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Myotonic Dystrophy Type 2

Synonym: Proximal Myotonic Myopathy (PROMM)

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Summary

Clinical characteristics

Myotonic dystrophy type 2 (DM2) is characterized by myotonia and muscle dysfunction (proximal and axial weakness, myalgia, and stiffness), and less commonly by posterior subcapsular cataracts, cardiac conduction defects, insulin-insensitive type 2 diabetes mellitus, and other endocrine abnormalities. While myotonia (involuntary muscle contraction with delayed relaxation) has been reported during the first decade, onset is typically in the third to fourth decade, most commonly with fluctuating or episodic muscle pain that can be debilitating and proximal and axial weakness of the neck flexors and the hip flexors. Subsequently, weakness occurs in the elbow extensors and finger flexors. Facial weakness and weakness of the ankle dorsiflexors are less common. Myotonia rarely causes severe symptoms. In a subset of individuals, calf hypertrophy in combination with brisk reflexes is notable.

Diagnosis/testing

The diagnosis of DM2 is established in a proband by identification of a heterozygous pathogenic expansion of a CCTG repeat within a complex repeat motif, $(TG)_n(TCTG)_n(CCTG)_n$ in *CNBP*. The number of CCTG repeats in a pathogenic expansion ranges from approximately 75 to more than 11,000, with a mean of approximately 5,000 repeats. The detection rate of a *CNBP* CCTG expansion is more than 99% with the combination of routine PCR, Southern blot analysis, and the PCR repeat-primed assay.

Management

Treatment of manifestations: Ankle-foot orthoses, wheelchairs, or other assistive devices as needed for weakness; routine physical activity appears to help maintain muscle strength and endurance and to control musculoskeletal pain; medications used with some success in myalgia management include mexilitene, gabapentin, pregabalin, nonsteroidal anti-inflammatory drugs, low-dose thyroid replacement, and tricyclic antidepressants; myotonia rarely requires treatment but mexilitene or lamotrigine may be beneficial in some individuals; removal of cataracts or epiretinal membrane that impair vision; defibrillator placement for those with arrhythmias;

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hormone substitution therapy for endocrine dysfunction; prokinetic agents may be helpful for gastrointestinal manifestations; cognitive behavioral therapy and modafinil may be helpful for fatigue and daytime sleepiness; vitamin D supplementation for those with deficiency; hearing aids for sensorineural hearing loss.

Prevention of secondary complications: Anesthetic risk may be increased and therefore assessment of cardiac and respiratory function before and after surgery are recommended. Prompt treatment of hypothyroidism and vitamin D deficiency to reduce secondary weakness and myotonia.

Surveillance: Annual evaluation with neurologist, occupational therapist, and physical therapist; annual ophthalmology evaluation for posterior subcapsular cataracts and epiretinal membranes; annual EKG, echocardiogram, and 24-hour Holter monitoring to detect/monitor cardiac conduction defects and cardiomyopathy; cardiac MRI per cardiologist; annual measurement of fasting serum glucose concentration, glycosylated hemoglobin level, thyroid hormone levels, and vitamin D; serum testosterone and FSH per endocrinologist.

Agents/circumstances to avoid: Cholesterol-lowering medications when associated with increased weakness.

Genetic counseling

DM2 is inherited in an autosomal dominant manner. To date, all individuals whose biological parents have been evaluated with molecular genetic testing have had one parent with a CCTG repeat expansion; *de novo* pathogenic variants have not been reported. Each child of an individual with a CCTG repeat expansion has a 50% chance of inheriting the expansion. There is no correlation between disease severity and CCTG repeat length. Prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible once the CCTG repeat expansion has been identified in an affected family member.

Diagnosis

In 2019, consensus-based care recommendations and recommendations on the molecular diagnosis of myotonic dystrophy type 2 (DM2) were published [Schoser et al 2019] (full text).

Suggestive Findings

DM2 **should be suspected** in individuals with the following findings:

- **Muscle weakness** with early, clinically detectable weakness on manual motor testing of neck flexors and finger flexors, and later, symptomatic weakness often involving hip-girdle muscles in climbing stairs and rising from chairs
- **Myotonia** (sustained muscle contraction) that can manifest as grip myotonia (the inability to release a tightened fist quickly) occurring as early as the first decade of life, percussion myotonia (sustained contraction after tapping a muscle with a reflex hammer), leg myotonia, especially while climbing a staircase or trying to run fast, or electrical myotonia (repetitive spontaneous discharges observed on EMG). The myotonia in individuals with DM2 is not always detectable by EMG and may require an extensive EMG examination of several muscle groups including proximal and paraspinal muscles [Dabby et al 2011].
- **Posterior subcapsular cataracts** detectable as nonspecific vacuoles and opacities on direct ophthalmoscopy or as pathognomonic posterior subcapsular red and green iridescent opacities on slit lamp examination
- **Cardiac conduction defects or progressive cardiomyopathy,** the former diagnosable as atrioventricular or various intraventricular conduction defects on routine EKG and the latter identifiable as a dilated cardiomyopathy on echocardiography

- **Insulin insensitivity** that can appear clinically as impaired normalization of glucose on a glucose tolerance test despite normal or elevated serum insulin concentrations, and which predisposes to hyperglycemia and diabetes mellitus
- **Hypogammaglobulinemia,** defined as low gamma protein fraction on serum protein electrophoresis or low immunoglobulin G or immunoglobulin M content on immunoprotein electrophoresis, which occurs in 75% of adults with DM2 but has not been associated with any clinical abnormalities. The frequency of concomitant autoimmune disorders is increased in individuals with DM2.

