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Myotonic Dystrophy Type 1

Synonym: Steinert's Disease

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Summary

Clinical characteristics

Myotonic dystrophy type 1 (DM1) is a multisystem disorder that affects skeletal and smooth muscle as well as the eye, heart, endocrine system, and central nervous system. The clinical findings, which span a continuum from mild to severe, have been categorized into three somewhat overlapping phenotypes: mild, classic, and congenital.

- Mild DM1 is characterized by cataract and mild myotonia (sustained muscle contraction); life span is normal.
- Classic DM1 is characterized by muscle weakness and wasting, myotonia, cataract, and often cardiac conduction abnormalities; adults may become physically disabled and may have a shortened life span.
- Congenital DM1 is characterized by hypotonia and severe generalized weakness at birth, often with respiratory insufficiency and early death; intellectual disability is common.

Diagnosis/testing

DM1 is caused by expansion of a CTG trinucleotide repeat in the noncoding region of *DMPK*. The diagnosis of DM1 is suspected in individuals with characteristic muscle weakness and is confirmed by molecular genetic testing of *DMPK*. CTG repeat length exceeding 34 repeats is abnormal. Molecular genetic testing detects pathogenic variants in nearly 100% of affected individuals.

Management

Treatment of manifestations: Use of ankle-foot orthoses, wheelchairs, or other assistive devices; special education support for affected children; treatment of hypothyroidism; management of pain; consultation with a cardiologist for symptoms or EKG evidence of arrhythmia; removal of cataracts if vision is impaired; hormone replacement therapy for males with hypogonadism; surgical excision of pilomatrixoma and basal cell carcinomas.

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Prevention of secondary complications: Choice of induction agents, airway care, local anesthesia, and neuromuscular blockade to minimize complications during surgery; cardiac pacemakers or implantable cardioverter-defibrillators may prevent life-threatening arrhythmias; continue physical activity and maintain appropriate weight.

Surveillance: Annual EKG or 24-hour Holter monitoring; annual measurement of fasting serum glucose concentration and glycosylated hemoglobin concentration; ophthalmology examination every two years; attention to nutritional status; polysomnography for sleep disturbances.

Agents/circumstances to avoid: Cholesterol-lowering medications (i.e., statins), which can cause muscle pain and weakness; the anesthetic agent vecuronium; succinylcholine, propofol, and doxorubicin; smoking; obesity; illicit drug use; excessive alcohol intake.

Evaluation of relatives at risk: Molecular genetic testing for early diagnosis of relatives at risk to allow treatment of cardiac manifestations, diabetes mellitus, and cataracts.

Genetic counseling

DM1 is inherited in an autosomal dominant manner. Offspring of an affected individual have a 50% chance of inheriting the expanded allele. Pathogenic alleles may expand in length during gametogenesis, resulting in the transmission of longer trinucleotide repeat alleles that may be associated with earlier onset and more severe disease than that observed in the parent. Prenatal testing and preimplantation genetic testing are possible when the diagnosis of DM1 has been confirmed by molecular genetic testing in an affected family member.

Diagnosis

Suggestive Findings

Myotonic dystrophy type 1 (DM1) **should be suspected** in adults with the following:

- Muscle weakness, especially of the distal leg, hand, neck, and face
- Myotonia (sustained muscle contraction), which often manifests as the inability to quickly release a hand grip (grip myotonia) and which can be demonstrated by tapping a muscle (e.g., the thenar muscles) with a reflex hammer (percussion myotonia)
- Posterior subcapsular cataracts detectable as red and green iridescent opacities on slit lamp examination

DM1 **should be suspected** in neonates with some combination of the following:

- Hypotonia
- Facial muscle weakness
- Generalized weakness
- Positional malformations including clubfoot
- Respiratory insufficiency

Establishing the Diagnosis

The diagnosis of DM1 **is established** in a proband with identification of a heterozygous pathogenic variant in *DMPK* by molecular genetic testing (see Table 1).

Allele sizes. Reference ranges for allele sizes were established by the Second International Myotonic Dystrophy Consortium (IDMC) in 1999 [International Myotonic Dystrophy Consortium 2000, Moxley & Meola 2008]. See Prior [2009] and Kamsteeg et al [2012] for technical standards and guidelines for testing.

- **Normal alleles.** 5-34 CTG repeats

- **Mutable normal (premutation) alleles.** 35-49 CTG repeats. Individuals with CTG expansions in the premutation range have not been reported to have symptoms, but their children are at increased risk of inheriting a larger repeat size and thus having symptoms.
- **Full-penetrance alleles.** >50 CTG repeats. Full-penetrance alleles are associated with disease manifestations.

See Published Guidelines / Consensus Statements.

Molecular Genetic Testing

Testing approaches include the following:

- **Targeted analysis** for an increased number (i.e., an expansion) of the CTG trinucleotide repeat in *DMPK*
- **A panel** that includes testing for the *DMPK* CTG repeat expansion and other disorders of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition as quickly as possible. Note: (1) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a panel that includes analysis for nucleotide repeats and other non-sequencing-based tests (e.g., *SMN1* copy number analysis, methylation testing for Prader-Willi syndrome, UPD14 analysis) is recommended (see Table 1). (2) Although the CTG repeat expansion will not be detected by a **multigene sequencing panel**, this testing may be appropriate for some conditions in the differential diagnosis. (3) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (4) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (5) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

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

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
DMPK	Targeted analysis for pathogenic variants [3]	100%

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Testing to quantitate the number of *DMPK* CTG trinucleotide repeats is performed by PCR analysis, which reliably detects expanded alleles with about 100-150 CTG repeats. Detection of larger CTG expansions requires Southern blot analysis.

