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Myotonic Dystrophy

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Abstract

Myotonic dystrophy (dystrophia myotonica, DM) is one of the most common lethal monogenic disorders in populations of European descent. Myotonic dystrophy type 1 (DM1) was first described over a century ago. DM1 is caused by expansion of a CTG triplet repeat in the 3' non-coding region of *DMPK*, the gene encoding the DM protein kinase. More recently a second form of the disease, myotonic dystrophy type 2 (DM2) was recognized, which results from repeat expansion in a different gene. The DM2 expansion involves a CCTG repeat in the first intron of *Zinc Finger 9* (*ZNF9*). Both disorders have autosomal dominant inheritance and multisystem features, including myotonic myopathy, cataract, and cardiac conduction disease. Studies suggest that the shared clinical features of DM1 and DM2 involve a novel genetic mechanism in which repetitive RNA exerts a toxic effect. The RNA toxicity stems from the expanded repeat in the transcripts from the mutant DM alleles. This chapter will review the clinical presentation and pathophysiology of DM, and discuss current management and future potential for developing targeted therapies.

Epidemiology

A population-based genetic screen to determine the true frequency of DM is now technically feasible but has not yet been performed on a large scale. The most ambitious genetic screen to date showed a DM gene frequency of 1 in 1,100 among Finnish blood donors, equally divided between DM1 and DM2.[1] However, the 95% confidence intervals were broad (1 in 500 to 1 in 3,700) because the sample size was small (n = 4,520). It is also possible that DM1-affected individuals were underrepresented in the blood donor pool. A referral center in England found that DM1 was the most common genetic disease of skeletal muscle, accounting for 29% of the population in a muscle clinic.[2] The estimated point prevalence of 1 in 9,400 was considered conservative because at-risk relatives were not systematically screened. Other DM1 prevalence estimates in Europe ranged from 1 in 8,300 to 1 in 10,700.[3, 4] Harper reviewed epidemiologic studies of DM1 in Europe and arrived at an estimated gene frequency of 1 in 7,400.[5] Studies of non-European populations indicated that

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DM1 was rare in Taiwan and sub-Saharan Africa, except among European descendants in South Africa.[6-8] DM1 is highly prevalent in certain founder populations. For example, the frequency was 1 in 550 among residents of Northeastern Quebec.[9] The epidemiology of DM1 in the United States has not been systematically studied.

There are fewer epidemiologic studies of DM2. The genetic diagnosis of DM1 and DM2 was made with similar frequency at a reference laboratory in Germany,[10] suggesting that the prevalence of the two disorders is similar in northern Europe. This observation agrees with the genetic screening studies in Finland cited above.[1] In Europeans the DM2 expansion only occurs on a specific chromosomal haplotype, suggesting the occurrence of a predisposing mutation in a common ancestral founder.[11] In the United States, clinical experience suggests that DM2 is roughly 5-fold less common than DM1.

Genetics

The discovery of the DM1 mutation in 1992 provided the third example (after Kennedy's disease and fragile X syndrome) of a human genetic disease caused by expansion of a tandem repeat.[12] Nine years later the expanded CCTG repeat was discovered in DM2.[13] Now the list of expanded repeat disorders has grown to more than 25.

The number of CTG repeats in the *DMPK* gene is variable in the general population, falling in a range of 5 to 37 repeats.[12] Individuals with DM1 have at least 50 and in some cases upwards of 3,000 CTG repeats in *DMPK*. At the DM2 locus the number of CCTG repeats in *ZNF9* is also polymorphic in the general population, ranging from 10 to 33 repeats.[13, 14] Although DM2 has been reported with CCTG expansions as small as 75 repeats, more than 90% of patients have > 1,000 CCTG repeats, and the mean expansion size is around 5,000 repeats.[15]