Establishing the Diagnosis

The diagnosis of DM2 **is established** in a proband with a heterozygous pathogenic expansion of a complex repeat in *CNBP* identified by molecular genetic testing (see Table 1).

Allele sizes. *CNBP* intron 1 contains a complex repeat motif: $(TG)_n(TCTG)_n(CCTG)_n$. All three repeat tracts (TG, TCTG, and CCTG) are present in all normal and pathogenic alleles (see Figure 1):

- **Normal**
  - ≤30 uninterrupted CCTG repeats
  - 11-26 CCTG repeats **with** any GCTC or TCTG interruptions
- **Unknown significance (normal vs mutable).** 27-29 CCTG repeats
- **Mutable normal (premutation) alleles.** ~30-~54 CCTG repeats
- **Unknown significance (premutation vs pathogenic).** ~55-74 CCTG repeats
- **Pathogenic.** ~75-11,000 CCTG repeats

Note: (1) The boundary between stable and unstable alleles is estimated to be 30 CCTG repeats, with alleles <30 CCTG being stable. Large interrupted alleles have also been observed to be stable with stability decreasing with increasing uninterrupted repeat length [Liquori et al 2001, Liquori et al 2003, Radvanszky et al 2013, Mahyera et al 2018]. (2) Due to variability in the TG and TCTG portions of the repeat tract, a total repeat size in base pairs is frequently reported and CCTG repeat length is often estimated [Liquori et al 2001, Liquori et al 2003, Radvanszky et al 2013, Mahyera et al 2018]. When close to a normal / mutable normal / premutation / pathogenic boundary, sequence analysis is necessary to better estimate the size of the CCTG repeat.

Molecular Genetic Testing

Testing approaches can include **targeted analysis** for an increased number (i.e., an expansion) of the CCTG nucleotide repeat. If routine PCR analysis detects only one allele, which occurs in 15% of unaffected individuals who are homozygous and in all affected individuals, it is necessary to perform both Southern blot analysis and the PCR repeat-primed assay to determine if the individual is homozygous for the normal-sized allele or has both a normal-sized allele and an expanded allele that fails to amplify by PCR because of its large size [Liquori et al 2001].

Figure 1. Complex repeat at the *CNBP* locus. The *CNBP* repeat tract is a complex repeat comprising TG, TCTG, and CCTG tracts, in this order. Each repeat can vary in length.

On normal alleles, the overall length of the CCTG portion ranges from 11 to 26 tetranucleotide repeats and typically includes single interruptions (represented by the two vertical lines) that are variable in number (0-2), in location within the CCTG tract, and in repeat motif, but that commonly include individual GCTC and TCTG interruptions separately located within the CCTG tract.

On pathogenic alleles, only the CCTG repeat tract expands, without interruptions, resulting in overall repeat lengths of 75 to more than 11,000 pure CCTG tetranucleotide repeats.

Table 1. Molecular Genetic Testing Used in Myotonic Dystrophy Type 2

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
CNBP	Targeted analysis for CCTG tetranucleotide repeat expansion in intron 1 [3]	>99% [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Testing to quantitate the number of *CNBP* CCTG repeats may involve:
a. Routine PCR, which detects normal-sized alleles but not abnormal-sized alleles because it cannot amplify across the expansion; PCR analysis alone can exclude a diagnosis of DM2 if two normal-sized alleles are clearly resolvable;
b. Southern blot analysis, which detects ~80% of expansions; the expansion size is an estimate because (1) expanded repeats exhibit somatic instability and (2) adjacent non-pathogenic repeats are polymorphic;
c. PCR repeat-primed assay, which aids in the detection of the CCTG repeat expansion but does not allow determination of the total length of the expansion. This assay, in which the primers are adjacent to and within the elongated CCTG repeat, differentially detects expanded alleles as a smear with varying repeat sizes but shows control alleles as a discrete band. The PCR repeat-primed assay products are probed with an internal probe to assure the necessary specificity.
4. Detection frequency varies by method used. When routine PCR analysis, Southern blot analysis, and PCR repeat-primed assay are all used, the variant detection frequency is greater than 99%.

Other Testing

Muscle biopsy. Although molecular genetic testing is the diagnostic test of choice, muscle biopsy remains a useful diagnostic tool. Muscle pathology includes atrophic fibers, scattered severely atrophic fibers with pyknotic myonuclei, and marked proliferation of fibers with central nuclei [Day et al 1999, Day et al 2003, Vihola et al 2003, Schoser et al 2004c], all of which occur in both DM2 and myotonic dystrophy type 1 (DM1) and thus cannot be used to distinguish between them.

