GENEReviews

Funded by the NIH · Developed at GeneTests (www.genetests.org), University of Washington, Seattle

Central Core Disease

May Christine V Malicdan, MD
National Center of Neurology and Psychiatry
National Institute of Neuroscience
Tokyo

Ichizo Nishino, MD, PhD
National Center of Neurology and Psychiatry
National Institute of Neuroscience
Tokyo

Initial Posting: May 16, 2007.

Summary

Disease characteristics. Central core disease (CCD) is characterized by muscle weakness ranging from mild to severe. Most affected individuals have mild disease with symmetric proximal muscle weakness and variable involvement of facial and neck muscles. The extraocular muscles are often spared. Motor development is usually delayed, but in general, most affected individuals acquire independent ambulation. Life span is usually normal. Severe disease is early in onset with profound hypotonia often accompanied by poor fetal movement, spinal deformities, hip dislocation, joint contractures, poor suck, and respiratory insufficiency requiring assisted ventilation. The outcome ranges from death in infancy to survival beyond age five years. Typically the weakness in CCD is not progressive.

Diagnosis/testing. The diagnosis of CCD is based on clinical findings of muscle weakness, the histopathologic findings of characteristic cores on muscle biopsy, and molecular genetic testing. Most CCD is associated with mutations in *RYR1*, the gene encoding the ryanodine receptor 1. Sequence analysis of select exons in known hotspots identifies mutations in 47%-67% of affected individuals.

Management. *Treatment of manifestations:* physical therapy for hypotonia and weakness that may include stretching and mild to moderate low-impact exercise; assistive devices as needed for ambulation; orthopedic surgery as needed for scoliosis, congenital hip dislocation, foot deformities; respiratory support, breathing exercises, chest physiotherapy as needed; dietary supplementation and nasogastric or gastrostomy feeding as needed. *Prevention of secondary complications:* intervention as needed to prevent respiratory compromise from scoliosis; immunization against influenza; prompt treatment of respiratory infection; mobility and physical therapy to prevent joint contractures. *Surveillance:* routine assessment of spine for scoliosis, joints for contractures, respiratory parameters [e.g., respiratory rate, peak expiratory flow rate (PEFR), forced vital capacity (FVC), and forced expiratory volume in one second (FEV1)], motor abilities to determine need for physical therapy, occupational therapy, assistive devices; sleep studies when signs of nocturnal hypoxia are present. *Agents/circumstances to avoid:* Although the actual risk for malignant hyperthermia susceptibility is unknown, it is prudent for individuals with CCD to avoid inhalational anesthetics and succinylcholine. *Testing of relatives at risk:* If the *RYR1* mutation is known, it is appropriate to offer at-risk relatives molecular genetic testing to identify those with possible increased malignant hyperthermia susceptibility.

Genetic counseling. Central core disease (CCD) is usually inherited in an autosomal dominant (AD) manner but can be inherited in an autosomal recessive (AR) manner. Most individuals

diagnosed with AD central core disease have an affected parent or an asymptomatic parent who has a disease-causing mutation. The proportion of AD CCD caused by *de novo* mutations is unknown. Each child of an individual with AD CCD has a 50% chance of inheriting the mutation. The parents of a child with AR CCD are obligate heterozygotes and therefore carry one mutant allele. Heterozygotes (carriers) are often asymptomatic. At conception, each sib of an individual with AR CCD 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. Prenatal diagnosis for pregnancies at increased risk for AD or AR CCD is possible once the disease-causing mutation(s) has/have been identified in an affected family member.

Diagnosis

Clinical Diagnosis

The diagnosis of central core disease (CCD) is based on a combination of clinical findings of muscle weakness and histopathologic findings of characteristic cores on muscle biopsy (see Testing), and confirmed, in most cases, by the presence of a disease-causing mutation in the gene *RYR1* (see Molecular Genetic Testing).

Because the clinical presentation ranges from the absence of symptoms to severe features including the need for ventilatory support, it is difficult to make the diagnosis of CCD based on clinical findings alone.

Note: Although controversial, the diagnostic criterion for CCD (for the purpose of this review) is the presence of CHARACTERISTIC cores in a significant number of fibers on muscle biopsy, even in individuals who are seemingly asymptomatic.

Clinical history. Although central core disease has a wide spectrum of symptoms and presentations, the following clinical findings can provide clues to the diagnosis:

- In early-onset disease:
  - Hypotonia and generalized weakness, often accompanied by perinatal complications, such as poor fetal movement, respiratory insufficiency, and poor suck
  - Delayed motor milestones (Independent ambulation is commonly achieved between ages three and four years, but varies depending on the severity of the disease.)
  - Spinal deformities, hip dislocation, high-arched palate, and joint contractures
- In later-onset disease (rare):
  - Mild symmetrical myopathy, predominantly involving the proximal muscles
  - Mildly affected facial muscles
  - Occasional involvement of the extraocular muscles (Ophthalmoplegia is relatively common in the autosomal recessive forms.)

Testing

Muscle biopsy

Histologic examination of muscle is essential to the diagnosis of central core disease. Diagnostic findings are the presence of a significant number of cores in type 1 fibers with the following characteristics (Figure1B):

- Often well demarcated
- May be centrally or peripherally located in the fibers
- Run down an appreciable length of the fiber on longitudinal sections
- Devoid of mitochondria
- Do not stain with oxidative enzyme stains (e.g., NADH-tetrazolium reductase, succinate dehydrogenase, cytochrome *c* oxidase)
- Deficient in phosphorylase activity and glycogen
- Sometimes surrounded by a thin rim of high oxidative enzyme activity, giving the appearance of "rimmed cores"

Less common but nonetheless important pathologic findings in the spectrum of cores include the following [Ferreiro, Quijano-Roy et al 2002, Jungbluth et al 2002, Sewry et al 2002]:

- More than one core can be observed within a single muscle fiber.
- The number of type 1 fibers with cores varies.
- The diameter of cores can vary.
- Foci of multiple minicores in focal areas can occur.

Other pathologic characteristics of muscle include:

- Type 1 fiber predominance or uniformity
- Mild to moderate fiber size variation
- Minimal to moderate endomysial fibrosis. Marked fibrosis and increase in adipose tissue have been noted in several cases.
- Occasional increase in internal and central nuclei

Note: (1) Nemaline bodies occurring together with cores have been seen in genetically confirmed cases of CCD. When rods are numerous this has sometimes been referred to as core-rod disease. In a large French pedigree demonstrating autosomal dominant inheritance, the association of this disease with *RYR1* mutations was confirmed [Monnier et al 2000]. Interestingly, some cases of nemaline myopathy may also show cores [Jungbluth et al 2002], blurring the pathologic distinction between these two diseases. (2) Facial muscle involvement and high-arched palate are almost always observed in infantile or childhood nemaline myopathy, but are rarely seen in CCD.