The clinical features of DM1 are shaped by two characteristics of the CTG expansion: (1) it is highly unstable so that new alleles with different repeat sizes are constantly generated; and (2) there is a bias for further expansion, rather than contraction, in the new alleles. On average, the CTG expansion increases by more than 200 repeats when transmitted from one generation to the next.[16, 17] This leads to anticipation, the genetic phenomenon whereby symptoms begin at an earlier age in successive generations. The CTG expansion is also unstable in somatic cells of a person throughout life. This component of instability occurs at different rates in different cells, which leads to variability of repeat length in different tissues. Against expectations, the DM1 expansion is actually more unstable in non-dividing cells of skeletal muscle, heart, and brain than in proliferating cells of the hematopoietic system.[18, 19] In skeletal muscle the DM1 expansion typically grows to more than 2,000 repeats by age 20,[20] and in patients older than 40 years the average repeat length in skeletal muscle was greater than 4,000 repeats, which was 3 to 25-fold larger than in blood.[21] These dramatic changes in post-mitotic cells are believed to result from aberrant (incorrect) DNA repair, through a mechanism that is coupled to transcription across the repeat tract.[22] It is possible that the age of onset and progression of symptoms is fundamentally linked to the age-dependent growth of the CTG repeat in somatic cells.

Other aspects of DM1 genetics that are pertinent for clinical care include the following.

1. Caution should be exercised in using CTG repeat size to predict future symptoms. The most reliable correlation is that patients with small expansions generally have mild symptoms. For example, people with 50-70 repeats may have normal neurologic exams even into the 6th decade.[23] Most commonly these individuals come to light when their affected children develop symptoms. CTG expansions that are slightly larger, comprising 70-90 repeats, are usually associated with mild symptoms that began after age 40. At the other end of the spectrum, congenital DM1 is usually associated with expansions of more than 1,000 repeats.[24] However, between these extremes, correlations between repeat size and disease severity are not highly robust.

2. Small expansions (50 to 80 repeats) may be transmitted for several generations with minor changes. These alleles display greater instability when passaged through the male germline.[23, 25] Accordingly, the jump from small expansion with minor symptoms to large expansion with classical DM1 is more likely to occur with paternal transmission.

3. In contrast, the massive intergenerational expansions to 1,000 or more repeats are more likely to occur with maternal transmission.[17, 24] This explains the near-exclusive maternal transmission of congenital DM1.

4. Anticipation is not inevitable. Occasionally the expanded repeat undergoes an intergenerational contraction (< 5% of transmissions).[26]

5. Around 5% of DM1 families have sequence interruptions within the CTG repeat.[27] Most commonly these are CCG or CGG triplets interspersed among CTG triplets. It appears that sequence interruptions tend to stabilize the repeat tract and reduce anticipation, and in some cases may lead to variant phenotypes. For example, one kindred with interrupted repeats had a variant phenotype of CMT-like polyneuropathy with paroxysmal encephalopathy.

In DM2 the CCTG expansions are also unstable in somatic cells and with intergenerational transmission. However, unlike DM1, DM2 does not have a strong bias for intergenerational expansion, and correlations between disease severity and expansion size are relatively weak.[15] Accordingly, there is less anticipation in DM2 than in DM1.[15, 28]

Clinical Presentation

The spectrum of DM1 severity extends from lethal effects in infancy to mild, late-onset symptoms. While DM1 commonly presents as an adult-onset multisystem degenerative disorder, it also may affect fetal development and postnatal growth in individuals who carry large expansions. The mix of developmental and degenerative features, and the patterns of multisystem involvement, are hugely variable between patients. Because the clinical heterogeneity is extreme, it is useful to subdivide DM1 into categories to provide a conceptual framework for pattern recognition and prognosis.

Congenital DM1 (CDM)

Around 15% of DM1-affected individuals have fetal-onset with involvement of muscle and the CNS.[29] CDM may occur with CTG expansions as small as 750 repeats, but more commonly it is caused by CTG expansions with more than 1,000 repeats. As described above, expansions in this size range are generated more frequently during oogenesis than spermatogenesis. The prenatal manifestations of CDM may include reduced fetal movement, polyhydramnios, and ultrasound findings of talipes equinovarus or borderline ventriculomegaly.[30] At birth the cardinal features are neonatal hypotonia and feeding or respiratory difficulty. A prospective study found that 79% of infants required nasogastric feeding and 53% required transient or prolonged ventilatory support.[31] The overall neonatal mortality was 18%. The possibility of CDM may be incorrectly dismissed when the family history is negative. However, it is important to note that more than half of the affected mothers do not carry a diagnosis of DM1 because their condition has gone unrecognized,[31] or has not generated any symptoms.[32] Later in childhood, individuals with CDM exhibit delayed motor milestones and a range of learning disabilities, including autism spectrum disorder.[29, 33] Oropharyngeal weakness is prominent, often producing a characteristic tented appearance of the upper lip, facial diplegia, marked dysarthria, and greater impairment of expressive than receptive communication. In the second or third decade, patients with CDM will develop the degenerative features of the disease, as described below under “classical DM1”.