- Type 1 fiber atrophy is a common feature in individuals with congenital DM1, distinguishing it from DM2.
- Preferential type 2 fiber atrophy has been observed in individuals with DM2 [Vihola et al 2003, Schoser et al 2004c, Pisani et al 2008, Giagnacovo et al 2012].

Clinical Characteristics

Clinical Description

Core phenotype characteristics of myotonic dystrophy type 2 (DM2) are myotonia, proximal and axial muscle weakness, and late muscle atrophy in combination with myalgia. DM2 is a multisystem disease and additional

features include cardiac conduction defects, posterior subcapsular cataracts, insulin-insensitive type 2 diabetes mellitus, and other endocrine dysfunctions.

To date, more than 1500 individuals in more than 700 families have been identified with a pathogenic variant in *CNBP* [Heatwole et al 2015, Montagnese et al 2017, Bozovic et al 2018, Wood et al 2018, De Antonio et al 2019]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Select Features of Myotonic Dystrophy Type 2

Feature	% of Persons with Feature	Comment
Muscle dysfunction (proximal & axial weakness, myalgia, late atrophy)	100%	
Myotonia	70%-90%	
Iridescent posterior subcapsular cataracts	50%-80%	Incidence ↑ w/age
Cardiac conduction defects & cardiomyopathy	10%-20%	
Insulin insensitivity & type 2 diabetes	25%-75%	Incidence ↑ w/age
Other endocrine dysfunction	20%	Incls thyroid dysfunction
Gastrointestinal complications	10%-20%	
Hearing impairment	10%-20%	

Onset. The onset of symptoms in individuals with DM2 is typically in the third to fourth decade, with the most common symptoms being muscle weakness and pain, although myotonia during the first two decades has been reported [Udd et al 2011, Montagnese et al 2017]. Note that unlike myotonic dystrophy type 1 (DM1), which can present in adulthood as a degenerative disorder or with variably severe congenital features, DM2 has not been associated with developmental abnormalities and thus does not cause severe childhood symptoms [Udd et al 2011, Montagnese et al 2017, De Antonio et al 2019]. The absence of developmental defects in any affected family members with DM2 is a reliable and clinically significant difference between DM1 and DM2.

Muscle dysfunction. Individuals with DM2 often come to medical attention because of proximal and axial muscle weakness, myalgia, and myotonia. The muscles affected in the earliest stages of the disease are the neck flexors and finger flexors. Subsequently, weakness is seen in the elbow extensors and the hip flexors and extensors. Fifty percent of individuals have hip-muscle weakness that develops after age 40 years. Facial weakness and weakness of the ankle dorsiflexors can also be present but are less common. Calf hypertrophy is seen in a subset of individuals, and is frequently associated with brisk reflexes and restless leg symptoms.

Myotonia (i.e., involuntary muscle contraction and delayed relaxation caused by muscle hyperexcitability) is present in almost all individuals with DM2 but only rarely causes severe symptoms. Proximal leg myotonia is a prominent finding.

Fluctuating or episodic muscle pain is reported by a majority of affected individuals and can be debilitating [Tieleman et al 2011, Suokas et al 2012, Moshourab et al 2016, Montagnese et al 2017, van Vliet et al 2018b].

In women with DM2, symptoms may worsen during pregnancy [Rudnik-Schöneborn et al 2006]. Polyhydramnios, a recognized feature of DM1, has not been reported in individuals with DM2.

Cataracts and epiretinal membranes. Posterior subcapsular iridescent cataracts can be seen on slit lamp examination as early as the second decade of life. The reported age of cataract extraction ranges from 28 to 74 years [Day et al 2003]. With aging, an increase in macular thickness based on epiretinal membranes can lead to visual impairment. Epiretinal membranes can be treated surgically [Kersten et al 2016].

Cardiac conduction defects and cardiomyopathy. Although cardiac involvement in individuals with DM2 appears more mild than in DM1 [Sansone et al 2013], DM2 can be associated with atrioventricular and intraventricular conduction defects, arrhythmias, left ventricular dysfunction, cardiomyopathy, and sudden death [Day et al 2003, Schoser et al 2004b, Wahbi et al 2009, Sansone et al 2013, Peric et al 2019]. Rarely, a Brugada-like syndrome can occur in individuals with DM2 [Rudnik-Schöneborn et al 2011].

Anesthetic complications have not been reported in individuals with DM2, and probably occur less frequently than in DM1, where intraoperative and postoperative cardiac arrhythmias, ventilatory suppression, and poor airway protection are recognized possible causes of significant morbidity and mortality [Kirzinger et al 2010, Weingarten et al 2010].

Endocrine abnormalities described in individuals with DM2 include insulin-insensitive type 2 diabetes mellitus, thyroid dysfunction, and hypogonadism in adult males [Day et al 2003, Savkur et al 2004, Montagnese et al 2017, Bozovic et al 2018].