Other Testing

Electromyography (EMG). A needle electrode placed in the muscle of an affected adult records myotonic discharges and myopathic-appearing motor units, predominantly in distal muscles. Electrical myotonic discharges are not usually seen during infancy, but fast runs of single-fiber discharges approaching the pattern of myotonic discharges are suggestive.

Serum CK concentration. Serum CK concentration may be mildly elevated in individuals with DM1 with weakness, but is normal in asymptomatic individuals.

Muscle biopsy. Pathologic features observed on muscle biopsy include rows of internal nuclei (having a boxcar appearance), ring fibers, sarcoplasmic masses, type I fiber predominance and atrophy, fibrosis and fatty infiltration, and a greatly increased number of intrafusal muscle fibers [Thornton 2014, Turner & Hilton-Jones 2014].

Note: Non-molecular testing that has been used in the past to establish the diagnosis of DM1 currently has little role in diagnosis and is primarily used if molecular testing of *DMPK* does not identify the CTG repeat expansion and other myopathies are being considered.

Clinical Characteristics

Clinical Description

DM1 is a systemic disease potentially affecting nearly every organ system. Clinical findings in myotonic dystrophy type 1 (DM1) span a continuum from mild to severe. Udd & Krahe [2012], Thornton [2014], Turner & Hilton-Jones [2014], and Hartman et al [2024] provide an excellent overview of all aspects of DM1. The clinical findings have been categorized into three somewhat overlapping phenotypes (mild, classic, and congenital) that generally correlate with CTG repeat size (Table 2). The CTG repeat ranges for the phenotypes in Table 2 have considerable overlap and CTG repeat size should not be used to predict disease severity [Moxley & Meola 2008, Wenninger et al 2018].

Table 2. Correlation of Phenotype and CTG Repeat Length in Myotonic Dystrophy Type 1

Phenotype	Clinical Signs	CTG Repeat Size [1, 2]	Age of Onset	Average Age of Death
Mutable normal (premutation)	None	35-49	NA	NA
Mild	• Cataracts • Mild myotonia	50-~150	20-70 yrs	60 yrs to normal life span
Classic	• Weakness • Myotonia • Cataracts • Balding • Cardiac arrhythmia	~100-~1,000	10-30 yrs	48-55 yrs
Congenital	• Infantile hypotonia • Respiratory deficits • Intellectual disability • Classic signs in adults	>1,000 [3]	Birth to 10 yrs	45 yrs [4]

From de Die-Smulders et al [1998], Mathieu et al [1999], International Myotonic Dystrophy Consortium [2000]
NA = not applicable
1. CTG repeat sizes are known to overlap between phenotypes.
2. Normal CTG repeat size is 5-34.
3. Redman et al [1993] reported a few individuals with congenital DM1 with repeats between 730 and 1,000.
4. Does not include neonatal deaths

Mild DM1

Individuals with mild DM1 may have only cataract, mild myotonia, or diabetes mellitus. They may have fully active lives and a normal or minimally shortened life span [Arsenault et al 2006].

Classic DM1

Within this range of CTG repeat size, only a rough correlation with severity of symptoms exists. Individuals with CTG repeat sizes in the 100-to-1,000 range usually develop classic DM1 with muscle weakness and wasting, myotonia, cataracts, and often cardiac conduction abnormalities.

While the age of onset for classic DM1 is typically in the 20s and 30s (and less commonly after age 40 years), classic DM1 may be evident in childhood, when subtle signs such as myotonia and typical facial features including ptosis, weak eyelid closure, weak smile, and thin face are observed.

Muscle. In individuals with classic DM1, the predominant symptom is distal muscle weakness, leading to foot drop / gait disturbance and difficulty performing tasks that require fine manual dexterity. The typical facial appearance is mainly caused by weakness of the facial and levator palpebrae muscles. Myotonia may interfere with daily activities such as using tools, household equipment, or doorknobs. Handgrip myotonia and strength may improve with repeated contractions (the so-called warm-up phenomenon) [Logigian et al 2005]. The warm-up phenomenon can also improve dysarthric speech [de Swart et al 2004]. Muscle weakness is progressive but slow, and correlates with disease duration and CTG repeat expansion size [Bouchard et al 2015].

Fatigue is a common finding [Kalkman et al 2005].

Musculoskeletal pain is fairly common, especially in the lower limbs.

Cardiac. Cardiac conduction defects of varying degrees of severity are common. In one series, 90% of individuals had conduction defects. These defects are a significant cause of early mortality in individuals with DM1 and are sometimes associated with sudden death. A cardiac pacemaker is sometimes indicated. Less commonly, dilated cardiomyopathy may occur [Benhayon et al 2015, Lau et al 2015, Chong-Nguyen et al 2017, Wahbi et al 2017]. Atrial fibrillation in DM1 carries an increased risk of stroke [Yoshida et al 2018].

Pulmonary. Progressive impairment of lung function can occur and may require mechanical ventilation [Thil et al 2017, Boussaïd et al 2018].