Childhood DM1

Children with onset of DM1 after the first year but before age 10 often present with predominant cognitive and behavioral features that are not accompanied by conspicuous muscle disease.[33-35] Around half of these children have intellectual impairment (full scale IQ in the range of 50-70). A range of psychiatric symptoms may occur, including attention deficit disorder, anxiety, and mood disorder, but autism is uncommon.[34] Notably, the risk of childhood-onset DM1 appears similar with maternal or paternal transmission.

Classical DM1

Around 75% of patients develop symptoms in the second, third, or fourth decade. The most common initial symptom is myotonia. Similar to recessive generalized myotonia (RGM), the myotonia in DM is more pronounced after rest and improves with muscle activity, the “warm-up phenomenon”. In contrast to RGM, the action myotonia in DM1 selectively involves specific muscle groups of the forearm, hand, tongue, and jaw. The cardinal finding on examination is the myotonic myopathy, consisting of action and percussion myotonia, weakness, and muscle wasting in a characteristic distribution, with preferential involvement of cranial, trunk, and distal limb muscles. All cranial muscles are potentially affected, producing a characteristic appearance of ptosis, wasting of temporalis and masseter, and facial weakness. The neck flexors are affected early. Diaphragmatic weakness may occur before there is any weakness of the limb girdle muscles. Among limb muscles the long finger flexors and ankle dorsiflexors are preferentially affected. As symptoms progress, some patients continue to exhibit a strong distal to proximal gradient, whereas others

develop shoulder and hip girdle weakness at a much earlier time. Severe weakness of the ankle dorsi- and plantar-flexors often produces a flail ankle with marked instability of stance. In contrast to most other dystrophies, including DM2, DM1 causes obvious tongue weakness and often there is modest limitation of ocular motility.

Minimal DM1

Small CTG expansions (in the range of 70 to 100 repeat) are usually associated with mild weakness, myotonia, and cataracts that begin after age 40.

Neuromuscular features of DM2

Symptoms of DM2 usually begin in the second to sixth decade (median age 48 years).[15] For many patients the first symptom is grip myotonia. However, in others the myotonia is not apparent and the presentation resembles an indolent form of limb-girdle dystrophy. Although progression is slow, in some patients it seems to accelerate after age 50. DM2 selectively affects the limb girdle, neck flexor, and elbow extensor muscles. The long finger flexors are often affected, but to a lesser extent than in DM1, and other distal limb muscles are usually spared until later in the course. Compared to DM1, there is no congenital disease in DM2, and there is much less cranial and respiratory muscle weakness. Muscle wasting is less pronounced, and some patients exhibit hypertrophy of calf and thigh muscles, which on histologic examination is true hypertrophy with conspicuous enlargement of muscle fibers. Pain is a common feature which seems to be muscular in origin but not necessarily connected to myotonia. A prior diagnosis of fibromyalgia is relatively common.

Systemic features: Cardiac disease

The cardiac impact of DM1 falls mainly on the conduction system. Cardiac dysrhythmia, particularly heart block, is the second leading cause of death after respiratory failure.[36] In a prospective study the risk of sudden death in a clinic population was 1.1% per year.[37] 65% of patients show prolongation of the PR interval or QRS duration. The conduction defects are progressive, and may lead to severe bradycardia or asystole due to atrioventricular block. Atrial tachycardias (flutter, fibrillation, or sinus tachycardia) are relatively common, and risk of ventricular tachycardia is also elevated. While the cardiac contractility is relatively preserved, heart failure may occur at later ages. 10% of patients in a large study had clinical or echocardiographic evidence of left ventricular systolic dysfunction (LVSD).[38] LVSD was rare before age 40, but after this age the frequency steadily increased, reaching a high of 30% by age 70.

