identified to carry compound heterozygous *RYR1* pathogenic variants distributed throughout the gene. Nine of these ten affected individuals had opthalmoplegia [Monnier et al 2008].

Malignant hyperthermia susceptibility (MHS) is caused by *RYR1* pathogenic variants 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* pathogenic variants. Malignant hyperthermia is also associated with pathogenic variants 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 variants of *RYR1* on the same allele in exons 50 and 53.

CFTD resulting from biallelic *RYR1* pathogenic variants has been identified by a recent study [Clarke et al 2010]. *RYR1* variants were responsible for 10%-20% of the individuals with CFTD, making this the second most common cause (after *TPM3*). Individuals with CFTD who have ophthalmoplegia are more likely to have *RYR1* pathogenic variants. Reduced ryanodine channel activity as a result of low protein expression has been postulated in some patients with recessive *RYR1* pathogenic variants [Monnier et al 2008]; however, the mechanism for type I fiber hypotrophy associated with CFTD is unknown.

Centronuclear myopathy (CNM). Pathogenic variants in *RYR1* have been recently identified as a common cause of CNM, further expanding the disease spectrum resulting from mutation of *RYR1* [Wilmshurst et al 2010]. While the majority of pathogenic variants were present as compound heterozygous changes, the detection of only a single *RYR1* pathogenic variant inherited from an asymptomatic parent was found in a few families, which could represent either monoallelic *RYR1* expression or missed promoter variants/copy number variations in the second allele. Disease severity in individuals with CNM who have either single or homozygous/compound heterozygous *RYR1* pathogenic variants is extremely variable, and like CFTD and core myopathies, opthalmoplegia is a common finding.

A missense *RYR1* variant was reported with dominant congenital myopathy in a family with both nemaline bodies and cores [Scacheri et al 2000].

Differential Diagnosis

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 multiminicore 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 pathogenic variants in *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* pathogenic variant [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 and needs 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
- Consultation with a clinical geneticist and/or genetic counselor

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 for insidious nocturnal hypoxia and sudden respiratory failure. Monitoring of respiratory function should include the following:
  - 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
  - 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* pathogenic variants are associated with both malignant hyperthermia susceptibility and MmD.

Evaluation of Relatives at Risk

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

Pregnancy Management

In women with MmD, there is risk for malignant hyperthermia during delivery if inhalational anesthetic agents are used. A woman who has a fetus affected by MmD may develop polyhydramnios during pregnancy and may report a history of poor fetal movements. Abnormal presentation of an affected fetus may complicate delivery.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe 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.

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

Multiminicore disease (MmD) is most often inherited in an autosomal recessive manner [Ferreiro et al 2000, Jungbluth et al 2002]. The occurrence of MmD in two generations in a few families has been reported, suggestive of autosomal dominant inheritance.

Note: Monoallelic expression of just the mutated allele in skeletal muscle has been seen in some persons heterozygous at the genomic DNA level for recessive *RYR1* pathogenic variants [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 mutated 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 mutated 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 (Heterozygote) Detection

Carrier testing for at-risk family members is possible once the pathogenic variants 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 pathogenic variants 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 (e.g., in populations/families with high rates of consanguinity).

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, are carriers, or are at risk of being carriers.

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 Diagnosis

Once the *SELENON* or *RYR1* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis for MmD 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.

- **RYR-1 Foundation**
  P.O. Box 13312
  Pittsburgh PA 15243
  Phone: 412-529-1482
  Email: lindsay@ryr1.org
  www.ryr1.org
- **Muscular Dystrophy Association - USA (MDA)**
  222 South Riverside Plaza
  Suite 1500
  Chicago IL 60606
  Phone: 800-572-1717
  Email: mda@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

- **Congenital Muscle Disease International Registry (CMDIR)**

  The CMDIR is a patient self-report registry with the goal to register the global congenital muscle disease population including persons with congenital myopathy, congenital muscular dystrophy, and congenital myasthenic syndrome. The CMDIR registers affected individuals of all ages with symptoms from birth through late onset (limb-girdle). Registrants will receive educational information and connections to others in the CMD community, and will be contacted about potential participation in clinical trials for their CMD subtype.

  19401 South Vermont Avenue

  Suite J100

  Torrance CA 90502

  Phone: 323-250-2399

  Fax: 310-684-2023

  Email: counselor@cmdir.org; sarah.foye@cmdir.org

  www.cmdir.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. Multiminicore Disease: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
RYR1	19q13.2	Ryanodine receptor 1	Leiden Muscular Dystrophy pages (RYR1)	RYR1	RYR1
SELENON	1p36.11	Selenoprotein N	SEPN1 homepage - Leiden Muscular Dystrophy pages	SELENON	SELENON

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 Multiminicore Disease (View All in OMIM)

117000	CENTRAL CORE DISEASE OF MUSCLE; CCD
180901	RYANODINE RECEPTOR 1; RYR1
255320	MINICORE MYOPATHY WITH EXTERNAL OPHTHALMOPLEGIA
602771	RIGID SPINE MUSCULAR DYSTROPHY 1; RSMD1
606210	SELENOPROTEIN N; SELENON

SELENON (*SEPN1*)

Gene structure. *SELENON* 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. For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign variants. Known non-pathogenic polymorphisms are included in Table 2 (pdf).

Pathogenic variants. The pathogenic variants in *SELENON* associated with MmD are summarized in Table 3 (pdf) [Ferreiro et al 2002a, Ferreiro et al 2002b, Tajsharghi et al 2005, Zorzato et al 2007].

Up to two thirds of pathogenic variants cause premature termination of translation; the remaining pathogenic variants are missense changes. Variants appear to be distributed throughout the gene.

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. *SELENON* mRNAs associated with frameshift or nonsense variants may be resistant to nonsense-mediated decay [Okamoto et al 2006].

RYR1

Gene structure. *RYR1* has 106 exons encompassing a total of 160 kb. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. More than 25 missense dominant variants in *RYR1* have been associated with malignant hyperthermia susceptibility and/or central core disease [Galli et al 2002]. Pathogenic variants in *RYR1* associated with MmD described to date have been homozygous (see Table 4 [pdf]) [Ferreiro et al 2002a, 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 pathogenic variants in individuals with core myopathies.

Normal gene product. *RYR1* encodes ryanodine receptor 1, the calcium release channel of skeletal muscle sarcoplasmic reticulum. Ryanodine receptor 1 is one of the largest known proteins, with 5038 amino acids. 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* pathogenic variants 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* pathogenic variants associated with MmD phenotype have shown variable dysregulation of calcium homeostasis. While the p.Pro3527Ser variant caused decreased calcium release after stimulation, there was no reduction in the case of the p.Ser71Tyr variant, and increased calcium release was noted with the p.Asn2283His variant. One hypothesis is that these pathogenic variants cause instability of the ryanodine receptor macromolecular complex leading to altered binding of regulatory proteins. In contrast, the pathogenic variants p.Arg109Trp and p.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].

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Chapter Notes

Author Notes

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Revision History

- 18 April 2019 (ma) Chapter retired: histologic diagnosis without strong genetic correlation
- 24 January 2013 (me) Comprehensive update posted live
- 10 April 2008 (me) Comprehensive update posted live
- 10 January 2006 (cd) Revision: *RYR1* mutation testing clinically available; *SEPN1* mutation testing available through custom laboratories
- 26 July 2005 (me) Comprehensive update posted live
- 25 March 2003 (me) Review posted live
- 6 December 2002 (ab) Original submission

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