Ultrastructural studies show:

- Virtual absence of mitochondria and sarcoplasmic reticulum (SR) in the core region. SR accumulation within the cores has been described on EM.
- Irregular zigzag pattern or complete disruption of the Z-lines but often preservation of the striation pattern
- Reduction in the intermyofibrillar space

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. Most cases of CCD are associated with mutations in *RYR1*, the gene encoding the ryanodine receptor 1.

Other loci. Studies have shown that mutants of the *RYR1*-associated proteins FKBP12 and CACNA1S cause excitation-contraction (EC) uncoupling in vitro, similar to the effect of some *RYR1* mutants [Avila, Lee et al 2003; Lyfenko et al 2004; Weiss et al 2004], raising a possibility that mutations in *FKBP12* and/or *CACNA1S* may also be responsible for CCD. It is possible that other disorders with EC uncoupling could be within the spectrum of CCD, but more studies are warranted.

Other candidate genes to be considered include those that code for proteins involved or associated with the triadin, which is the anatomic site of EC uncoupling, and include triadin, junctin, histidine-rich calcium-binding protein, calsequestrin, JP-45, and mitsugamin-29 [Treves et al 2005]. To date, no mutation in these genes has been associated with CCD.

Clinical testing

- **Sequence analysis of select exons.** The *RYR1* mutations associated with CCD so far identified are clustered in three relatively restricted regions ("hot spots"), which encode domain 1 (exons 1-17), domain 2 (exons 39-46), and domain 3 (exons 90-104) of the ryanodine receptor 1 [Treves et al 2005] (Figure2).

  Although most mutations associated with CCD are clustered in the C-terminal domain 3, which comprises the transmembrane/luminal and pore-forming region of the channel, recent studies have shown that mutations in CCD are likewise found in domains 1 and 2, in which mutations are more commonly associated with malignant hyperthermia (see Allelic Disorders).

  Sequence analysis of select exons in known hotspots detected mutations in 47%-67% of affected individuals [Monnier et al 2001, Davis et al 2003, Shepherd et al 2004]; extending the central "hotspot" to include exons 47 and 48 may increase mutation detection rate to 89% [Wu et al 2006].

- **Sequence analysis of cDNA.** The entire *RYR1* cDNA has been sequenced by a number of groups [Lynch et al 1999; Monnier et al 2000; Ferreiro, Monnier et al 2002; Romero et al 2003; Zhou, Brockington et al 2006; Zhou, Yamaguchi et al 2006].

Research testing

- **Sequence analysis of the entire coding region.** Because the *RYR1* gene encodes the ryanodine receptor 1, one of the largest known proteins, direct sequencing of all exons is labor-intensive, but also most informative. Among 27 individuals diagnosed to have CCD on muscle biopsy, *RYR1* mutations were documented in 93% [Wu et al 2006], suggesting that CCD may not be a genetically heterogenous disease, as previously thought.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Central Core Disease

Test Method	Mutations Detected	Mutation Detection Frequency [1]	Test Availability
Sequence analysis of select exons [2]	*RYR1* sequence variants	47%-67% [3]	Clinical Testing
Complementary DNA sequence analysis		Variable	
Genomic DNA sequence analysis		>90% [4]	Research only

1. Proportion of affected individuals with a mutation(s) as classified by gene/locus, phenotype, population group, genetic mechanism, and/or test method
2. Exons sequenced vary by laboratory
3. In autosomal dominant CCD
4. Results from Wu et al 2006

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

If only one mutation is identified in a simplex case (i.e., a single occurrence in a family), it is difficult to distinguish between:

- A *de novo* dominant mutation
- Autosomal recessive inheritance with a known *RYR1* mutation on one allele and a second as-yet unidentified mutation on the second allele.

To resolve these two issues, the following can be considered:

- Testing both parents for the mutation, when possible, can confirm or exclude a *de novo* mutation.
- Complete analysis of the coding gene either on gDNA (106 exon sequencing) or on cDNA (transcript sequencing) may identify the mutation in *trans* configuration (i.e., on the second allele) if present.

Note: The pathogenicity of a mutation may be established by functional studies or testing in an animal model if one exists.

Testing Strategy

To confirm the diagnosis of CCD in a proband

- If clinical evaluation reveals characteristic findings (see Clinical Diagnosis), muscle biopsy to establish the diagnosis based on histologic findings
- Molecular genetic testing of *RYR1* to confirm the diagnosis

Carrier testing for relatives at risk of being heterozygous for autosomal recessive central core disease requires prior identification of the disease-causing mutations in the family.

Note: Carriers are heterozygous for an autosomal recessive disorder and are not at risk of developing the disorder. In the majority of cases CDD is inherited in an autosomal dominant manner; therefore, carrier testing is relevant in only that minority of cases caused by autosomal recessive inheritance.

Prenatal diagnosis for at-risk pregnancies requires prior identification of the disease-causing mutation(s) in the family.

Genetically Related (Allelic) Disorders

Malignant hyperthermia susceptibility (MHS). MHS is a pharmacogenetic disorder of skeletal muscle calcium regulation resulting in uncontrolled skeletal muscle hypermetabolism. Manifestations of malignant hyperthermia (MH) are triggered by certain volatile anesthetics (i.e., halothane, isoflurane, sevoflurane, desflurane, enflurane) either alone or in conjunction with depolarizing muscle relaxants (succinylcholine). The triggering substances release calcium stores from the sarcoplasmic reticulum, causing contracture of skeletal muscles, glycogenolysis, and increased cellular metabolism, resulting in production of heat and excess lactate. Affected individuals experience acidosis, hypercapnia, tachycardia, hypoxemia, rhabdomyolysis with subsequent increase in serum creatine kinase (CK), hyperkalemia with a risk of cardiac arrhythmia or even arrest, and myoglobinuria with a risk of renal failure. In nearly all cases, the first manifestations of MH, tachycardia, and tachypnea occur in the operating room, but MH may also occur in the early postoperative period. Death results unless the individual is promptly treated.

A clinical grading scale helps determine if a malignant hyperthermia (MH) episode has occurred. Contracture testing, the standard diagnostic test for MH since the mid-1970s, relies on the in vitro measurement of contracture response of biopsied muscle to graded concentrations of caffeine and the anesthetic halothane. Alternatively, calcium-induced calcium release (CICR) test can be performed, but has only been done in Japan. (For further information see Malignant Hyperthermia Susceptibility).

RYR1 is one of three known MHS genes. Domains 1 and 2 of *RYR1* are located in the soluble cytoplasmic regions of the protein and are hot spots for MH; however, mutations in these two domains have also been associated with CCD (see Molecular Genetic Testing).

The precise association of MHS and *RYR1* mutations is not clear and thus all individuals with a *RYR1* mutation are considered at risk for malignant hyperthermia and advised of appropriate precautions.

