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Myotonic Dystrophy Type 1

[*Steinert's Disease*]

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Summary

Disease 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; mental retardation is common.

Diagnosis/testing. DM1 is caused by expansion of a CTG trinucleotide repeat in the gene *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 mutations in nearly 100% of affected individuals and is clinically available.

Management. *Treatment of manifestations:* use of ankle-foot orthoses, wheelchairs, or other assistive devices; treatment of hypothyroidism; management of pain; consultation with a cardiologist for symptoms or ECG evidence of arrhythmia; removal of cataracts if vision is impaired; hormone replacement therapy for males with hypogonadism; surgical excision of pilomatrixoma. *Surveillance:* annual ECG or 24-hour Holter monitoring; annual measurement of fasting serum glucose concentration and glycosylated hemoglobin concentration; eye examination every two years; attention to nutritional status. *Agents/circumstances to avoid:* cholesterol-lowering medications (i.e., statins), which can cause muscle pain and weakness; the anesthetic agent vecuronium. *Testing 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 individual with an expanded allele have a 50% chance of inheriting the mutant allele. Disease-causing 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 is possible for pregnancies at increased risk when the diagnosis of DM1 has been confirmed by molecular genetic testing in an affected family member.

Diagnosis

Clinical Diagnosis

Myotonic dystrophy type 1 (DM1) is 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 is suspected in neonates with some combination of the following:

- Hypotonia
- Facial muscle weakness
- Generalized weakness
- Positional malformations including club foot
- Respiratory insufficiency

Testing

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* is normal and other myopathies are being considered. Tests include the following:

- **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, ring fibers, sarcoplasmic masses, type I fiber atrophy, and a greatly increased number of intrafusal muscle fibers.

Molecular Genetic Testing

Molecular Genetic Testing —Gene. *DMPK* is the only gene known to be associated with myotonic dystrophy type 1 (DM1). Essentially 100% of individuals with DM1 have an increased number (i.e., an expansion) of the CTG trinucleotide repeat in the *DMPK* gene.

Allele sizes. Allele sizes were established by the Second International Myotonic Dystrophy Consortium (IDMC) in 1999 [Second IDMC 2000].

- **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 [Martorell et al 2001].

- **Full penetrance alleles:** >50 CTG repeats. Full penetrance alleles are associated with disease manifestations.

Clinical testing

- **Targeted mutation analysis.** Testing to quantitate the number of *DMPK* CTG trinucleotide repeats is performed by PCR analysis (to detect repeat sizes ≤100 repeats) and Southern blot analysis (to detect CTG expansions >100 repeats).

Table 1 summarizes molecular genetic testing for this disorder.

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

Test Method	Mutations Detected	Mutation Detection Frequency [1]	Test Availability
Targeted mutation analysis	CTG trinucleotide repeat expansion	100%	Clinical Testing

1. Proportion of affected individuals with a mutation(s) as classified by test method

Testing Strategy

To establish the diagnosis in a proband

- Molecular genetic testing of *DMPK* is the basis of diagnosis of DM1.
- Non-molecular testing used in the past to establish the diagnosis of DM1 currently has little role in diagnosis; it is primarily used if molecular testing of *DMPK* is normal.

Predictive testing for at-risk asymptomatic adult family members requires prior confirmation of the diagnosis of DM1 by molecular genetic testing of *DMPK* in an affected family member.

Prenatal diagnosis and preimplantation diagnosis for at-risk pregnancies require prior confirmation of the diagnosis of DM1 by molecular genetic testing of *DMPK* in an affected family member.

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with mutations in *DMPK*.

Clinical Description

Natural History

Clinical findings in myotonic dystrophy type 1 (DM1) span a continuum from mild to severe. 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 caution must be used in predicting disease severity on the basis of CTG repeat size [Harris et al 1996,Roses 1997,Gharehbaghi-Schnell et al 1998,Second IDMC 2000].