Gastrointestinal complications are common in DM2 and can include constipation, dysphagia, and abdominal pain [Tieleman et al 2008, Hilbert et al 2017].

Hypogammaglobulinemia. Individuals with DM2, like those with DM1, have a high incidence of hypogammaglobulinemia, with lower-than-normal levels of both IgG and IgM. A higher incidence of concomitant autoimmune disorders is recognized in individuals with DM2 [Montagnese et al 2017].

Daytime sleepiness, fatigue, and sleep disturbance. A range of sleep disturbances including daytime sleepiness, insomnia, REM behavior disorders, and restless leg syndrome have been observed in case reports and case series of individuals with DM2 [Day et al 1999, Bhat et al 2012, Chokroverty et al 2012, Shepard et al 2012, Silvestri et al 2014, Montagnese et al 2017, Romigi et al 2019]. Daytime sleepiness can be associated with restless leg syndrome [Silvestri et al 2014].

Hearing impairment. Cochlear sensorineural hearing impairment is reported in about 60% of individuals with DM2, suggesting an early presbycusis [van Vliet et al 2018a].

Cancer risk. Retrospective studies have shown that individuals with DM2 appear to be at a higher risk of developing cancer. A cross-sectional analysis of a large DM study showed that tumor risk is higher in DM1 than DM2. Cancer in individuals with DM2 may involve the colon, brain, thyroid, pancreas, ovary, prostate, and endometrium [Gadalla et al 2011, Das et al 2012, Win et al 2012].

Brain MRI findings. Central nervous system abnormalities reported in individuals with DM2 include white matter changes apparent on MRI and reduced cerebral blood flow in the frontal and temporal region apparent on PET scan [Franc et al 2012]. A longitudinal observational study over a period of five years found unchanged pattern of white matter alterations in DM2. Gray matter appears unaffected in DM2 [Gliem et al 2019]. FDG-PET and detailed neuropsychological testing showed executive and naming dysfunction in DM2. FDG-PET showed the most prominent glucose hypometabolism in prefrontal, temporal, and pericentral regions with additional affect on insula and subcortical grey matter in DM2. Executive dysfunction in DM2 was more common in individuals with prefrontal and insular hypometabolism, right parietotemporal and frontotemporal hypometabolism, as well as left striatal hypometabolism. Individuals with parietotemporal defect on FDG-PET were more likely to have naming dysfunction ($p<0.01$) [Peric et al 2017]. These anatomic changes appear to have some effect on cognition, behavior, and personality, although unlike DM1, DM2 has not been associated with intellectual disability [Meola et al 2002, Meola et al 2003].

Genotype-Phenotype Correlations

No significant correlation exists between CCTG repeat size and age of onset of weakness or other measures of disease severity (e.g., age of cataract extraction). The observation that phenotypic features in individuals with

CCTG repeat expansions in both *CNBP* alleles are as severe as those seen in their heterozygous sibs and parents further demonstrates that CCTG repeat number does not alter the clinical course [Schoser et al 2004a].

A correlation does exist between the repeat size and the age of the individual with DM2 at the time that the repeat size is measured, indicating that the repeat length increases with age [Day et al 2003].

Penetrance

Penetrance is age dependent and approaches 100%.

Anticipation

Anticipation is not observed in DM2. There is no correlation between disease severity and CCTG repeat length; therefore, intergenerational changes in repeat length would not be expected to worsen disease severity.

Nomenclature

The International Myotonic Dystrophy Consortium (IDMC) and Online Mendelian Inheritance in Man (OMIM) both recognize that DM2 and the historical term proximal myotonic myopathy (PROMM) refer to the same condition. PROMM is still sometimes used to refer to the clinical phenotype if the causative variant is unknown; however, when the diagnosis is established through molecular genetic testing of *CNBP*, the more precise term "DM2" is preferable.

No other genetic causes of multisystem myotonic dystrophies have been confirmed, although their existence has been suggested. The International Myotonic Dystrophy Consortium has agreed that any newly identified multisystem myotonic dystrophies will be sequentially named as forms of myotonic dystrophy.

One family posited to have a myotonic dystrophy type 3 (DM3) [Le Ber et al 2004] has subsequently been shown to have Inclusion Body Myopathy with Paget Disease of Bone and/or Frontotemporal Dementia caused by a pathogenic variant in *VCP*.

Prevalence

Prevalence appears to differ in various populations; however, few definitive demographic studies have been performed. A higher prevalence of DM2 is observed in Germany, Czech Republic, Serbia, and Poland and in individuals of German or Polish descent [Udd et al 2003, Montagnese et al 2017]. In Finland, the incidence of DM2 (1:1,830) is higher than DM1 [Suominen et al 2011]. In Germany, cumulative empiric evidence suggests an estimated prevalence of DM2 of roughly 9:100,000; therefore, DM2 is as prevalent as DM1 [Mahyera et al 2018]. DM2 has been reported worldwide.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *CNBP*.