In several reports cores have been present in muscle biopsy of persons proven to have MH, thus raising controversy as to whether these patients have CCD with MHS or MHS with cores. Further analysis is needed.

Multiminicore disease (MmD). The diagnosis of MmD is based on the presence of multiple "minicores" visible on muscle biopsy oxidative stains. Minicores are small zones of sarcomeric disorganization and/or diminished oxidative activity typically extending only a few sarcomeres in the fiber longitudinal axis that correlate with lack of mitochondria in muscle fibers. 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.

Four clinical categories of MmD have been identified: 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 occurs in early 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.

Mutations in two genes account for about half the cases of MmD. Although further genetic heterogeneity is suggested, no other candidate region or gene has been identified to date.

- *SEPN1* mutations inherited in an autosomal recessive manner account for about 30% of all cases of MmD and about 40% of cases of classic MmD.

- *RYR1* mutations inherited in an autosomal recessive manner account for some forms of MmD, and in particular, those with ophthalmoplegia. Ophthalmoplegia is an exclusion criterion for *SEPN1* mutations.

Congenital neuromuscular disorder with uniform fiber type 1 (CNMDU1). CNMDU1 is pathologically defined by the almost exclusive presence of type 1 fibers in muscle sections (i.e., type 1 fibers comprise more than 99% of the fibers) and the absence of specific structural abnormalities such as cores and nemaline bodies.

CNMDU1 histologic findings are thought to be an earlier manifestation of CCD, as an individual with pathologically confirmed CCD had a muscle biopsy consistent with CNMDU1 earlier in childhood [Sewry et al 2002]. Furthermore, Quinlivan et al (2003) reported *RYR1* mutations in a family with CCD in which the youngest member showed uniform fiber typing, suggesting that adults have CCD while children had CNMDU1. These data imply that CNMDU1 is an earlier manifestation of the CCD spectrum; however, this may not be the case. Recently, mutations in the C-terminal region of *RYR1* were identified in 40% of individuals with CNMDU1 [Sato et al, in press]. In this report, electron microscopic analysis of a patient with CNMDU1 showed virtually normal histology, devoid of signs of early core formation, also suggesting that CNMDU1 may be a distinct entity and more possibly allelic to CCD. Moreover, there has been no report of overlap between the two disorders with respect to histologic findings (i.e., uniform type 1 fiber with cores in only a few fibers), casting doubt on the hypothesis that these two diseases belong to a single spectrum.

Clinical Description

Natural History

The expressivity of central core disease (CCD) is variable, clinically ranging from mild (i.e., almost asymptomatic) to severe (i.e., ventilator-dependent) and histologically varying in the extent and localization of cores in the muscle fibers.

Most individuals have mild disease characterized by mild, symmetric weakness that preferentially affects the proximal muscles. The facial and neck muscles may be mildly involved in some cases. The extraocular muscles are often spared in the classic, autosomal dominant form, but are typically involved in the autosomal recessive form. Motor development is usually delayed, but in general, most affected individuals acquire independent ambulation. Hypotonia in infancy and respiratory insufficiency can also occur in those with mild disease. Life span is usually normal.

Muscle cramps have been documented in some individuals with CCD, and this may be associated with MH susceptibility.

Severe disease is characterized by infantile onset associated with profound hypotonia and respiratory dysfunction requiring continuous assisted ventilation. In severely affected individuals, death may result from respiratory infection or respiratory insufficiency.

Fetal akinesia has been associated with both autosomal dominant and autosomal recessive forms of *RYR1*-related CCD [Romero et al 2003]. The clinical phenotype consisted of severe hypotonia, arthrogryposis multiplex congenita, amyotrophy, and respiratory failure, requiring mechanical ventilation. The outcome, however, was variable (ranging from early death to survival beyond age five years).

Typically CCD is not progressive, although slow progression has been reported [Lamont et al 1998]. Scoliosis can be progressive, resulting in respiratory insufficiency.

Intellectual ability is intact.

Other. Serum creatine kinase concentration may be normal or mildly elevated.

Electromyography may confirm the presence of myopathy and reveal brief, short action potentials and early recruitment.

Muscle imaging has demonstrated that certain muscles are selectively involved in *RYR1*-related myopathies, including quadriceps, sartorius, adductor magnus, soleus, gastrocnemii, and peroneal group; certain muscles are relatively spared, including rectus, femoris, gracilis, adductor longus, and tibialis anterior [Jungbluth et al 2004].

Genotype-Phenotype Correlations

Although most *RYR1* mutations that result in CCD are inherited in an autosomal dominant manner, reports of autosomal recessive inheritance are increasing. At the moment, it is not possible to predict the mode of inheritance based on the mutation alone.

Some studies have shown that autosomal recessive CCD, often associated with *RYR1* mutations outside the C-terminal region, can be severe [Romero et al 2003; Zhou, Yamaguchi et al 2006]. Thus, it may be possible to consider most autosomal dominant forms of CCD as milder in phenotype than autosomal recessive forms of CCD.

In a study of 25 individuals with genetically confirmed CCD, Wu et al (2006) determined that:

- The 16 individuals with C-terminal *RYR1* mutations had certain clinical features including hypotonia during infancy, delayed motor development, and limb muscle weakness and certain pathologic findings on muscle biopsy that delineate C terminal mutations from other groups including (1) type 2 fiber deficiency and interstitial fibrosis, (2) characteristic cores with clearly demarcated borders that are observed in almost all type 1 muscle fibers, (3) higher than average frequency of "rimming" on the borders of these cores.
- Most individuals with CCD with at least one *RYR1* mutation outside the C-terminal region had only mild musculoskeletal abnormalities such as joint contractures and scoliosis. Inheritance was autosomal dominant, consistent with previous reports of mild CCD phenotype.

Malignant hyperthermia susceptibility. MHS-related *RYR1* mutations are predominantly located in the hydrophilic N-terminal and central portions of the ryanodine receptor 1 (RyR1) protein, whereas CCD-related *RYR1* substitutions mainly occur in the hydrophobic pore-forming region of the channel [Monnier et al 2000, Monnier et al 2001, Davis et al 2003, Zorzato et al 2003]. Previous reports have asserted that persons without muscle disease who are susceptible to malignant hyperthermia (MH) have mutations in the C-terminal region of ryanodine receptor 1; however, limited histopathologic evaluation of these individuals has revealed the presence of cores that are not characteristic of the cores of CCD [Ibarra et al 2006]; thus, they are most appropriately labeled as having "MH with cores."

Individuals with CCD who have mutations in the N-terminal domain may have a higher probability of malignant hyperthermia susceptibility than those with mutations in the C-terminal domain [Wu et al 2006].

Penetrance

In general, the penetrance of CCD is variable. Mutations in the C-terminal region of ryanodine receptor 1, including p.Ile4898Thr [Lynch et al 1999] and p.Tyr4796Cys [Monnier et al

2000] in the luminal domain were associated with more severe phenotype, and, hence, full penetrance, and autosomal dominant inheritance.