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 to 49	NA [3]	NA [3]
Mild	Cataracts Mild myotonia	50 to ~150	20 to 70 yrs	60 yrs to normal life span
Classic	Weakness Myotonia Cataracts Balding Cardiac arrhythmia Others	~100 to ~1000	10 to 30 yrs	48 to 55 yrs
Congenital	Infantile hypotonia Respiratory deficits Mental retardation Classic signs present in adults	>2000 [4]	Birth to 10 yrs	45 yrs [5]

From de Die-Smulders et al 1998, Mathieu et al 1999, Second IDMC 2000

1. CTG repeat sizes are known to overlap between phenotypes.
2. Normal CTG repeat size is 5-34.
3. NA = not applicable
4. Redman et al 1993 reported a few individuals with congenital DM1 with repeats between 730 and 1000.
5. 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-1000 range usually develop classic DM1 with muscle weakness and wasting, myotonia, cataracts, and often cardiac conduction abnormalities.

The age of onset for classic DM1 is typically in the 20s and 30s, and less commonly after age 40 years. However, classic DM1 may be evident in childhood, when subtle signs such as myotonic facies and myotonia are observed.

In individuals with classic DM1, the predominant symptom is distal muscle weakness, leading to foot drop/gait disturbance and difficulty with performing tasks requiring fine dexterity of the hands. The typical facies 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 speech production [de Swart et al 2004].

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

An axonal peripheral neuropathy may add to the weakness [Krishnan & Kiernan 2006].

Smooth muscle involvement may produce dysphagia, constipation, or diarrhea. Some affected individuals have ophthalmoplegia and others may have dysarthria with nasal speech.

Cataracts can eventually be observed by slit lamp examination in nearly all affected individuals.

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. Less commonly, cardiomyopathy may occur [Bassez et al 2004, Chebel et al 2005, Dello Russo et al 2006].

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 2004, Gaul et al 2006].

Avoidant, obsessive-compulsive, and passive-aggressive personality features have been reported [Delaporte 1998, Winblad et al 2005].

Gallstones occur as a result of increased tone of the gall bladder sphincter.

Liver function tests are often elevated for unclear reasons [Heatwole et al 2006].

Hypersomnia and sleep apnea are other well-recognized manifestations of the disease that appear later [Rubinsztein et al 1998].

Endocrinopathies including hyperinsulinism, 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 [Garcia de Andoin et al 2005].

Pilomatrixomata and epitheliomas can occur, especially on the scalp, and can be confused with sebaceous cysts [Geh et al 1999, Cigliano et al 2005].

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]. 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. In the study of Die-Smulders et al (1998) 50% of individuals with DM1 were either partially or totally wheelchair bound shortly before death. Anxiety and depression are often seen and general quality of life can be seriously impaired [Antonini et al 2006].

Women with DM1 are at risk for complications during pregnancy including increased spontaneous abortion rate, prolonged labor, retained placenta, and postpartum hemorrhage [Sarnat et al 1976, Webb et al 1978]. Complications related to the presence of congenital DM1 in the fetus include reduced fetal movement and polyhydramnios.

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, but 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 [De Temmerman et al 2004, Rakocevic-Stojanovic et al 2005].

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

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 high.

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 [Joseph et al 1997].

Mental retardation is present in 50%-60% of individuals with congenital DM1. The cause of the mental retardation is unclear, but cerebral atrophy and ventricular dilation are often evident at birth. Mental retardation may result from a combination of early respiratory failure and a direct effect of the *DMPK* mutation on the brain [Spranger et al 1997, Ashikawa 1998].

Neuropathology. Brain neurons may contain tau-associated neurofibrillary tangles [Maurage et al 2005, Oyamada et al 2006].

Genotype-Phenotype Correlations

In general, longer CTG repeat expansions correlate with an earlier age of onset and more severe disease (Table 2).

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.

Penetrance

Penetrance is high (nearly 100%) when all manifestations of the disease, even those that are subtle, are sought. However, mild cases (for example, persons with only cataracts) may be missed.