Differential Diagnosis

Multisystem Myotonic Myopathies

Routine clinical evaluation can reliably identify myotonic dystrophy. Molecular genetic testing is required for definitive diagnosis of myotonic dystrophy type 1 (DM1) and myotonic dystrophy type 2 (DM2); however, suggestive findings can be used to clinically distinguish between DM2 and DM1.

- The most robust clinical difference between DM1 and DM2 is that clubfeet, neonatal weakness and early respiratory insufficiency, developmental delay / intellectual disability, craniofacial abnormalities, and childhood hypotonia and weakness have been reported in individuals with DM1 only. DM2 has not been associated with developmental abnormalities and thus does not cause severe childhood manifestations [Udd et al 2011, Montagnese et al 2017, De Antonio et al 2019]. The absence of developmental defects in any affected family members with DM2 is a reliable and clinically significant difference between the two forms of DM.
- Adults with DM1 often have more weakness and myotonia than adults with DM2.
- Individuals with DM1 tend to have more pronounced facial, bulbar, and distal weakness; as well as muscle atrophy, cardiac involvement, and central nervous system abnormalities including central hypersomnia [Meola et al 2002, Ranum & Day 2002, Ranum & Day 2004, Day & Ranum 2005, Montagnese et al 2017, De Antonio et al 2019].

Note: The cataracts in individuals with DM1 and DM2 are indistinguishable.

Other Myopathies to Consider

The other major group in the differential diagnosis of DM2 is distal myopathy (see Table 3).

Table 3. Myopathies of Interest in the Differential Diagnosis of Myotonic Dystrophy Type 2

Gene	Disorder	MOI	Mean Age at Onset (yrs)	Initial Muscle Group Involved	Serum Creatine Kinase Concentration	Characteristic Features
DES	Desminopathy (OMIM 601419)	AD AR	20-60	Anterior compartment in the legs, later arms	2-10x normal	• Weakness of ankle dorsiflexion usually at age 20-60 yrs, then slow progression to proximal leg & arm muscles • ± dilated cardiomyopathy & conduction defects
GNE	*GNE* myopathy	AR	15-20	Anterior compartment in legs	<10x normal	• Foot drop & a steppage gait • Progression to loss of ambulation after 12-15 yrs
LDB3	Zaspopathy (OMIM 609452)	AD	>40	Anterior compartment in legs	Normal or slightly ↑	• Weakness of ankle dorsiflexion usually starting in late 40s, then slow progression to finger & wrist extensor muscles & intrinsic hand muscles • Eventually proximal leg muscles become involved. • ± dilated cardiomyopathy & conduction defects
MYOT	Myotilinopathy (OMIM 609200)	AD	>40	Posterior > anterior in legs	Slightly ↑	• Weakness of ankle extension usually starting in late 40s, then slow progression to proximal leg muscles • ± neuropathy & contractures

Table 3. continued from previous page.

Gene	Disorder	MOI	Mean Age at Onset (yrs)	Initial Muscle Group Involved	Serum Creatine Kinase Concentration	Characteristic Features
VCP	Inclusion body myopathy w/Paget disease of bone &/or frontotemporal dementia (valosin containing protein myopathy)	AD	30-60	Proximal muscles lower limb	5-10x normal	• Distal paresis & difficulties climbing stairs • Progresses to proximal & axial muscles • Later: Paget disease of bone & rapidly progressive frontotemporal dementia

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance

Nondystrophic Myotonias

Electrical myotonia occurs in several conditions (e.g., hypothyreosis) but the presence of myotonia in multiple family members restricts diagnostic possibilities to either DM1 or DM2, or to the nondystrophic myotonias, which are caused by mutation of chloride, sodium, or calcium channel genes, resulting in myotonia congenita, paramyotonia congenita (OMIM 168300), and periodic paralyses (see Hypokalemic Periodic Paralysis and Hyperkalemic Periodic Paralysis). Those conditions are not associated with the muscular dystrophy or multisystem features typical of DM1 and DM2 and can thus be distinguished on clinical grounds.

Other

Occasionally, individuals with DM2 have been misdiagnosed as having atypical motor neuron disease [Rotondo et al 2005], inflammatory myopathy, fibromyalgia, rheumatoid arthritis, or metabolic myopathy.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with myotonic dystrophy type 2 (DM2), the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended. Detailed international guidelines and recommendations for evaluation of individuals with DM2 have been published [Rastelli et al 2018, Schoser et al 2019].

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Myotonic Dystrophy Type 2

System/ Concern	Evaluation	Comment
Neurologic	Clinical eval of muscle strength & functional status	The quick motor function test can be helpful as a baseline to allow long-term monitoring.
Ophthalmologic	Exam by an ophthalmologist familiar w/ posterior subcapsular cataracts & epiretinal membranes	To establish a baseline
Cardiologic	Cardiac eval incl EKG to establish a baseline for future comparison	• Consider echocardiogram &/or cardiac MRI to evaluate for cardiomyopathy. [1] • Holter monitoring or invasive electrophysiologic testing if symptomatic or significant rhythm or conduction abnormalities on routine EKG

Table 4. continued from previous page.