Anticipation

Anticipation is not observed.

Nomenclature

CCD has also been referred to as Shy-Magee syndrome, after the individuals who initially reported it.

Some cases called core-rod disease are not associated with a *RYR1* mutation; thus, "core-rod disease" is not a true synonym for CCD.

Prevalence

The precise incidence and prevalence of CCD, considered to be the most frequently occurring congenital myopathy, are unknown.

Differential Diagnosis

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

The clinical findings of central core disease (CCD) are variable and not disease-specific; they can be seen in other congenital myopathies. Thus, from a clinical standpoint CCD cannot be readily distinguished from other congenital myopathies, such as multiminicore disease, CNMDU1 (see Allelic Disorders), the intermediate form of nemaline myopathy, fingerprint body myopathy, congenital fiber-type disproportion, hyaline body myopathy, reducing body myopathy, and cylindrical spirals myopathy.

The phenotype of CCD is relatively heterogeneous with a variable age of onset. Thus, CCD must be considered in persons of all ages with scoliosis or severe spinal deformity, unexplained muscle weakness, and multiple joint problems [Mertz et al 2005, Sestero & Perra 2005].

The 'central core' histologic changes are nonspecific and may occur in other myopathies. The central cores characteristic of CCD have been reported with mutations in the following genes:

- *SEPN1*. Mutations in this gene are also associated with minicores [Ferreiro, Quijano-Roy et al 2002], but no individual with a *SEPN1* mutation and the typical long, well-delimited central cores characteristic of CCD has been reported.
- *MYH7*, in hypertrophic cardiomyopathy [Fananapazir et al 1993]
- *ACTA1* and *TNNT1* in nemaline myopathy [Ilkovski et al 2001]. *ACTA1* mutations were found in a congenital myopathy with few cores on muscle biopsy [Kaindl et al 2004]; like other disorders with cores, however, these disorders are better considered as myopathies with cores, not CCD.
- Structures similar to cores have been observed in the myofibers of individuals with neurogenic atrophy but are more appropriately called "target fibers" in this setting because of the darker band around the pale central area, giving it a target-like appearance. In addition, core-like lesions devoid of this band can also be seen in these conditions.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with central core disease (CCD), the following evaluations are recommended:

- Neurologic examination with attention to features of congenital myopathy (hypotonia, failure to thrive, joint contractures, scoliosis), weakness of the limbs, and muscle cramps
- Physical and occupational therapy assessments
- Evaluation for feeding difficulties, including assessment for sucking and ability to swallow
- Pulmonary function testing in most patients, especially those with scoliosis, hypotonia, signs of respiratory distress, and/or history of recurrent chest infections. History should be taken for symptoms of nocturnal hypoxia including early morning headaches, daytime drowsiness, loss of appetite, and deteriorating school performance.

Treatment of Manifestations

Since prognosis is mainly influenced by respiratory status and scoliosis, treatment geared towards these manifestations is essential.

Treatment depends on the severity of symptoms, but mainly consists of supportive measures and rehabilitation that address the following problems:

- Hypotonia and weakness. Patients may benefit from physical therapy. Interventions may include stretching programs and mild to moderate low-impact exercise but activities should be balanced in such a way that exhaustion is avoided.
- Scoliosis and joint contractures. Some patients may only require physical therapy, while others may need orthopedic surgery (e.g., scoliosis surgery, corrective surgery for congenital hip dislocation and foot deformities).
- Respiratory. Patients with more severe symptoms may require respiratory support. Breathing exercises and chest physiotherapy for handling secretions may also be beneficial.
- Feeding difficulties. Individuals may require diet supplementation and feeding by means of nasogastric/orogastric routes or gastrostomy.

Prevention of Secondary Complications

Secondary complications can include respiratory compromise from scoliosis; hence, orthopedic intervention may reduce the risk of this problem.

Immunization against influenza is encouraged.

Prompt treatment of respiratory infection is important.

Joint contractures may be prevented by encouraging mobility and by active participation in physical therapy.

Surveillance

- Routine assessment of the spine for scoliosis and joints for contractures

- Routine assessment of respiratory parameters such as respiratory rate, peak expiratory flow rate (PEFR), forced vital capacity (FVC), and forced expiratory volume in one second (FEV1)
- Sleep studies especially when patients show signs of nocturnal hypoxia
- Regular assessment of motor abilities in order to determine need for physical therapy, occupational therapy, and assistive devices for ambulation, such as a wheelchair

Agents/Circumstances to Avoid

Although it is unknown how CCD is associated with malignant hyperthermia susceptibility or which mutations in *RYR1* are absolutely related to MH susceptibility, it is prudent for individuals with CCD to avoid inhalational anesthetics and succinylcholine. (See Malignant Hyperthermia Susceptibility for more details.)

Individuals suspected of having MH susceptibility are advised to avoid extremes of heat, but this does not mean restriction of athletic activity.

Testing of Relatives at Risk

Because CCD is associated with an increased risk for MH susceptibility, it is appropriate to test at-risk relatives of a proband (whether symptomatic or not) for the *RYR1* mutation identified in the proband in order to caution those with the mutation about potential risks of inhalational anesthetics and succinylcholine. (See Malignant Hyperthermia Susceptibility for more details.)

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

Central core disease (CCD) is usually inherited in an autosomal dominant manner, but it can be inherited in an autosomal recessive manner [Manzur et al 1998; Ferreiro, Monnier et al 2002; Jungbluth et al 2002; Romero et al 2003; Wu et al 2006; Zhou, Yamaguchi et al 2006; Kossugue et al 2007].

Risk to Family Members — Autosomal Dominant Inheritance

Parents of a proband

- Most individuals diagnosed with autosomal dominant CCD have an affected parent or an asymptomatic parent who has a disease-causing mutation.
- A proband with autosomal dominant CCD may have the disorder as the result of a new gene mutation. The proportion of cases caused by *de novo* mutations is unknown.
- If the disease-causing mutation found in the proband cannot be detected in the DNA of either parent, two possible explanations are germline mosaicism in a parent or a *de novo* mutation in the proband. Although no instances of germline mosaicism have been reported, it remains a possibility.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include muscle biopsy and molecular genetic testing. Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of failure by health care professionals to recognize the syndrome and/or a milder phenotypic presentation. Therefore, an apparently negative family history cannot be confirmed until appropriate evaluations have been performed.

Note: (1) Although most individuals diagnosed with CCD 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, late onset of the disease in the affected parent, or reduced penetrance. (2) If the parent is the individual in whom the mutation first occurred s/he may have somatic mosaicism for the mutation and may be mildly/minimally affected.