GI. Smooth muscle involvement may produce dysphagia, constipation, intestinal pseudo-obstruction, or diarrhea [Rönnblom et al 1996, Bellini et al 2006, Glaser et al 2015, Hilbert et al 2017]. Oropharyngeal dysphagia and swallowing problems have been studied by Ercolin et al [2013].

Gallstones occur as a result of increased tone of the gallbladder sphincter [Hilbert et al 2017].

Liver function tests (e.g., transaminases) are often elevated for unclear reasons [Heatwole et al 2006].

Cognition and CNS changes. Minor intellectual deficits are present in some individuals, but in others intelligence may be incorrectly assumed to be reduced because of the dull facial expression. Age-related cognitive decline has been reported in some adults [Modoni et al 2008]. Overall full-scale IQ tends to be lower in individuals with both mild and classic DM1 [Jean et al 2014]. Working memory, executive function, and processing speed can be reduced [Fujino et al 2018].

Frontal-parietal lobe deficits have been documented on formal testing [Sistiaga et al 2010].

Avoidant, obsessive-compulsive, and passive-aggressive personality features have been reported [Delaporte 1998, Winblad et al 2005]. Peric et al [2014] reported pathologic personality traits in 58% of 62 individuals tested, the two most common being dependent and/or paranoid personality.

In one study of 200 individuals with DM1, personality traits and psychological symptoms were usually in the normal range, but 27% were at high risk of developing a psychiatric disorder [Bertrand et al 2015].

Anxiety and depression are often seen and general quality of life can be seriously impaired [Antonini et al 2006].

Hypersomnia and sleep apnea are other well-recognized manifestations that appear later [Rubinsztein et al 1998, Laberge et al 2009]. Excessive daytime sleepiness is often caused by a central dysfunction of sleep regulation, but all types of sleep disorders have been reported [Dauvilliers & Laberge 2012, Bonanni et al 2018]. Twenty of 40 individuals with DM1 had obstructive sleep apnea [Pincherle et al 2012].

Brain MRI may demonstrate mild cortical atrophy and white matter abnormalities. The white matter changes can be diffuse and extensive [Caso et al 2014, Okkersen et al 2017]. Proton magnetic resonance spectroscopy shows probable glutamatergic neuronal degeneration in frontal cortex and white matter [Takado et al 2015].

At autopsy, brain neurons may contain tau-associated neurofibrillary tangles [Caillet-Boudin et al 2014].

Nerve. An axonal peripheral neuropathy may add to the weakness but may be uncommon [Bae et al 2008]. Peric et al [2013] found evidence of neuropathy by nerve conduction studies in one third of 111 individuals with DM1.

Eye. Cataracts can eventually be observed as having characteristic multicolored "Christmas tree" appearance by slit lamp examination in nearly all affected individuals. They may cause visual symptoms at any age, but usually in the 30s-40s.

Some affected individuals have ophthalmoplegia.

Endocrine. Endocrinopathies including hyperinsulinism, thyroid dysfunction, diabetes mellitus, calcium dysregulation, testicular atrophy, and possible abnormalities in growth hormone secretion can be observed, although they are rarely clinically significant. Infertility may occur in otherwise asymptomatic persons [Matsumura et al 2009]. The largest published study of these endocrine abnormalities is that of Ørngreen et al [2012]. Secondary hyperparathyroidism with normal serum calcium and low 25-hydroxy vitamin D has been reported in up to 18% of affected persons [Passeri et al 2013].

Skin. Pilomatrixomata and epitheliomas can occur, especially on the scalp, and can be confused with sebaceous cysts [Zampetti et al 2015]. Androgenic alopecia is also common [Campanati et al 2015].

Cancer risk. Individuals with DM1 may be at increased risk for thyroid, uterine, choroidal melanoma, and possibly colon, testicular, and prostate cancers [Win et al 2012, Abbott et al 2016, Emparanza et al 2018]. There was no increased risk of cancer in relatives who did not have DM [Lund et al 2014]. Risk of skin cancer is increased, especially basal cell [Marcoval et al 2016, Wang et al 2018]. Maya-González et al [2024] have confirmed an increased risk of several types of cancer including brain tumor and non-thyroid endocrine tumors.

Disease course. Rarely, after several decades of disease, DM1 progresses to the point of wheelchair confinement. Weakness/myotonia of the diaphragm and a susceptibility to aspiration increase the risk for respiratory compromise, usually in individuals with advanced disease [Roses 1997]. Slow progression of weakness has been documented in a nine-year study [Raymond et al 2017]. Falls resulting in bone fractures are common [Jiménez-Moreno et al 2018].

Several studies have evaluated life span and mortality in DM1 (Table 2) [de Die-Smulders et al 1998, Mathieu et al 1999]. The most common causes of death are pneumonia / respiratory failure, cardiovascular disease, sudden death / arrhythmia, and neoplasms [Benhayon et al 2015, Johnson et al 2015]. In the study of de Die-Smulders et al [1998] 50% of individuals with DM1 were either partially or totally wheelchair bound shortly before death. The cumulative probability of 15-year survival in Belgrade was 50% [Mladenovic et al 2006]. Both early age of onset and decreased survival correlate with larger CTG repeat expansions [Groh et al 2011]. Survival correlates with age, diabetes, need for walking support, cardiac arrhythmia, blood pressure, and vital capacity [Wahbi et al 2018].