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, which is 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. Although anticipation typically occurs in maternal transmission of the disease, paternal inheritance is possible.

Prevalence

Estimates of the prevalence of DM1 range from approximately 1:100,000 in some areas of Japan to approximately 1:10,000 in Iceland, with an overall worldwide prevalence of approximately 1:20,000.

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

Differential Diagnosis

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

The distinction between myotonic dystrophy type 1 (DM1) and other inherited myopathies is made by determining the number of CTG repeats in *DMPK*.

Myotonic dystrophy type 2 (DM2), previously termed proximal myotonic myopathy (PROMM), is the condition most similar clinically to DM1 [Meola et al 1996, Udd et al 1997, Day et al 1999]. DM2 is a multisystem disorder characterized by myotonia (90%) and muscle dysfunction (82%), as well as a consistent constellation of seemingly unrelated clinical features including: cardiac conduction defects (19%), iridescent posterior subcapsular cataracts (36%-78%, increasing with age), and a specific set of endocrine changes including insulin insensitivity (25%-75%, increasing with age) and testicular failure (29%-65%). The onset of DM2 is typically in the third decade, with the most common symptom being muscle dysfunction, although myotonia during the first decade has been reported [Day et al 1999, Day et al 2003]. A congenital form is not observed.

ZNF9, the gene encoding zinc finger protein 9, is the only gene known to be associated with DM2. *ZNF9* intron 1 contains a complex repeat motif (TG)n(TCTG)n(CCTG)n. Expansion of the CCTG repeat causes DM2 [Liquori et al 2001]. Inheritance is autosomal dominant.

No other genetic causes of multisystem myotonic dystrophies have been identified, although they likely exist. The 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 (IBMPFTD) [Udd et al 2006], caused by mutations in *VCP*.

If the *DMPK* CTG repeat length is in the normal range and if DM2 has been excluded by molecular genetic testing of *ZNF9*, further testing with EMG, serum CK concentration, and/or muscle biopsy is often warranted to evaluate for other causes of muscle disease.

The differential diagnosis for hereditary distal myopathies includes hereditary inclusion body myositis (IBM), hereditary myofibrillar myopathy (MFM), distal muscular dystrophy (e.g., Miyoshi, Nonaka, Welander, Markesbery-Griggs), and the limb-girdle muscular dystrophies.

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

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

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in children diagnosed with congenital myotonic dystrophy type 1 (DM1), the following evaluations are recommended:

- Baseline neurologic examination
- Baseline ophthalmologic examination
- Assessment of motor skills
- Assessment of cognitive ability

To establish the extent of disease in adults with classic DM1, the following evaluations are recommended:

- Baseline neurologic examination
- Baseline examination by an ophthalmologist familiar with the iridescent posterior subcapsular cataract characteristic of DM1
- Assessment of thyroid function
- ECG, Holter monitoring, and echocardiogram to evaluate syncope, palpitations, and other symptoms of potential cardiac origin
- Assessment of strength [Whittaker et al 2006]
- Assessment of cognitive ability
- Fasting blood glucose determination

Treatment of Manifestations

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

A physiatrist, occupational therapist, or physicial therapist can help evaluate affected individuals regarding the need for ankle-foot orthoses, wheelchairs, or other assistive devices as the disease progresses.

Increased weakness in DM1 has been associated with both hypothyroidism and certain cholesterol-lowering medications (i.e. statins), so that some strength can 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 mexilitene or carbamazepine.

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 mexilitene, gabapentin, nonsteroidal anti-inflammatory drugs (NSAIDs), 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 ECG 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.

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].

Surveillance

The following are appropriate:

- Annual ECG to detect asymptomatic cardiac conduction defects. Some centers perform annual 24-hour Holter monitoring of individuals with DM1 who do not have

cardiac symptoms. Tissue Doppler monitoring has also been proposed [Parisi et al 2007].