System/ Concern	Evaluation	Comment
Endocrine	Fasting lipid profile, glucose, & glycosylated hemoglobin concentrations	To assess for evidence of insulin insensitivity & diabetes mellitus
	Thyroid studies	Hypothyroidism from any cause has been assoc w/↑ muscle weakness & myotonia.
	Serum testosterone & FSH concentrations	In post-pubertal males to assess gonadal function
Audiologic	Hearing assessment	
Other	Serum CK, transaminases (AST & ALT), & γ-glutamyltransferase (GGT)	Serum AST, ALT, & GGT are frequently ↑ in DM2; it is unclear if this is hepatocellular or myogenic in origin. Determination of baseline ↑ transaminase & GGT activities can help avoid unneeded liver testing.
	Serum protein electrophoresis & immunoprotein electrophoresis	To establish a baseline & prevent misinterpretation of future studies demonstrating hypogammaglobulinemia
	Consultation w/clinical geneticist &/or genetic counselor	

1. Spengos et al [2012]

Treatment of Manifestations

Detailed guidelines for treatment are provided in the new international care recommendations for DM2 [Schoser et al 2019].

Table 5. Treatment of Manifestations in Individuals with Myotonic Dystrophy Type 2

Manifestation/ Concern	Treatment	Considerations/Other
Weakness	Eval & treatment per physical medicine & rehab physician, OT, or PT	To determine need for ankle-foot orthoses, wheelchairs, or other assistive devices as disease progresses
	Routine physical activity & training	To maintain muscle strength & endurance & help control pain
Myalgia	Mexilitene, gabapentin, pregabalin, NSAIDs, low-dose thyroid replacement, tricyclic antidepressants	No single drug has been consistently effective; low-dose narcotic analgesics, when used as part of a comprehensive pain mgmt program, may help but may also → development of tolerance & escalating doses.
Myotonia	Myotonia is typically mild.	Mexilitene or lamotrigine may be beneficial in some cases.
Cataracts / Epiretinal membranes	Cataract or epiretinal membrane removal if they impair vision	Direct ophthalmoscopy & slit lamp exam can underestimate the functional significance of cataracts because the alteration of vision depends on location, not just number of subcapsular opacities.
Arrhythmia/ Cardiomyopathy	Treatment per cardiologist	• Fatal arrhythmias can occur before onset of other symptoms. • Defibrillators are beneficial for those w/arrhythmias; the role of pacemaker/ defibrillators in asymptomatic persons is unknown. [1]
Insulin insensitivity & type II diabetes	Treatment per endocrinologist	

Table 5. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Thyroid dysfunction	Thyroid hormone substitution per endocrinologist	To maintain normal thyroid hormone levels to avoid weakness & myotonic exaggeration
Hypogonadism	Testosterone replacement therapy	Beneficial in males w/symptomatic hypogonadism
Gastrointestinal manifestations	Prokinetic agents (e.g., metochlopromide, tegaserod)	May be beneficial in those w/postprandial abdominal pain, bloating, constipation, & diarrhea
Fatigue & daytime sleepiness	Cognitive behavioral therapy & modafinil may be helpful in some cases.	Evaluate for other causes (e.g., pulmonary dysfunction, ventilator insufficiency).
Vitamin D deficiency	Vitamin D supplementation	Deficiency may contribute to weakness & daytime sleepiness.
Sensorineural hearing impairment	Consider hearing aids.	

NSAIDS = nonsteroidal anti-inflammatory drugs; OT = occupational therapist; PT = physical therapist
1. Schoser et al [2004b], Sansone et al [2013]

Prevention of Secondary Complications

Anesthetic risk may be increased in those with DM2; therefore, careful assessment of cardiac and respiratory function before and after surgery is recommended [Kirzinger et al 2010, Veyckemans & Scholtes 2013].

Increased weakness in individuals with DM2 has been associated with hypothyroidism and vitamin D deficiency; thus, some strength may return if hypothyroidism or vitamin D deficiency is treated.

Surveillance

Detailed guidelines for surveillance are provided in recently published international care recommendations for DM2 [Schoser et al 2019].

Table 6. Recommended Surveillance for Individuals with Myotonic Dystrophy Type 2

System/Concern	Evaluation	Frequency
Neurology – weakness & myotonia	Eval by neurologist, OT, & PT	Annually
Ophthalmology – cataracts	Ophthalmology exam for posterior subcapsular cataracts & epiretinal membranes	
Cardiac arrhythmia & cardiomyopathy	• EKG • Echocardiogram • 24-hr Holter monitoring	
	Consider cardiac MRI.	Per cardiologist
Endocrine	• Fasting serum glucose concentration • Glycosylated hemoglobin level • Thyroid hormone levels • Serum vitamin D	Annually
	Serum testosterone & FSH concentrations in males	Frequency as per sign/symptoms of hypogonadism or per endocrinologist

OT = occupational therapist; PT = physical therapist

Agents/Circumstances to Avoid

Increased weakness has been associated with the use of certain cholesterol-lowering medications. In these cases, some strength can return if statin-type cholesterol-lowering medications are eliminated.