Congenital DM1

A transmission ratio distortion at conception favors transmission of larger CTG repeats than those present in the parent [Dean et al 2006]. The mother is almost always the parent who transmits the larger repeat, although transmission by the father has been reported [Zeesman et al 2002]. Presence of a large repeat may lead to earlier onset and more severe disease, known as congenital DM1 [Rakocević-Stojanović et al 2005].

Prenatal. Congenital DM1 often presents before birth as polyhydramnios and reduced fetal movement.

Neonatal. After delivery, the main features are severe generalized weakness, hypotonia, and respiratory compromise. Typically, affected infants have an inverted V-shaped (also termed "tented" or "fish-shaped") upper lip, which is characteristic of significant facial diplegia (weakness). Mortality from respiratory failure is common.

Infancy and childhood. Surviving infants experience gradual improvement in motor function. Affected children are usually able to walk; however, a progressive myopathy occurs eventually, as in the classic form [Harper 2001, Johnson et al 2016]. These individuals may develop any of the typical features of DM1 including weakness, myotonia, cataracts, and cardiac problems. Strength improves during early childhood, then begins to decrease during the second decade [Kroksmark et al 2017].

- **Intellectual disability.** Fifty to 65% of individuals with congenital DM1 have a very low IQ score [Patel et al 2024]. The cause of the intellectual disability is unclear, but cerebral atrophy and ventricular dilatation are often evident at birth. Intellectual disability may result from a combination of early respiratory failure and a direct effect of the *DMPK* pathogenic variant on the brain [Ekström et al 2009]. Autism spectrum disorder may be observed [Ekström et al 2008]. Douniol et al [2012] have reported common mood/anxiety disorders, impaired attention, and abnormal visual-spatial abilities. Delusions and psychotic features can occur [Jacobs et al 2017].
- **Vision.** Children with DM1 may have low visual acuity, hyperopia, or astigmatism [Ekström et al 2010].
- **Sleep.** Excessive daytime sleepiness can affect quality of life [Ho et al 2017].

Genotype-Phenotype Correlations

In general, longer CTG repeat expansions correlate with an earlier age of onset and more severe disease [Logigian et al 2004] (Table 2). Small but abnormal repeats (50-99) are often associated with a mild or asymptomatic phenotype [Arsenault et al 2006].

The *DMPK* CTG trinucleotide repeat length is mitotically unstable in individuals with DM1. Such instability very often leads to somatic mosaicism for the size of the CTG expansion; therefore, correlation between CTG repeat size observed in one tissue and disease severity may not be possible [Moxley & Meola 2008]. Studies have attempted to estimate the progenitor allele CTG repeat length (ePAL) and somatic mutational dynamics [Cumming et al 2019]. ePAL refers to the subject's CTG repeat size at the time of birth, which often increases over the next decades. It is also known that 3%-8% of DM1 expansions contain variant repeats such as CCG and CGG. These are referred to as variant repeat interruptions and may be associated with later onset and milder phenotype [Miller et al 2020].

A person who was a compound heterozygote for expanded alleles with 1,260 and 60 CTG repeats was reported to have cerebral abnormalities [Cerghet et al 2008].

Penetrance

Penetrance is high (nearly 100% by age 50 years) when all manifestations of the disease, even those that are subtle, are sought. However, mild cases (e.g., persons with only cataracts) may be missed [Moxley & Meola 2008].

Anticipation

Because *DMPK* alleles of CTG length greater than 34 repeats are unstable and may expand in length during meiosis, at-risk offspring may inherit repeat lengths considerably longer than those present in the transmitting parent. This phenomenon results in anticipation, the occurrence of increasing disease severity and decreasing age of onset in successive generations.

Most often a child with early-onset, severe DM1 (i.e., congenital DM1) has inherited the expanded *DMPK* allele from the mother [Martorell et al 2007]. Although anticipation typically occurs in maternal transmission of the disease, anticipation with paternal transmission is possible [Moxley & Meola 2008].

In a study of children of parents with small expansions (50-100 CTG repeats), those with expanded alleles transmitted paternally had a larger increase in CTG repeats (median: 425 repeats; range: 70-2,000) than did those with maternally transmitted expanded alleles (median: 200 repeats; range: 57-1,400) [Pratte et al 2015].

Prevalence

Estimates of the prevalence of DM1 range from 1:100,000 in some areas of Japan to 1:10,000 in Iceland, with an overall estimated worldwide prevalence of 1:20,000 [Theadom et al 2014, Liao et al 2022].

A report in 2021 found a prevalence of 4.76:10,000 for DMPK CTG expansions of ≥50 CTG repeats in a newborn blood spot screening program in New York State [Johnson et al 2021]. A prevalence of 19.1:10,000 was found for premutations of 35-49 CTG repeats. These remarkably high prevalences are for DNA CTG repeat expansions and not for clinical diagnoses of myotonic dystrophy as in previous epidemiologic studies. More than half of the individuals reported by Johnson et al [2021] had CTG expansions in the 50-150 range consistent with the probability that many such individuals have few if any symptoms of myotonic dystrophy and are likely to be undiagnosed later in life. Such persons remain at risk for cardiac irregularities and may transmit an expanded CTG repeat to offspring.

Founder effects may increase the prevalence in specific regions, such as Quebec [Yotova et al 2005, Pratte et al 2015].

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Hypotonia in infancy is seen in many disorders, including Prader-Willi syndrome, multiminicore disease (OMIM 606210, 180901), nemaline myopathy (OMIM PS161800), X-linked centronuclear myopathy, other centronuclear myopathies (OMIM PS160150), and maternal uniparental disomy for chromosome 14.