- Annual measurement of fasting serum glucose concentration and glycosylated hemoglobin concentration, with treatment for diabetes mellitus if indicated
- Ophthalomologic examination every two years to evaluate for cataract formation
- Attention to nutritional status [Motlagh et al 2005]

Agents/Circumstances to Avoid

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

Patients with DM1 have been reported to occasionally have adverse reactions to anesthetic agents including vecuronium [Nishi et al 2004].

Mathieu et al (1997) noted that

numerous cases of perioperative complications in DM patients have been reported. Hazards have been associated with the use of thiopentone, suxamethonium, neostigmine, and halothane. A retrospective study of perioperative complications was conducted for 219 DM patients who had their first surgery under general anesthesia at the Chicoutimi Hospital. The overall frequency of complications was 8.2% (18 of 219). Most complications (16 of 18) were pulmonary, including five patients with acute ventilatory failure necessitating ventilatory support, four patients with atelectasis, and three patients with pneumonia. Using multivariate analysis, we found that the risk of perioperative pulmonary complications (PPC) was significantly higher after an upper abdominal surgery and for patients with a severe muscular disability, as assessed by the presence of proximal limb weakness. The likelihood of 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 DM patients, particularly those with a severe muscular disability or those who have undergone an upper abdominal surgery [Mathieu et al 1997].

Testing of Relatives at Risk

It is appropriate to offer molecular genetic testing to at-risk adult relatives to allow 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.

Therapies Under Investigation

Treatment trials of myotonia are few in number and not carefully conducted [Trip et al 2006].

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Moderate-intensity strength training does no harm, but it is unclear whether it offers measurable benefits [van der Kooi et al 2005].

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

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

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 have inherited their expanded CTG allele from a parent who also has an allele in the mutant range (>34 CTG repeats).
- New mutations — the expansion of a normal allele (≤34 CTG repeats) into the abnormal range — are rare.
- Some individuals diagnosed with DM1 have an obviously affected parent; others do not. 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.
- If both parents of an index case 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.

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%.

Offspring of a proband

- All offspring of an individual with a mutant allele (>34 CTG repeats) have a 50% chance of inheriting the mutant allele.
- A mutant allele may expand 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.

Other family members of a proband. The risk to other family members depends on the status of the proband's parent. If a parent is affected, his or her family members are at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* mutation. When the parents of a proband are unaffected and do not have a CTG expansion in the abnormal range (>34 repeats), possible non-medical explanations including alternate paternity or undisclosed adoption could be explored.

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy. Similarly, decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made before pregnancy. It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk of being affected.

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 100 or higher, the risk for a child who has inherited the abnormal allele of having an expansion of 730 or more CTG repeats (and thus congenital DM1) is 62%.
- 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%.

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.

Presymptomatic testing

- **Testing of at-risk asymptomatic adults.** Testing of at-risk asymptomatic adults is available using the same techniques described in Molecular Genetic Testing. This testing is not useful in predicting age of onset, severity, type of symptoms, or rate of progression in asymptomatic individuals. Routine testing of asymptomatic at-risk individuals with nonspecific or equivocal symptoms is predictive testing, not diagnostic testing. When testing at-risk individuals, an affected family member should be tested first to confirm the molecular diagnosis in the family.

  At-risk asymptomatic adult family members may seek testing in order to make personal decisions regarding reproduction, financial matters, and career planning [Smith et al 2004]. Others may have different motivations including simply the "need to know." Testing of asymptomatic at-risk adult family members usually involves pretest interviews in which the motives for requesting the test, the individual's knowledge of myotonic dystrophy, the possible impact of positive and negative test results, and neurologic status are assessed. Those seeking testing should be counseled about possible problems that they may encounter with regard to health, life, and disability insurance coverage, employment and educational discrimination, and changes in social and family interaction. Other issues to consider are implications for the at-risk status of other family members. Informed consent should be procured and

records kept confidential. Individuals with a positive test result need arrangements for long-term follow-up and evaluations.