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 the disease-causing mutation found in the proband cannot be detected in the DNA of either parent, the risk to sibs is low, but greater than that of the general population because the possibility of germline mosaicism exists.

Offspring of a proband. Each child of an individual with autosomal dominant CCD has a 50% chance of inheriting the mutation.

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

Risk to Family Members — Autosomal Recessive Inheritance

Parents of a proband

- The parents of an affected child are obligate heterozygotes and therefore carry one mutant allele.
- Heterozygotes (carriers) are often 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 risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. The offspring of an individual with autosomal recessive CCD are obligate heterozygotes (carriers) for a disease-causing mutation.

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 family members at risk of being heterozygous for autosomal recessive CCD is available on a clinical basis once the mutations have been identified in the proband.

Related Genetic Counseling Issues

See Testing of Relatives at Risk for information on testing of relatives for malignant hyperthermia susceptibility.

Simplex cases. Kossugue et al (2007) reported several simplex cases with CCD in whom at least one mutation was identified. The cause of CCD in these individuals may be (1) a *de novo* dominant mutation or (2) autosomal recessive inheritance of a known *RYR1* mutation and a second as-yet unidentified mutation.

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or undisclosed adoption could also be explored.

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.

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%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Although prenatal diagnosis has not been reported, prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. The disease-causing allele(s) of an affected family

member must be identified or linkage established in the family 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 mutation(s) has/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 Central Core Disease

Gene Symbol	Chromosomal Locus	Protein Name
RYR1	19q13.1	Ryanodine receptor 1

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 Central Core Disease

117000	CENTRAL CORE DISEASE OF MUSCLE
180901	RYANODINE RECEPTOR 1; RYR1

Table C. Genomic Databases for Central Core Disease

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

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

Molecular Genetic Pathogenesis

The skeletal muscle isoform of ryanodine receptor 1 (RyR1) mediates Ca^{2+} release during excitation-contraction (EC) coupling; hence, mutations in the *RYR1* gene are expected to cause disturbance in this process. However, the precise pathophysiology of central core disease (CCD) is not fully understood and remains controversial. Two fundamentally distinct cellular mechanisms (leaky channels and EC uncoupling) are proposed to explain how altered release channel function caused by different mutations in *RYR1* could result in muscle weakness in CCD [Dirksen & Avila 2002]. Although it is commonly believed that cores are not specific to CCD, it has recently been demonstrated that calcium-handling proteins are abnormally distributed in *RYR1*-associated core myopathies: RyR1 protein was depleted from the cores, while calsequestrin, SERCA1/2, triadin, and DHPR had accumulated within or around the lesions [Herasse et al 2007]. These findings suggest that EC uncoupling may indeed lead to muscle weakness.

Certain *RYR1* mutations are associated with both CCD and MH susceptibility. In a previous report, the effects of mutations that involve CCD plus MH susceptibility and MH susceptibility only on Ca^{2+} handling and EC coupling have been characterized; it has been suggested that SR Ca^{2+} depletion and increased basal Ca^{2+} levels are preferentially associated with *RYR1* mutations that result in combined MH susceptibility and CCD [Dirksen & Avila 2004]. Furthermore, the authors also found that MH susceptibility-only mutations modestly increase basal release-channel activity in a manner insufficient to alter net SR Ca^{2+} content

("compensated leak"), whereas the combined MH susceptibility and CCD phenotype arises from mutations that enhance basal activity to a level sufficient to promote SR Ca^{2+} depletion, elevate [Ca^{2+}]i, and reduce maximal VGCR ("decompensated leak").

Zhou, Brockington et al (2006) presented evidence that in individuals with autosomal recessive core myopathies, *RYR1* frequently undergoes polymorphic, tissue-specific, and developmentally regulated allele silencing apparently mediated by hypermethylation. The resulting monoallelic expression of *RYR1* can unveil recessive mutations in the remaining *RYR1* allele in persons with core myopathies. Zhou, Brockington et al (2006) also suggested that imprinting is a likely mechanism for this phenomenon, which can play a role in human phenotypic heterogeneity and in irregularities of inheritance patterns.

Normal allelic variants: *RYR1* consists of 106 exons (two of which are alternatively spliced) encompassing a total of 160 kb and producing one of the largest proteins in humans with 5038 amino acids [Phillips et al 1996]. Several polymorphisms have been noted in *RYR1*, including: p.Ala1832Gly, p.Val2550Leu [Monnier et al 2000]; p.Val4849Ile [Monnier et al 2001]; p.Gly2060Cys, p.Met485Val [Zhou, Yamaguchi et al 2006].

Pathologic allelic variants: At least 72 reported *RYR1* mutations have been associated with the autosomal dominant or autosomal recessive forms of CCD, including 67 missense mutations and five deletions, clustered in three regions of the gene. More than half of the *RYR1* mutations are private.

The most common mutations are shown in Table 2 (pdf).

Table 3 (pdf) shows the most common pathogenic amino acid variants in *RYR1* that are associated with autosomal dominant central core disease.

Normal gene product: *RYR1* encodes the ryanodine receptor 1 protein, a skeletal muscle calcium-release channel located in the sarcoplasmic reticulum (SR). The functional channel is a homotetramer of 560-kd subunits and releases calcium stored in the SR in response to membrane depolarization transduced by the dihydropyridine receptor (DHPR). The cytoplasmic domain of ryanodine receptor 1, also called the foot structure, comprises the first 4000 amino acids that bridge the gap between the SR and the transverse tubular system. The last 1000 amino acids from the transmembrane domain contain the pore of the channel [Tilgen et al 2001, Lehmann-Horn et al 2003].

Ryanodine receptors belong to the superfamily of intracellular Ca^{2+} release channels present on endoplasmic reticulum/sarcoplamic reticulum (SR) membranes, having three different isoforms. Functional units are homotetramers of approximately 5,000 amino acids per subunit coded by 150-kb genes. *RYR1*, forming the SR calcium release channel, has a large hydrophilic NH2-terminal domain and a hydrophobic COOH-terminal domain containing several transmembrane domains as well as the channel pore. The 563-kd protein is predominantly expressed not only in skeletal muscle but also in human B-lymphocytes and immature murine dendritic cells.

Abnormal gene product: Alterations in the ryanodine receptor 1 protein lead to an abnormal, sustained increase in myoplasmic calcium concentration in skeletal muscle because of a "leaky channel" or uncoupling with its voltage sensor, which is encoded by the voltage-gated calcium channel gene, *DHPR* [Nelson 2001, Wehner et al 2003].

In vitro studies suggest that a high basal activity of the mutant Ca^{2+} channel could explain the muscle weakness and muscle atrophy observed in persons with CCD in one family [Lynch et al 1999]. In vitro expression of ryanodine receptor 1 with a single mutation (p.Ile4898Thr) in

the C-terminal transmembrane/luminal domain in HEK293 cells resulted in loss of channel activation and reduction in ryanodine binding, possibly by disrupting the ligand binding site located in the C terminus of the protein. Further analysis, however, showed that this mutation leads to a significant increase in the sensitivity of the channel to the activating effects of calcium.