Myotonic dystrophy type 2 (DM2) is characterized by myotonia (90% of affected individuals) and muscle dysfunction (weakness, pain, and stiffness) (82%), and less commonly by cardiac conduction defects, iridescent posterior subcapsular cataracts, insulin-insensitive type 2 diabetes mellitus, and testicular failure. Although myotonia has been reported during the first decade, onset is typically in the third decade, most commonly with fluctuating or episodic muscle pain that can be debilitating and weakness of the neck flexors and finger flexors. Subsequently, weakness occurs in the elbow extensors and the hip flexors and extensors. Facial weakness and weakness of the ankle dorsiflexors are less common. Myotonia rarely causes severe symptoms. A detailed comparison between DM1 and DM2 has been reported [Wenninger et al 2018]. DM2 is caused by pathogenic variants in *CNBP*. *CNBP* intron 1 contains a complex repeat motif, (TG)n(TCTG)n(CCTG)n. Expansion of the CCTG repeat causes DM2. Inheritance is autosomal dominant.

DM2 is the only other known genetic form of multisystem myotonic dystrophy identified to date (although others likely exist). The distinction between DM1, DM2, and other inherited myopathies is made by determining the number of CTG repeats in *DMPK*. If the *DMPK* CTG repeat length is in the normal range and if DM2 has been excluded by molecular genetic testing of *CNBP*, further testing with EMG, serum CK concentration, and/or muscle biopsy is often warranted to evaluate for other causes of muscle disease.

Note: The International Myotonic Dystrophy Consortium (IDMC) has agreed that any newly identified multisystem myotonic dystrophies will be sequentially named as forms of myotonic dystrophy. One family posited to have DM3 [Le Ber et al 2004] was subsequently shown to have an unusual presentation of inclusion body myopathy with Paget disease and frontotemporal dementia [Udd et al 2006] caused by pathogenic variants in *VCP*.

Hereditary distal myopathies. The differential diagnosis for hereditary distal myopathies includes *GNE*-related myopathy (hereditary inclusion body myopathy 2), myofibrillar myopathy (OMIM PS601419), distal muscular dystrophy (e.g., dysferlinopathy, Welander [OMIM 604454]), and the limb-girdle muscular dystrophies.

Hereditary myotonia. Other hereditary disorders associated with myotonia are: myotonia congenita (also called Thomsen disease or Becker disease), caused by pathogenic variants in *CLCN1*; paramyotonia congenita (OMIM 168300) and its variants, caused by pathogenic variants in *SCN4A*; and hyperkalemic periodic paralysis, caused by pathogenic variants in *SCN4A*.

Occasionally, DM1 has been misdiagnosed as motor neuron disease (see Spinal Muscular Atrophy and Spinal and Bulbar Muscular Atrophy), cerebral palsy, nonspecific intellectual disability, or, because of "masked face" and slow movements, parkinsonism.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs **in adults with classic myotonic dystrophy type 1 (DM1)**, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended. Consensus-based care recommendations have been published both for adults [Ashizawa et al 2018] and for persons with congenital- and childhood-onset DM1 [Johnson et al 2019] and are available at www.myotonic.org.

Table 3. Recommended Evaluations Following Initial Diagnosis in Adults with Myotonic Dystrophy Type 1

System/Concern	Evaluation	Comment
Neurologic	Baseline neurologic evaluation for strength, balance, sensation	Excessive daytime sleepiness is common.
Other	Developmental assessment	To incl assessment of strength & cognitive function
	Consultation w/clinical geneticist &/or genetic counselor	
Eyes	Ophthalmologic evaluation	By an ophthalmologist familiar w/iridescent posterior subcapsular cataract characteristic of DM1
Cardiovascular	EKG & Holter monitoring	To evaluate syncope, chest pains, palpitations, & other symptoms of potential cardiac origin
	Echocardiogram	Consider cardiology referral.
Respiratory	Pulmonary function tests	Pneumonia & flu vaccinations
		Referral to pulmonologist if symptomatic
Endocrine	Assessment of thyroid function	Liver enzyme elevation is common.
	Fasting blood glucose & HbA1C determination	

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
GI	Clinical assessment for poor swallowing, pseudo-obstruction, diarrhea, gallbladder dysfunction	Consider internal medicine &/or gastroenterology consultation.
Surgery	Evaluate for history of adverse reactions to drugs & anesthesia	Consensus guidelines
Pregnancy	Obstetric consultation	Miscarriage & preterm delivery is common in affected women; see Pregnancy Management.

To establish the extent of disease and needs **in children diagnosed with congenital DM1**, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Children with Myotonic Dystrophy Type 1

System/Concern	Evaluation	Comment
Neurologic	Baseline neurologic eval	
Other	Developmental assessment	To incl assessment of motor, cognitive, & psychosocial function
	Consultation w/clinical geneticist &/or genetic counselor	
Eyes	Ophthalmologic eval	By ophthalmologist familiar w/iridescent posterior subcapsular cataract characteristic of DM1
Cardiovascular	EKG	To evaluate syncope, palpitations, & other symptoms of potential cardiac origin
	Cardiology consultation	
Respiratory	Pulmonary function tests	Pneumonia risk
Endocrine	Fasting blood glucose or HbA1c	

Treatment of Manifestations

Management guidelines have been developed [Turner & Hilton-Jones 2014, Ashizawa et al 2018, Johnson et al 2019].