- **Testing of at-risk asymptomatic individuals younger than age 18 years.** Consensus holds that individuals younger than age 18 years who are at risk for adult-onset disorders should not have testing in the absence of symptoms. The principal arguments against testing asymptomatic individuals under age 18 years are that it removes their choice to know or not know this information, it raises the possibility of stigmatization within the family and in other social settings, and it could have serious educational and career implications. Individuals younger than age 18 who are symptomatic usually benefit from having a specific diagnosis established. See also the National Society of Genetic Counselors resolution on genetic testing of children and the American Society of Human Genetics and American College of Medical Genetics points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents (pdf; Genetic Testing).

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

A priori high risk. Prenatal diagnosis for pregnancies at 50% risk for DM1 is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. The presence of an expanded *DMPK* allele in an affected family member should be confirmed before prenatal testing is performed.

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 730-1000 or greater are more likely to be associated with congenital DM1 [Redman et al 1993]. (2) Ultrasound examination in the second and third trimesters may reveal decreased fetal movement and polyhydramnios, possible indicators of congenital DM1. (3)Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

A priori low risk. For fetuses not known to be at increased risk for DM1, molecular genetic testing of DNA extracted from fetal cells obtained by amniocentesis may be considered if polyhydramnios and/or decreased fetal activity are observed on ultrasound examination in the third trimester.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified [de Die-Smulders et al 2004]. For laboratories offering PGD, see

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Molecular Genetics

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

Table A. Molecular Genetics of Myotonic Dystrophy Type 1

Gene Symbol	Chromosomal Locus	Protein Name
DMPK	19q13.2-q13.3	Myotonin-protein kinase

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Myotonic Dystrophy Type 1

160900	DYSTROPHIA MYOTONICA 1
605377	DYSTROPHIA MYOTONICA PROTEIN KINASE; DMPK

Table C. Genomic Databases for Myotonic Dystrophy Type 1

Gene Symbol	Entrez Gene	HGMD
DMPK	1760 (MIM No. 605377)	DMPK

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

Note: HGMD requires registration.

Normal allelic variants: The *DMPK* gene has 15 exons covering approximately 13 kb of genomic DNA and codes for a protein with 624 amino acids.

Pathologic allelic variants: Myotonic dystrophy type 1 (DM1) appears to be caused by a single mutational mechanism: expanded CTG trinucleotide repeat (>34). Other types of mutations (e.g., point mutations, 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.

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 unclarified issues remain [Harris et al 1996]. 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, and the insulin receptor, resulting in increased risk of diabetes mellitus [Savkur et al 2001, Mankodi et al 2002, Kanadia et al 2003, Ranum & Day 2004, Day & Ranum 2005, Cooper 2006].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Myotonic Dystrophy: Making an Informed Choice About Genetic Testing
Booklet providing information about myotonic dystrophy and genetic testing.
depts.washington.edu/neurogen/Myotonic.pdf

National Library of Medicine Genetics Home Reference
Myotonic dystrophy

NCBI Genes and Disease
Myotonic dystrophy

Muscular Dystrophy Association (MDA)
3300 East Sunrise Drive
Tucson AZ 85718-3208
Phone: 800-FIGHT-MD (800-344-4863); 520-529-2000
Fax: 520-529-5300
Email: mda@mdausa.org
www.mdausa.org

Muscular Dystrophy Campaign
7-11 Prescott Place
SW4 6BS
United Kingdom
Phone: (+44) 0 020 7720 8055
Fax: (+44) 0 020 7498 0670
Email: info@muscular-dystrophy.org
www.muscular-dystrophy.org

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

American Society of Human Genetics and American College of Medical Genetics (1995) Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents.

National Society of Genetic Counselors (1995) Resolution on prenatal and childhood testing for adult-onset disorders.

Second International Myotonic Dystrophy Consortium (2000) New nomenclature and DNA testing guidelines for myotonic dysptrophy type 1 (DM1).

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Chapter Notes

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- 9 August 2004 (tb) Revision
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- 17 September 1999 (me) Review posted to live Web site
- 31 December 1998 (ca) Original submission