The association of C-terminal mutations with clinically evident muscle weakness may be explained by the leaky-channel model and the excitation-contraction (EC) uncoupling model.

- Some non-C-terminal mutations in ryanodine receptor 1 promote the leak of Ca^{2+} ions from the SR that may or may not be compensated by the activity of the sarco-endoplasmic reticulum Ca^{2+} ATPase (SERCA), resulting in elevation of resting cytosolic Ca^{2+} and depletion of SR Ca^{2+} stores.

C-terminal mutations, especially those in the pore region of ryanodine receptor 1, may directly affect the channel gating properties, resulting in an abolition of orthograde activation by the voltage-gated L-type Ca^{2+} channel or, in other words, EC uncoupling. However, no compensatory mechanism increases Ca^{2+} release as the SERCA pumps do in the leaky model. Nevertheless, the effect of mutations in the C-terminal region remains controversial and at best unlikely because a number of mutations in this area were also shown to be "leaky." Interestingly, several mutations in *RYR1* exon 102 were shown to lead to varying degrees of EC uncoupling, indicating that this region is a primary locus of EC uncoupling in CCD [Avila, O'Connell 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.

Malignant Hyperthermia Association of the United States (MHAUS)
PO Box 1069
11 East State Street
Sherburne NY 13460
Phone: 800-644-9737 (US and Canada); 607-674-7901; 001-1-315-428-7925 (International)
Fax: 607-674-7910
Email: info@mhaus.org
www.mhaus.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

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.

Literature Cited

Avila G, Lee EH, Perez CF, Allen PD, Dirksen RT. FKBP12 binding to RyR1 modulates excitation-contraction coupling in mouse skeletal myotubes. J Biol Chem. 2003;278:22600–8. [PubMed: 12704193]

Avila G, O'Connell KM, Dirksen RT. The pore region of the skeletal muscle ryanodine receptor is a primary locus for excitation-contraction uncoupling in central core disease. J Gen Physiol. 2003;121:277–86. [PubMed: 12642598]

Davis MR, Haan E, Jungbluth H, Sewry C, North K, Muntoni F, Kuntzer T, Lamont P, Bankier A, Tomlinson P, Sanchez A, Walsh P, Nagarajan L, Oley C, Colley A, Gedeon A, Quinlivan R, Dixon J, James D, Muller CR, Laing NG. Principal mutation hotspot for central core disease and related myopathies in the C-terminal transmembrane region of the RYR1 gene. Neuromuscul Disord. 2003;13:151–7. [PubMed: 12565913]

Dirksen RT, Avila G. Altered ryanodine receptor function in central core disease: leaky or uncoupled Ca (2+) release channels? Trends Cardiovasc Med. 2002;12:189–97. [PubMed: 12161072]

Dirksen RT, Avila G. Distinct effects on Ca2+ handling caused by malignant hyperthermia and central core disease mutations in RyR1. Biophys J. 2004;87:3193–204. [PubMed: 15347586]

Fananapazir L, Dalakas MC, Cyran F, Cohn G, Epstein ND. Missense mutations in the beta-myosin heavy-chain gene cause central core disease in hypertrophic cardiomyopathy. Proc Natl Acad Sci U S A. 1993;90:3993–7. [PubMed: 8483915]

Ferreiro A, Monnier N, Romero NB, Leroy JP, Bonnemann C, Haenggeli CA, Straub V, Voss WD, Nivoche Y, Jungbluth H, Lemainque A, Voit T, Lunardi J, Fardeau M, Guicheney P. A recessive form of central core disease, transiently presenting as multi-minicore disease, is associated with a homozygous mutation in the ryanodine receptor type 1 gene. Ann Neurol. 2002;51:750–9. [PubMed: 12112081]

Ferreiro A, Quijano-Roy S, Pichereau C, Moghadaszadeh B, Goemans N, Bonnemann C, Jungbluth H, Straub V, Villanova M, Leroy JP, Romero NB, Martin JJ, Muntoni F, Voit T, Estournet B, Richard P, Fardeau M, Guicheney P. Mutations of the selenoprotein N gene, which is implicated in rigid spine muscular dystrophy, cause the classical phenotype of multiminicore disease: reassessing the nosology of early-onset myopathies. Am J Hum Genet. 2002;71:739–49. [PubMed: 12192640]

Herasse M, Parain K, Marty I, Monnier N, Kaindl AM, Leroy JP, Richard P, Lunardi J, Romero NB, Ferreiro A. Abnormal distribution of calcium-handling proteins: a novel distinctive marker in core myopathies. J Neuropathol Exp Neurol. 2007;66:57–65. [PubMed: 17204937]

Ibarra M CA, Wu S, Murayama K, Minami N, Ichihara Y, Kikuchi H, Noguchi S, Hayashi YK, Ochiai R, Nishino I. Malignant hyperthermia in Japan: mutation screening of the entire ryanodine receptor type 1 gene coding region by direct sequencing. Anesthesiology. 2006;104:1146–54. [PubMed: 16732084]

Ilkovski B, Cooper ST, Nowak K, Ryan MM, Yang N, Schnell C, Durling HJ, Roddick LG, Wilkinson I, Kornberg AJ, Collins KJ, Wallace G, Gunning P, Hardeman EC, Laing NG, North KN. Nemaline myopathy caused by mutations in the muscle alpha-skeletal-actin gene. Am J Hum Genet. 2001;68:1333–43. [PubMed: 11333380]

Jungbluth H, Davis MR, Muller C, Counsell S, Allsop J, Chattopadhyay A, Messina S, Mercuri E, Laing NG, Sewry CA, Bydder G, Muntoni F. Magnetic resonance imaging of muscle in congenital myopathies associated with RYR1 mutations. Neuromuscul Disord. 2004;14:785–90. [PubMed: 15564033]

Jungbluth H, Muller CR, Halliger-Keller B, Brockington M, Brown SC, Feng L, Chattopadhyay A, Mercuri E, Manzur AY, Ferreiro A, Laing NG, Davis MR, Roper HP, Dubowitz V, Bydder G, Sewry CA, Muntoni F. Autosomal recessive inheritance of RYR1 mutations in a congenital myopathy with cores. Neurology. 2002;59:284–7. [PubMed: 12136074]

Kaindl AM, Ruschendorf F, Krause S, Goebel HH, Koehler K, Becker C, Pongratz D, Muller-Hocker J, Nurnberg P, Stoltenburg-Didinger G, Lochmuller H, Huebner A. Missense mutations of ACTA1 cause dominant congenital myopathy with cores. J Med Genet. 2004;41:842–8. [PubMed: 15520409]