Note: Not all individuals with DM2 have an adverse response to statin medications, and thus diagnosis of DM2 is not an absolute contraindication to use of these drugs.

Evaluation of Relatives at Risk

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

Pregnancy Management

The effects of DM2 on both smooth and striated muscle can complicate pregnancy, labor, and delivery and increase myotonia. Careful gynecologic monitoring is advised.

See MotherToBaby for further information on medication use during pregnancy.

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

Myotonic dystrophy type 2 (DM2) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- To date, all probands whose biological parents have been evaluated with molecular genetic testing have had one parent with a *CNBP* CCTG repeat expansion.
- Probands with *de novo* pathogenic variants have not been reported.
- If a positive family history for DM2 has not already been established, molecular genetic testing is recommended for the parents (and adult children) of a proband.
- The family history of some individuals diagnosed with DM2 may appear to be negative because of failure to recognize the disorder in family members (see Penetrance) or early death of the parent before the onset of symptoms. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has been performed on the parents of the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the parents:

- If a parent of the proband is affected and/or is known to have a CCTG repeat expansion, the risk to the sibs is 50%.
- The CCTG repeat expansion shows size differences between generations in the same family. In general, the repeat size appears to contract when passed on to the subsequent generation and then to increase in size as the affected individual ages (see Related Genetic Counseling Issues, **Somatic mosaicism**). There is no maternal or paternal preference for contraction or expansion. Anticipation (i.e., early onset with a more severe disease course) is not observed in DM2.

Offspring of a proband

- Each child of an individual with a CCTG repeat expansion has a 50% chance of inheriting the expansion.
- The CCTG repeat tract tends to contract when passed from one generation to the next and then to increase in size as the affected individual ages. Anticipation is not observed in DM2.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has a CCTG repeat expansion, his or her family members are at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Somatic mosaicism. The CCTG repeat expansion is highly unstable and tends to increase in size with age of the affected individual. The results of multiple tests performed on distinct peripheral blood samples drawn from affected individual at the same time or at different ages may differ in expansion size. In addition, an individual may have more than one expanded repeat size detectable by Southern blot analysis in a single sample of peripheral blood. Neither the size of a predominant CCTG repeat length nor the total number of different detectable repeat expansions in a single sample can predict age of onset or clinical manifestations of the condition.

Predictive testing (i.e., testing of asymptomatic at-risk individuals)

- Predictive testing for at-risk relatives is possible once a CCTG repeat expansion has been identified in an affected family member.
- Predictive testing can determine whether an individual has a CCTG repeat expansion, and thus whether that individual is at risk of developing the disease. However, there is no correlation between repeat size and age of onset or clinical manifestations.
- Potential consequences of such testing (including but not limited to socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing.

Predictive testing in minors (i.e., testing of asymptomatic at-risk individuals age <18 years)

- For asymptomatic minors at risk for adult-onset conditions for which early treatment would have no beneficial effect on disease morbidity and mortality, predictive genetic testing is considered inappropriate, primarily because it negates the autonomy of the child with no compelling benefit. Further, concern exists regarding the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause.
- For more information, see the National Society of Genetic Counselors position statement on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American

College of Medical Genetics and Genomics policy statement: ethical and policy issues in genetic testing and screening of children.

In a family with an established diagnosis of DM2, it is appropriate to consider testing of symptomatic individuals regardless of age.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once the CCTG repeat expansion has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible. Note: Age of onset and clinical manifestations cannot be predicted by the CCTG repeat length.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

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.

- **MDF Clinic Visit Planner**

  Planner that enables families to discuss upcoming clinic visits and jot down important questions and information to help ensure that it was shared at the appointment.

  MDF Clinic Visit Planner

- **Myotonic**

  1004A O'Reilly Avenue

  San Francisco CA 94129

  Phone: 415-800-7777; 86-MYOTONIC (866-968-6642)

  Email: info@myotonic.org

  www.myotonic.org

- **National Library of Medicine Genetics Home Reference**

  Myotonic dystrophy

- **TREAT-NMD**

  Neuromuscular Network

  Email: info@treat-nmd.org

  Myotonic Dystrophy

- **Muscular Dystrophy UK**

United Kingdom
Phone: 0800 652 6352
musculardystrophyuk.org

- **Myotonic Dystrophy Family Registry (MDFR)**
  Phone: 602-435-7496
  Email: coordinator@myotonicregistry.org
  myotonicregistry.patientcrossroads.org
- **National Registry of Myotonic Dystrophy and FSHD Patients and Family Members**
  National Registry of Myotonic Dystrophy and FSHD
  601 Elmwood Avenue
  Box 673
  Rochester NY 14642
  Phone: 888-925-4302
  Fax: 585-273-1255
  Email: dystrophy_registry@urmc.rochester.edu
  National Registry for Myotonic Dystrophy (DM) & Facioscapulohumeral Dystrophy (FSHD)

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. Myotonic Dystrophy Type 2: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CNBP	3q21.3	CCHC-type zinc finger nucleic acid binding protein	CNBP database	CNBP	CNBP

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 Myotonic Dystrophy Type 2 (View All in OMIM)

116955	CCHC-TYPE ZINC FINGER NUCLEIC ACID-BINDING PROTEIN; CNBP
602668	MYOTONIC DYSTROPHY 2; DM2

Molecular Pathogenesis

The presence of an expanded $(TG)_n(TCTG)_n(CCTG)_n$ repeat within *CNBP* causes DM2. No sequence variants in *CNBP* have been associated with genetic disease.