No specific treatment exists for the progressive weakness in individuals with DM1.

A physiatrist, occupational therapist, or physical therapist can help evaluate affected individuals regarding the need for ankle-foot orthoses, wheelchairs, or other assistive devices as the disease progresses. Orthopedic surgery may benefit children with musculoskeletal deformities [Canavese & Sussman 2009].

Special education support is indicated for children with DM1.

Increased weakness in DM1 has been associated with both hypothyroidism and certain cholesterol-lowering medications (i.e., statins); thus, some strength may return if these causative factors are eliminated.

Myotonia in DM1 is typically mild to moderate and rarely requires treatment [Ricker et al 1999]. Anecdotally, some individuals have responded to mexiletine or carbamazepine. Logigian et al [2010] and Heatwole et al [2021] found mexiletine 150-200 mg 3x/day effective and safe for treating myotonia.

Pain management can be an important part of DM1 treatment. Different medications and combinations of medications work for some individuals, although none has been routinely effective; medications that have been used include mexiletine, gabapentin, nonsteroidal anti-inflammatory drugs, low-dose thyroid replacement, low-

dose steroids, and tricyclic antidepressants. When used as part of a comprehensive pain management program, low-dose analgesics may provide relief.

Consultation with a cardiologist is appropriate for individuals with cardiac symptoms or EKG evidence of arrhythmia because fatal arrhythmias can occur prior to other symptoms in individuals with DM1. More advanced, invasive electrophysiologic testing of the heart may be required [Sovari et al 2007, Sochala et al 2017, Russo et al 2018].

Cataracts can be removed if they impair vision. Recurrence after surgery has been reported [Garrott et al 2004].

Males with low serum concentration of testosterone require hormone replacement therapy if they are symptomatic.

In most cases, surgical excision of pilomatrixoma including clear margins and its overlying skin is the preferred treatment [Cigliano et al 2005]. Basal cell cancers require removal.

An extensive review found no evidence for successful treatment of hypersomnia with routine psychostimulants [Annane et al 2006], although others have reported benefit [Talbot et al 2003, Wintzen et al 2007].

Prevention of Secondary Complications

Veyckemans & Scholtes [2013] have reviewed the anesthetic management of individuals with DM1. Choice of induction agents, airway care, local anesthesia, and neuromuscular blockade were found to minimize complications during surgery in individuals with DM1. Avoid using succinylcholine. Propofol-induced pain can induce myotonia. Sevoflurane has been used uneventfully.

Cardiac pacemakers or implantable cardioverter-defibrillators may prevent life-threatening arrhythmias [Wahbi et al 2012, Facenda-Lorenzo et al 2013].

Gagnon et al [2013] presented evidence that obesity, tobacco smoking, physical inactivity, and alcohol / illicit drug consumption are lifestyle risk factors associated with more severe DM1 phenotypes.

Mechanical ventilation for pulmonary insufficiency may be needed [Boussaïd et al 2018].

Gallbladder removal is sometimes required [Hilbert et al 2017].

Careful attention to anesthetic management during surgery is required [Veyckemans & Scholtes 2013, Gorelik & Flores 2018].

Surveillance

Turner & Hilton-Jones [2014] provide guidelines for surveillance.

The following are appropriate:

- Annual EKG to detect asymptomatic cardiac conduction defects. Some centers perform annual 24-hour Holter monitoring of individuals with DM1 who do not have cardiac symptoms [Sá et al 2007, Sovari et al 2007, Cudia et al 2009]. Tissue Doppler monitoring has also been proposed [Parisi et al 2007, Wahbi et al 2012].
- Annual measurement of fasting serum glucose concentration and glycosylated hemoglobin concentration, with treatment for diabetes mellitus if indicated [Matsumura et al 2009]
- Ophthalmologic examination every two years to evaluate for cataract formation
- Attention to nutritional status including mastication and trouble eating [Motlagh et al 2005, Engvall et al 2009, Umemoto et al 2009]
- Polysomnographic follow up of sleep complaints [Kumar et al 2007]

Agents/Circumstances to Avoid

Statins used to lower cholesterol may sometimes cause muscle pain and weakness.

Mathieu et al [1997] noted that "[n]umerous cases of perioperative complications in patients with DM have been reported. Hazards have been associated with the use of thiopentone, suxamethonium, neostigmine, and halothane. Most complications were pulmonary. The likelihood of perioperative pulmonary complications (PPC) was not related to any specific anesthetic drug. Because of the increased risk of PPC, careful monitoring during the early postoperative period, protection of the upper airways, chest physiotherapy, and incentive spirometry are mandatory in all symptomatic patients with DM, particularly those with a severe muscular disability or those who have undergone an upper abdominal surgery."

Veyckemans & Scholtes [2013] and Gorelik & Flores [2018] have reviewed appropriate anesthetic care for individuals with DM1 and DM2.

Malignant hyperthermia during anesthesia including the use of vecuronium [Nishi et al 2004] has been reported in DM1 but is very uncommon [Kirzinger et al 2010]. (See Malignant Hyperthermia Susceptibility.)

Aggressive doxorubicin-based chemotherapy for lymphoma in a person with DM1 produced sudden atrial fibrillations [Montella et al 2005].