Kossugue PM, Paim JF, Navarro MM, Silva HC, Pavanello RC, Gurgel-Giannetti J, Zatz M, Vainzof M. Central core disease due to recessive mutations in RYR1 gene: Is it more common than described? Muscle Nerve. 2007;35:670–674. [PubMed: 17226826]

Lamont PJ, Dubowitz V, Landon DN, Davis M, Morgan-Hughes JA. Fifty year follow-up of a patient with central core disease shows slow but definite progression. Neuromuscul Disord. 1998;8:385–91. [PubMed: 9713855]

Lehmann-Horn F, Lerche H, Jurkatt-Rott K. Skeletal muscle channelopathies: myotonias, periodic paralyses and malignant hyperthermia. In: Stalber E (ed) Clinical Neurophysiology of Disorders of Muscle and Neuromuscular Junction, Including Fatigue (Handbook of Clinical Neurophysiology), Vol 2. Elsevier, Amsterdam, pp 457-83. 2003

Lyfenko AD, Goonasekera SA, Dirksen RT. Dynamic alterations in myoplasmic Ca2+ in malignant hyperthermia and central core disease. Biochem Biophys Res Commun. 2004;322:1256–66. [PubMed: 15336973]

Lynch PJ, Tong J, Lehane M, Mallet A, Giblin L, Heffron JJ, Vaughan P, Zafra G, MacLennan DH, McCarthy TV. A mutation in the transmembrane/luminal domain of the ryanodine receptor is associated with abnormal Ca2+ release channel function and severe central core disease. Proc Natl Acad Sci U S A. 1999;96:4164–9. [PubMed: 10097181]

Manzur AY, Sewry CA, Ziprin J, Dubowitz V, Muntoni F. A severe clinical and pathological variant of central core disease with possible autosomal recessive inheritance. Neuromuscul Disord. 1998;8:467–73. [PubMed: 9829276]

Mertz KD, Jost B, Glatzel M, Min K. Progressive scoliosis in central core disease. Eur Spine J. 2005;14:900–5. [PubMed: 15926054]

Monnier N, Romero NB, Lerale J, Landrieu P, Nivoche Y, Fardeau M, Lunardi J. Familial and sporadic forms of central core disease are associated with mutations in the C-terminal domain of the skeletal muscle ryanodine receptor. Hum Mol Genet. 2001;10:2581–92. [PubMed: 11709545]

Monnier N, Romero NB, Lerale J, Nivoche Y, Qi D, MacLennan DH, Fardeau M, Lunardi J. An autosomal dominant congenital myopathy with cores and rods is associated with a neomutation in the RYR1 gene encoding the skeletal muscle ryanodine receptor. Hum Mol Genet. 2000;9:2599–608. [PubMed: 11063719]

Nelson TE. Heat production during anesthetic-induced malignant hyperthermia. Biosci Rep. 2001;21:169–79. [PubMed: 11725865]

Phillips MS, Fujii J, Khanna VK, DeLeon S, Yokobata K, de Jong PJ, MacLennan DH. The structural organization of the human skeletal muscle ryanodine receptor (RYR1) gene. Genomics. 1996;34:24–41. [PubMed: 8661021]

Quinlivan RM, Muller CR, Davis M, Laing NG, Evans GA, Dwyer J, Dove J, Roberts AP, Sewry CA. Central core disease: clinical, pathological, and genetic features. Arch Dis Child. 2003;88:1051–5. [PubMed: 14670767]

Romero NB, Monnier N, Viollet L, Cortey A, Chevallay M, Leroy JP, Lunardi J, Fardeau M. Dominant and recessive central core disease associated with RYR1 mutations and fetal akinesia. Brain. 2003;126:2341–9. [PubMed: 12937085]

Sestero AM, Perra JH. A case report of severe kyphoscoliosis and autofusion of the posterior elements in two siblings with central core disease. Spine. 2005;30:E50–5. [PubMed: 15644748]

Sewry CA, Muller C, Davis M, Dwyer JS, Dove J, Evans G, Schroder R, Furst D, Helliwell T, Laing N, Quinlivan RC. The spectrum of pathology in central core disease. Neuromuscul Disord. 2002;12:930–8. [PubMed: 12467748]

Shepherd S, Ellis F, Halsall J, Hopkins P, Robinson R. RYR1 mutations in UK central core disease patients: more than just the C-terminal transmembrane region of the RYR1 gene. J Med Genet. 2004;41:e33. [PubMed: 14985404]

Tilgen N, Zorzato F, Halliger-Keller B, Muntoni F, Sewry C, Palmucci LM, Schneider C, Hauser E, Lehmann-Horn F, Muller CR, Treves S. Identification of four novel mutations in the C-terminal membrane spanning domain of the ryanodine receptor 1: association with central core disease and alteration of calcium homeostasis. Hum Mol Genet. 2001;10:2879–87. [PubMed: 11741831]

Treves S, Anderson AA, Ducreux S, Divet A, Bleunven C, Grasso C, Paesante S, Zorzato F. Ryanodine receptor 1 mutations, dysregulation of calcium homeostasis and neuromuscular disorders. Neuromuscul Disord. 2005;15:577–87. [PubMed: 16084090]

Wehner M, Rueffert H, Koenig F, Olthoff D. Calcium release from sarcoplasmic reticulum is facilitated in human myotubes derived from carriers of the ryanodine receptor type 1 mutations Ile2182Phe and Gly2375Ala. Genet Test. 2003;7:203–11. [PubMed: 14641996]

Weiss RG, O'Connell KM, Flucher BE, Allen PD, Grabner M, Dirksen RT. Functional analysis of the R1086H malignant hyperthermia mutation in the DHPR reveals an unexpected influence of the III-IV loop on skeletal muscle EC coupling. Am J Physiol Cell Physiol. 2004;287:C1094–102. [PubMed: 15201141]

Wu S, Ibarra MC, Malicdan MC, Murayama K, Ichihara Y, Kikuchi H, Nonaka I, Noguchi S, Hayashi YK, Nishino I. Central core disease is due to RYR1 mutations in more than 90% of patients. Brain. 2006;129:1470–80. [PubMed: 16621918]

Zhou H, Brockington M, Jungbluth H, Monk D, Stanier P, Sewry CA, Moore GE, Muntoni F. Epigenetic allele silencing unveils recessive RYR1 mutations in core myopathies. Am J Hum Genet. 2006;79:859–68. [PubMed: 17033962]

Zhou H, Yamaguchi N, Xu L, Wang Y, Sewry C, Jungbluth H, Zorzato F, Bertini E, Muntoni F, Meissner G, Treves S. Characterization of recessive RYR1 mutations in core myopathies. Hum Mol Genet. 2006;15:2791–803. [PubMed: 16940308]