Few studies have examined the cardiac effects of DM2, but it is clear that conduction disease and heart failure may both occur. One study found that the frequency of conduction disease was lower in DM2 than in DM1, but LVSD was more common.[39] DM2 is also associated with higher risk of sudden death.[40]

Ocular

Cataracts before the age of 55, or family history of premature cataracts, suggests the diagnosis of DM1 or DM2 in patients with muscle symptoms. By direct ophthalmoscopy the cataracts of DM are nonspecific and appear as punctate opacities. By slit lamp examination they have a multicolored iridescent appearance and are located in the posterior lens capsule, findings that are highly suggestive of DM1 or DM2. Premature cataracts may also occur in mitochondrial, centronuclear, or myofibrillar (αB crystallin) myopathies.

CNS

The neuropsychiatric features of congenital and childhood-onset DM1 were discussed above. The CNS features of classical DM1 have been the subject of several recent reviews,[41, 42] and will be briefly summarized here. While the CNS features are highly variable between patients, DM1 is commonly associated with sleep disturbance, behavioral effects, and changes of cognition. The most common CNS symptom, effecting around 80% of patients, is daytime hypersomnolence. In some individuals this is coupled with a global disorganization of sleep habits and diurnal rhythm. Studies have shown sleep-onset REM in 26-54% of patients.[43-45] DM1 is also associated with a variable constellation of behavioral and cognitive changes, that may include anxiety, avoidant behavior, apathy, memory impairment, executive dysfunction, and problems with visuospatial processing (reviewed in references [41, 42]). Brain MRI scans may demonstrate extensive alterations of white matter signal intensity in both types of DM, especially in the frontal and temporal lobes.[46, 47] The underlying cellular or neuropathologic basis for this change has not been determined.

Other systemic features

1. Gastrointestinal symptoms are highly prevalent in DM1.[48] The frequency of cholelithiasis is increased, which may reflect involvement of smooth muscle in the gallbladder.[49] Intestinal dysmotility is common, producing symptoms of bowel urgency and diarrhea, often alternating with constipation. Whether these symptoms result from involvement of smooth muscle, enteric neurons, or both, has not been determined.
2. Epidemiologic studies have confirmed the clinical impression that DM1 is associated with higher risk of cancer, most notably involving the thyroid gland, ovary, colon, endometrium, brain, and eye (choriodal melanoma).[50-52]
3. Primary hypogonadism is common in men with DM1, and to a lesser extent in DM2. This may produce testicular atrophy, reduced fertility, erectile dysfunction, and low testosterone.[53]
4. DM1 is associated with metabolic derangements including insulin resistance, increased cholesterol, and hypertriglyceridemia.[54, 55]
5. Abnormal liver function tests are common in DM1 and DM2.[55, 56] Modest elevations of alanine and aspartate aminotransferase levels, gamma-glutamyltransferase, and alkaline phosphatase may occur. Generally these abnormalities are nonprogressive and do not require liver biopsy unless there is

corollary evidence of another disease process. It is unknown whether these changes represent a primary effect of DM on hepatocytes or a secondary consequence of metabolic derangements, biliary stasis, or fatty liver.

6. Balding can occur in men and women with DM1.

Laboratory and Electrophysiologic Testing

Genetic testing

Genetic testing for DM is definitive and cost effective. Except for rare examples of laboratory error, a negative genetic test excludes the diagnosis. Therefore, when clinical signs point to DM, no diagnostic evaluation other than genetic testing is necessary. Repeat-primed PCR is a low-cost method to determine whether an expanded repeat is present or absent, without measuring the size of the repeat tract. In most cases a Southern blot is still required to determine CTG or CCTG expansion size, but this may change as new PCR methods and sequencing technologies become available. Since DM1 and DM2 are distinguishable on clinical grounds, it is usually reasonable to test for one disorder or the other, as opposed to automatic testing for both.

Electrophysiology

The needle examination in DM1 is characterized by distal-predominant myotonic discharges, myopathic motor units, and early recruitment. The short exercise test shows a transient drop of CMAP amplitude in DM1,[57, 58] a finding that is qualitatively similar to RGM, and consistent with chloride channelopathy (see below). The distribution of myotonic discharges is less consistent in DM2. In some DM2 patients the EMG myotonia is altogether absent or confined to paraspinal or proximal muscles.[15, 59] Compared to DM1, a predominance of waning myotonic discharges occurs in DM2. Notably, the finding of electromyographic myotonia that is not accompanied by action or percussion myotonia may prompt a fruitless search for DM1 or DM2. Myotonic or high frequency discharges without clinical myotonia can be observed in late-onset Pompe's disease, centronuclear myopathies, several myofibrillar myopathies, and myopathies with inclusion bodies.[60]