Gagnon et al [2013] presented evidence that obesity, tobacco smoking, physical inactivity, and alcohol / illicit drug consumption are lifestyle risk factors associated with more severe DM1 phenotypes.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic at-risk adult relatives of an affected individual to allow for early diagnosis and treatment of cardiac manifestations, diabetes mellitus, and cataracts.

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

Pregnancy Management

Women with DM1 are at risk for complications during pregnancy including increased spontaneous abortion rate, premature labor, prolonged labor, retained placenta, placenta previa, and postpartum hemorrhage [Zaki et al 2007, Argov & de Visser 2009]. Special surveillance during pregnancy of women with DM1 includes ultrasound examination; evaluation for placenta previa; and anticipation of possible polyhydramnios, prolonged labor, and/or need for delivery by cesarean section [Argov & de Visser 2009].

Complications related to the presence of congenital DM1 in the fetus include reduced fetal movement and polyhydramnios. Awater et al [2012] found increased rates of cesarean birth and preterm delivery among women with DM1.

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

Other

Moderate-intensity strength training does no harm, but it is unclear whether it offers measurable benefits [van der Kooi et al 2005]. A controlled study of an exercise program for DM1 showed neither beneficial nor detrimental effects [Kierkegaard et al 2011].

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 1 (DM1) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Virtually all individuals with DM1 inherited their expanded CTG allele from a parent who also has an allele in the abnormal range (>34 CTG repeats); however, the parent with the expanded allele may or may not appear to be affected. The parent may appear to be unaffected because of failure to recognize symptoms of mild DM1 or the parent may have no symptoms and have an abnormal, but small, CTG repeat expansion.
- New expansions of a normal allele (≤34 CTG repeats) into the abnormal range are rare.
- If both parents of a proband are asymptomatic, it is appropriate to offer *DMPK* molecular genetic testing to both for the purpose of genetic counseling of other family members. In this instance, genetic counseling issues relevant to **presymptomatic testing** should be addressed.
- If a CTG expansion in the abnormal range (>34 repeats) cannot be detected in the leukocyte DNA of either parent, possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption could be explored.

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

- If one parent has an expanded *DMPK* allele, the risk to each sib is 50%.
- An expanded *DMPK* allele may expand further in length during gametogenesis, resulting in transmission of an allele with a larger CTG repeat that may be associated with earlier onset and more severe disease than that in the parent (see Clinical Characteristics, Anticipation; Related Genetic Counseling Issues, **Empiric risks for congenital DM1**).

Offspring of a proband

- Each child of an individual with an expanded *DMPK* allele (>34 CTG repeats) has a 50% chance of inheriting the expanded *DMPK* allele.
- An expanded *DMPK* allele may expand further in length during gametogenesis, resulting in transmission of an allele with a larger CTG repeat that may be associated with earlier onset and more severe disease than that in the parent (see Clinical Characteristics, Anticipation and Related Genetic Counseling Issues, **Empiric risks for congenital DM1**).

Other family members. The risk to other family members depends on the status of the proband's parent: if a parent is affected or has a CTG expansion in the abnormal range (>34 repeats), the parent's family members are at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

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.

Empiric risks for congenital DM1. Data concerning the likelihood that a mother with a particular CTG repeat size will have a child with a particular CTG repeat size or phenotype may be useful in recurrence risk counseling. The available data have wide confidence limits, making specific risk estimates difficult.

- Redman et al [1993] found that for women with a CTG repeat length of 100 or higher, the risk to a child who has inherited the abnormal allele of having an expansion of 730 or more CTG repeats (and thus congenital DM1) is 62%. Martorell et al [2007] found a similar frequency of 63% of fetuses with more than 1,000 repeats in 31 of 49 maternal transmissions of the expanded allele (mothers' abnormal allele size ranging from 65 to 1,333 CTG repeats).
- Cobo et al [1995] determined that for women with a CTG repeat size smaller than 300, the risk to a child who has inherited the abnormal allele of having congenital DM1 is 10%, and for women with a CTG repeat size greater than 300, the risk to a child who has inherited the abnormal allele of having congenital DM1 is 59%. Martorell et al [2007] found a similar correlation, but there was no statistical analysis.

Diagnosis of mildly affected individuals during family evaluation. Individuals with mild DM1 are often unaware of having DM1 and may only be diagnosed in the course of evaluation of a more severely affected family member. This often occurs when an asymptomatic mother having a CTG repeat size under 100 gives birth to an infant with congenital DM1 with a CTG repeat length in the thousands.

Testing of at-risk asymptomatic adult relatives of individuals with DM1 is possible after molecular genetic testing has identified the expanded *DMPK* allele in an affected family member. Such testing should be performed in the context of formal genetic counseling and is not useful in predicting age of onset, severity, type of symptoms, or rate of progression in asymptomatic individuals. Testing of asymptomatic at-risk individuals with nonspecific or equivocal symptoms is predictive testing, not diagnostic testing.

Predictive testing in minors (i.e., testing of asymptomatic at-risk individuals younger than 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 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.

Testing is appropriate to consider in symptomatic individuals in a family with an established diagnosis of DM1 regardless of age.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from

probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

A priori high risk. Once an expanded *DMPK* allele has been identified in an affected family member, prenatal testing for a pregnancy at 50% risk for DM1 and preimplantation genetic testing (PGT) are possible. No effect of trinucleotide repeat size on reproductive outcome in PGT was observed in 78 couples in which 54 females and 24 males had DM1 [Verpoest et al 2010]. In these individuals the CTG repeat size ranged from 50 to 1,330 with a mean of 410. The cumulative delivery rate was 46% in 205 cycles [Verpoest et al 2008]. In 59 cycles in 35 couples Fernández et al [2017] found a live birth per cycle rate of 18.6%. Less favorable rates were found in affected women compared to affected men.