Zorzato F, Yamaguchi N, Xu L, Meissner G, Muller CR, Pouliquin P, Muntoni F, Sewry C, Girard T, Treves S. Clinical and functional effects of a deletion in a COOH-terminal lumenal loop of the skeletal muscle ryanodine receptor. Hum Mol Genet. 2003;12:379–88. [PubMed: 12566385]

Chapter Notes

Revision History

- 16 May 2007 (me) Review posted to live Web site
- 8 December 2006 (in) Original submission

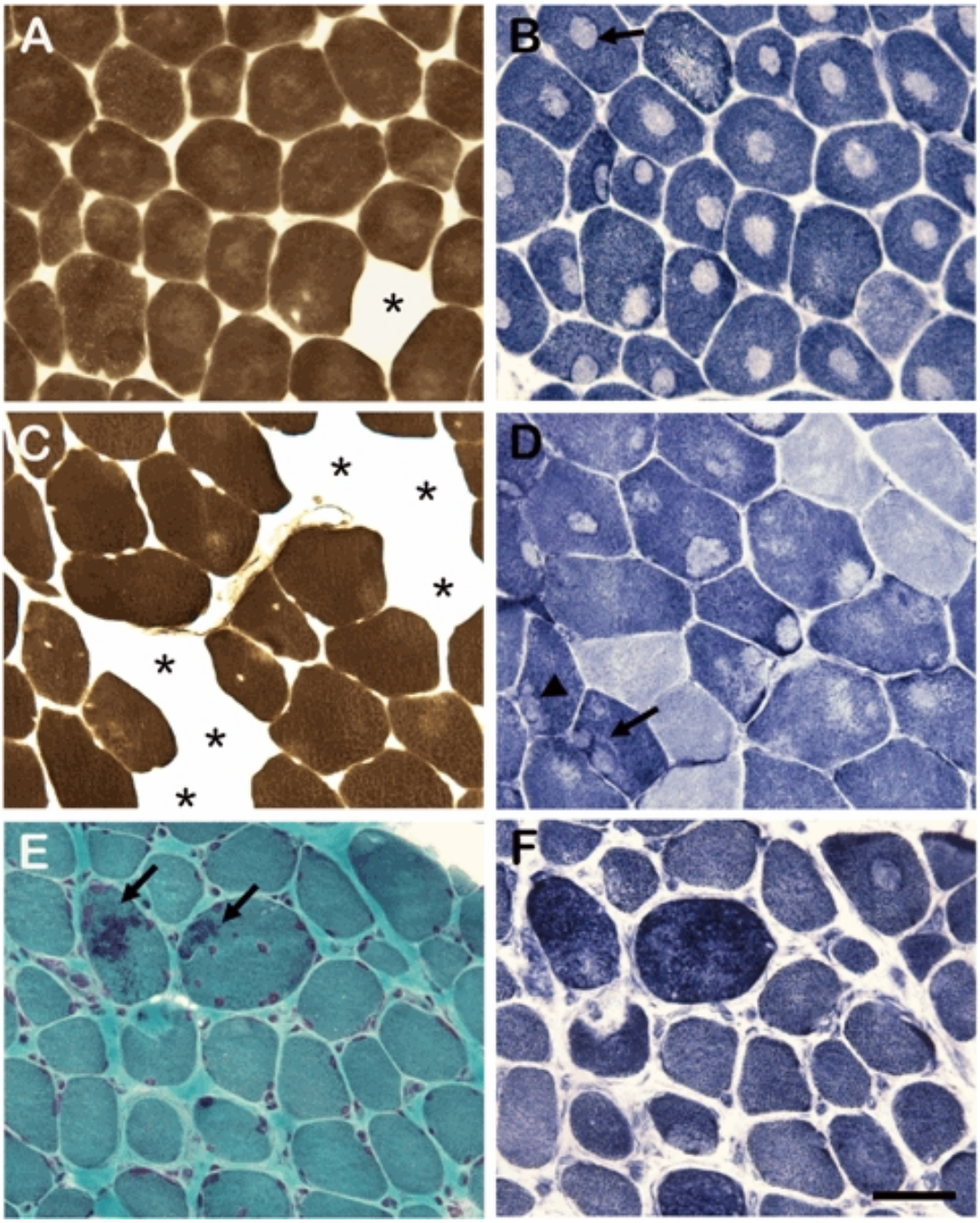

Figure 1. Histologic features of muscle observed in central core disease

A-B. Sections from a nine-year-old depicting the classic description of CCD

A. Pronounced type 2 fiber deficiency is seen with myosin ATPase staining with acidic pre-incubation (* shows type 2 fiber).

B. In NADH-TR staining, central cores are seen in almost all fibers, with "rimming" of cores in some fibers (arrow).

C-D. Sections from a 63-year-old showing the other features of cores seen in CCD

C. Type 2 fiber deficiency is also seen but is not as marked as in **A** (* shows type 2 fiber).

D. Cores are seen, but not in all type 1 fibers. Cores are sometimes found in the subsarcolemmal

area or periphery of the fiber, and more than one core can be present in a single fiber (arrow). Cores lacking clearly demarcated borders, (arrowhead) can be seen in higher frequency.
E-F. Sections from a three-year-old boy with cores and few fibers with rods
E. Nemaline bodies are observed with modified Gomori-trichrome staining (arrows).
F. Few cores are seen in NADH-TR staining.

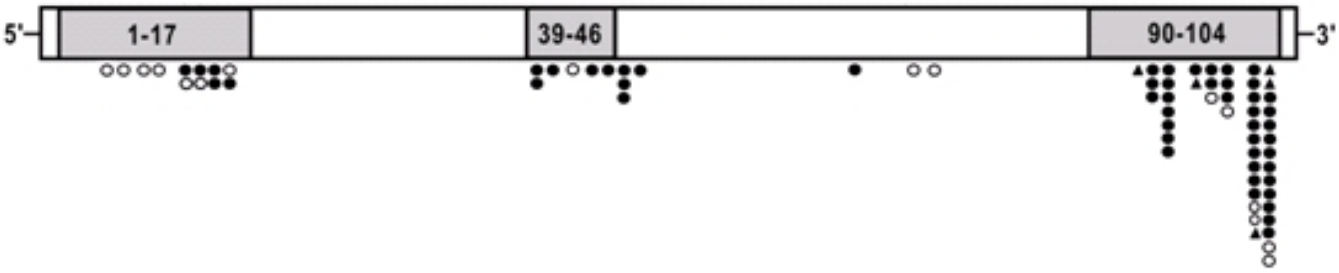

Figure 2.*RYR1* mutation map for CCD
The three shaded mutational hot spot areas:
Exons 1-17 (domain 1)
Exons 39-46 (domain 2)
Exons 90-104 (domain 3)
Closed circles = missense mutations
Open circles = autosomal recessive mutations
Triangles = deletions
The most common mutations are shown in Table 2 (pdf).
Adapted from Wu et al 2006