Mechanism of disease causation. Gain of function. Similarities between myotonic dystrophy type 1 (DM1) and myotonic dystrophy type 2 (DM2) strongly suggest that the untranslated RNAs that contain the repeat expansion are responsible for the pathologic features common to both disorders:

- Gain-of-function RNA mechanism in which the CUG and CCUG repeats (respectively) alter cellular function, including alternative splicing of various genes [Tapscott & Thornton 2001, Ranum & Day 2002, Ranum & Day 2004, Day & Ranum 2005]
- RNA foci containing RNA of the abnormally expanded allele that colocalize with several forms of the RNA-binding protein muscleblind [Mankodi et al 2001, Fardaei et al 2002]
- Sequestration of splicing factors of the muscleblind-like (MBNL) family, a key mechanisms for RNA toxicity in DM, may also contribute to DM2 since MBNL proteins have a high affinity for CUG or CCUG repeats. Reduced MBNL proteins affect alternative splicing, polyadenylation, or expression level for hundreds of genes.
- Expanded RNA repeats can result in repeat-associated non-ATG (RNA) translation, leading to production of neurotoxic peptides [Thornton et al 2017, Zu et al 2017].
- CELF1, an RNA-binding protein involved in RNA metabolism, is upregulated in DM2 muscle tissue [Schoser & Timchenko 2010].

This toxic gain-of-function RNA process results in missplicing of the chloride channel, cardiac troponin T, and the insulin receptor contributing to the myotonia, cardiac involvement, and insulin insensitivity [Thornton et al 2017].

Table 7. *CNBP*-Specific Laboratory Technical Considerations

Technical Issue	Comment [Reference]
Sequence of repeat	$(TG)_n(TCTG)_n(CCTG)_n$: • All 3 repeat tracts (TG, TCTG, & CCTG) are present in all normal & pathogenic alleles. • TG & TCTG repeat tracts are highly polymorphic; for methods other than sequencing, **allele sizes are reported in overall bp length rather than CCTG repeat number**. Sequence variation w/in $(TG)_n(TCTG)_n(CCTG)_n$: • The CCTG repeat tract in normal alleles typically contains ≥1 tetranucleotide interruptions (TCTG or GCTG) [Liquori et al 2003]. • CCTG sequence interruptions are routinely found on normal alleles, but not pathogenic CCTG expansions, suggesting that loss of these interruptions from normal alleles may ↑ instability & predispose to germline expansion.
Methods to detect expanded allele	Methods to detect $(TG)_n(TCTG)_n(CCTG)_n$ repeat expansion by Southern blotting & repeat-primed PCR (RP-PCR) have been described [Liquori et al 2001, Radvanszky et al 2013, Mahyera et al 2018].
Somatic instability	• Abnormal CCTG repeat size ↑ w/age. • >25% of affected individuals have ≥2 CCTG expansion sizes detectable in peripheral blood. • Somatic heterogeneity of CCTG repeat size makes it difficult to establish a pathogenic threshold [Liquori et al 2001, Day et al 2003].
Germline instability	• During germline transmission $(TG)_n(TCTG)_n(CCTG)_n$ repeat length sometimes ↓ dramatically. • No significant difference by sex of transmitting parent [Day et al 2003]

Methods to characterize *CNBP* $(TG)_n(TCTG)_n(CCTG)_n$ repeats. Due to the technical challenges of detecting and sizing $(TG)_n(TCTG)_n(CCTG)_n$ repeats within *CNBP*, multiple methods may be needed to rule out or detect an expanded repeat (see Table 7).

Due to variability in the TG and TCTG portions of the repeat tract, a total repeat size in base pairs is frequently reported [Liquori et al 2001, Liquori et al 2003, Radvanszky et al 2013, Mahyera et al 2018]. When close to a normal / mutable normal / premutation / pathogenic boundary, sequence analysis is necessary to better estimate the size of the CCTG repeat.

Expanded $(TG)_n(TCTG)_n(CCTG)_n$ repeats may be detected by RP-PCR or Southern blotting [Liquori et al 2001, Radvanszky et al 2013, Mahyera et al 2018]. An RP-PCR has been designed to differentiate an interrupted from an uninterrupted repeat [Radvanszky et al 2013]. In addition, somatic and germline instability of expanded repeats must be considered.

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Chapter Notes

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Revision History

- 19 March 2020 (sw) Comprehensive update posted live
- 3 July 2013 (me) Comprehensive update posted live
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