Muscle pathology

Muscle biopsy was never a key diagnostic procedure for DM1, and now it is entirely superseded by genetic testing. If, however, muscle tissue is examined, the pathologist is likely to provide the correct diagnosis. There is no pathognomonic feature on conventional stains, but the constellation of dramatically increased central nuclei, ring fibers, pyknotic nuclear clumps, and selective atrophy of type 1 fibers is strongly suggestive of DM1. Compared to other dystrophies, muscle fiber necrosis and collagen deposition is less conspicuous in DM1, but fiber atrophy is more profound. DM2 shares many of the same findings, except that there is selective atrophy of type 2 fibers, and a population of fibers with marked hypertrophy.[61] As described below, both disorders exhibit nuclear inclusions of CUG/CCUG repeat RNA and MBNL protein.[62] These staining procedures are diagnostic of DM but have not been implemented in most laboratories, presumably because processing of DM samples is relatively uncommon.

Pathogenesis

RNA toxicity

The DM1 and DM2 gene discoveries were perplexing because *DMPK* and *ZNF9* have no obvious functional connections and the repeat expansions are located in genomic segments that do not encode proteins. The evidence now supports a unifying theory of RNA-mediated pathogenesis in which both disorders result from toxicity of repetitive RNA.[63, 64] DM1 has been examined in more detail but it appears that the disease process is broadly similar in DM2.

Sequestration of Muscleblind-like (MBNL) proteins

The expanded repeat in DM1 is located in the terminal part of the *DMPK* gene, close to the signal for polyadenylation. Even when highly expanded, the repeat sequence does not block the synthesis or processing of *DMPK* RNA . This results in production of a mutant mRNA that contains several thousand CUG repeats. These unusual transcripts are not exported to the cytoplasm, but instead are retained in the nucleus in discrete clumps or "foci".[65, 66] These collections of mutant RNA were not previously detected by conventional tinctorial or histochemical stains. They were first revealed by staining tissue with probes that hybridize to the repeat sequence. As expected, the foci are most conspicuous in cells with large expansions and high levels of *DMPK* expression: muscle fibers, smooth muscle cells, cardiomyoctes, and neurons.[67-69]

Proteins in the MBNL family bind to CUG repeat RNA with high affinity.[70] These proteins normally act to regulate splicing of several hundred transcripts.[71] They also have a role in regulating RNA transport and decay.[72] However, these functions are lost when MBNL proteins are trapped in nuclear foci of CUG repeats.[70, 73] This results in expression of many incorrect splice products and protein isoforms. For example, mis-splicing of the *ClC-1* chloride channel leads to reduced chloride conductance in muscle fibers,[74, 75] a physiologic state that is known to produce myotonia. Splicing defects of other transcripts, including insulin receptor, BIN1, dystrophin, and L-type calcium channels, are suspected to cause insulin resistance and myopathy.[21, 76-78] However, not all investigators agree that MBNL sequestration is an important determinant of DM disease.[79]

Signaling changes and aberrant translation of expanded repeats

Studies suggest that RNA toxicity also involves the activation of signaling pathways by mutant *DMPK* RNA.[80] The mechanisms for this effect are not clearly defined. It is possible that components of the innate immune system, that normally detect the intrusion of viral RNAs, are mistakenly activated by the RNA with expanded CUG repeats.[81] One downstream consequence is to induce phosphorylation and stabilization of another splicing factor, CUGBP1.[80] When CUGBP1 accumulates to high levels, it further aggravates the problem with splicing regulation.[82] Recent studies also show that expanded repeat RNAs may have unusual interactions with the protein synthesis machinery, which leads to translation of the repeat sequence even though it is not located in a conventional protein-coding region.[83] If this occurs *in vivo*, the repetitive peptides would be expected to have cellular toxicity.

Other effects

The transcripts from the mutant *DMPK* allele are retained in the nucleus and therefore they are not efficiently translated,[66] which leads to a partial (around 50%) reduction of DMPK protein.[84] Some studies suggest that CCTG expansions cause reduction of ZNF9 protein in DM2,[85-87] but there are conflicting data on this point.[88] While these effects may contribute to pathogenesis at some level, they do not appear to be major determinants of disease.