Note: (1) Abnormal test results do not predict the age of onset or severity of the disease because of the overlap of CTG repeat length associated with the three phenotypes and the possibility of somatic mosaicism for the size of the CTG expansion. However, CTG repeat lengths of 730-1,000 or greater are more likely to be associated with congenital DM1 [Redman et al 1993, Martorell et al 2007]. (2) Ultrasound examination in the second and third trimesters may reveal decreased fetal movement and polyhydramnios, possible indicators of congenital DM1.

A priori low risk. For fetuses not known to be at increased risk for DM1, molecular genetic testing for an expanded *DMPK* allele may be considered if polyhydramnios and/or decreased fetal activity are observed on ultrasound examination in the third trimester.

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

- **Medical Home Portal**

  Myotonic Muscular Dystrophy Type 1

- **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

- **Myotonic Dystrophy: Making an Informed Choice About Genetic Testing**

  Booklet providing information about Myotonic Dystrophy and genetic testing (PDF file)

  University of Washington Medical Center, Medical Genetics and Neurology

  Seattle WA

  depts.washington.edu/neurolog/images/neurogenetics/myotonic.pdf

- **National Library of Medicine Genetics Home Reference**
  Myotonic dystrophy
- **NCBI Genes and Disease**
  Myotonic dystrophy
- **TREAT-NMD**
  Neuromuscular Network
  Email: info@treat-nmd.org
  Myotonic Dystrophy
- **Muscular Dystrophy Association (MDA) - USA**
  Phone: 833-275-6321
  Email: ResourceCenter@mdausa.org
  mda.org
- **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 1: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

DMPK	19q13.32	Myotonin-protein kinase	DMPK database	DMPK	DMPK

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 1 (View All in OMIM)

160900	MYOTONIC DYSTROPHY 1; DM1
605377	DYSTROPHIA MYOTONICA PROTEIN KINASE; DMPK

Gene structure. *DMPK* has 14 exons covering approximately 13 kb of genomic DNA. For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign variants. Normal alleles have 5-34 CTG repeats. Alleles with 35-49 CTG repeats are mutable normal (or premutation) alleles. Individuals with CTG expansions in the premutation range have not been reported to have symptoms, but their children are at increased risk of inheriting a larger repeat size and thus having symptoms [Martorell et al 2001].

Pathogenic variants. Myotonic dystrophy type 1 (DM1) appears to be caused by a single mutational mechanism: expanded CTG trinucleotide repeat (>49). Other types of pathogenic variants (e.g., single-nucleotide variants, deletions, insertions) in *DMPK* have not been reported to be associated with DM1. The CTG repeat that is expanded in DM1 lies in the 3' untranslated region of *DMPK*. Abnormal repeat lengths may reach several thousand, particularly in individuals with congenital DM1.

Table 5. *DMPK* Variants Discussed in This *GeneReview*

Variant Classification	DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
Benign	c.*224_226CTG(5-34) [1] (normal range 5-34 CTG repeats)	--	NM_001081563.1
	c.*224_226CTG(35-49) [1] (mutable normal range 35-49 CTG repeats)	--	
Pathogenic	c.*224_226CTG(50-?) [1] (full-penetrance mutated alleles >50 CTG repeats)	--	

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
NA = not applicable
1. The CTG variant is in the 3' untranslated region of the gene (indicated by *), with the first nucleotide after the stop codon numbered as *1. Parentheses indicate the range of numbers of the CTG repeats, here indicating that normal alleles range from 5 to 34 repeats. A specific single allele with five repeats would be designated c.*224_226CTG[5].

Normal gene product. Myotonin-protein kinase (DMPK), a 69-kd serine-threonine protein kinase, has been localized to specialized cell structures in heart and skeletal muscle that are associated with intercellular conduction and impulse transmission. It is closely related to cyclic-AMP-dependent protein kinases and to Rho-binding kinases. DMPK may interact with a GTP-binding protein that is a regulatory subunit of myosin phosphatase.

Abnormal gene product. The effect of the CTG repeat remains complex and many issues are being clarified [Fiszer & Krzyzosiak 2013, Meola & Cardani 2015, Thomas et al 2018]. The effects of an expanded CTG repeat

may occur via abnormal RNA transcript processing. Two homologous RNA CUG-binding proteins (CUG-BP and MBNL1 [muscleblind]) have been identified. These proteins are mutually antagonistic mediators of a subgroup of alternative splicing events that are disrupted in DM, in which embryonic forms of some proteins now predominate. These proteins include: a chloride channel, resulting in myotonia; the insulin receptor, resulting in increased risk of diabetes mellitus; and microtubule-associated protein tau, encoded by *MAPT*, a gene associated with cognitive function [Savkur et al 2001, Mankodi et al 2002, Kanadia et al 2003, Ranum & Day 2004, Day & Ranum 2005, Cooper 2006, Leroy et al 2006, Wheeler & Thornton 2007, Carpentier et al 2014, Echeverria & Cooper 2014]. There is considerable somatic mosaicism between various organs in DM1, which partially explains the wide phenotypic variability.

Chapter Notes

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