Pathophysiology of congenital DM1

A major unresolved question regarding DM1 relates to the pathophysiology of congenital disease. There is little information on this topic from studies of affected infants or animal models. In flies, muscleblind protein is required for normal muscle development.[89] In mice, combinatorial knockout of two MBNL proteins, MBNL1 and MBNL2, is lethal during prenatal development.[90] [Note that both of these proteins are sequestered by CUG repeat RNA.] Cell culture experiments have shown that expression of expanded CUG repeat RNA can interfere with myogenic differentiation.[91] Taken together, these observations are consistent with the concept that RNA toxicity, and possibly MBNL sequestration, may contribute to developmental phenotypes of DM1. However, if that is the case, it is unclear why congenital disease does not also occur in DM2, considering that CCUG repeats are similarly effective for sequestering MBNL proteins.

Therapy and Management

No treatments are currently available that fundamentally alter the course of DM1 or DM2. The management of DM is based on genetic counseling, preserving function and independence, preventing cardiopulmonary complications, and providing symptomatic treatment for myotonia, hypersomnolence, and pain.

In DM1 the combined effects of sleep disordered breathing, increased abdominal adipose, and weakness of the diaphragm and oropharyngeal muscles often lead to respiratory impairment and nocturnal hypoventilation. It is useful to monitor FVC and FEV1 changes from sitting to supine position at clinic visits.[92] The threshold for obtaining polysomnography in this population should be low. Many patients will progress to a point of requiring non-invasive nighttime ventilatory support.

Placement of a pacemaker or cardiac defibrillator can be lifesaving in DM1, but presently there is no consensus about indications for cardiac referral or device implantation. The ECG should be monitored annually. Holter monitoring is a useful adjunct to detect nocturnal bradycardia or other intermittent arrhythmias. One expert recommended annual echocardiograms,[93] although the utility of this before age 40 is unclear. The risk of sudden death in DM1 increases if the PR interval is above 240 ms, the QRS duration above 120 ms, or with atrial tachyarrhythmia.[37] It is reasonable, therefore, to refer patients with these findings for further cardiac evaluation. The size of the CTG repeat expansion is not particularly useful for stratifying risk, as it does not predict sudden death or LVSD.[38] Patients and family members should be educated that symptoms of palpitations, syncope, or near-syncope require prompt evaluation.

Case series and observational studies have suggested that daytime hypersomnolence in DM1 can be successfully managed with stimulant medications, such as methylphenidate.[94] Small therapeutic trials of modafinil have shown mixed results.[95, 96]

Anabolic agents were tested in DM1 in an effort to overcome the muscle wasting. However, despite some improvement of muscle mass with testosterone or recombinant insulin-like growth factor, consistent improvement of functional ability was not achieved.[97-99]

Improvement of myotonia has been reported in DM1 using various anticonvulsant or antiarrhythmic drugs.[100] A randomized placebo-controlled crossover study of mexiletine showed reduction of grip myotonia by up to 50% in DM1 patients after 7 weeks of treatment.[101] A study to assess safety and functional improvement with longer term treatment is currently underway (RT Moxley, personal communication).

Experimental treatments

Elucidation of disease mechanisms in DM1 and DM2 has led to the identification of novel targets for therapeutic intervention. In preclinical studies, evidence for engagement of these targets and therapeutic benefit has been obtained using several different approaches. Antisense oligonucleotides (ASOs), gene therapy vectors, and small molecules have been used to reduce the levels of toxic RNA.[102-105] Small molecules and ASOs have also been used to inhibit MBNL binding to CUG or CCUG repeat RNAs, or block the signaling pathways that lead to overexpression of CUGBP1.[106-109] Gene therapy vectors have been used to increase the expression of MBNL1 protein.[110] Taken together, these studies have suggested that DM-associated biochemical and physiologic defects are reversible in transgenic mouse models. Further chemical optimization and preclinical testing is necessary, but it seems possible that several of these therapeutic strategies may advance to clinical trials.

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-Myotonic dystrophy (dystrophia myotonica, DM) is one of the most common lethal monogenic disorders in populations of European descent.

-Myotonic dystrophy type 1 (DM1) was first described over a century ago.

-DM1 is caused by expansion of a CTG triplet repeat in the 3' non-coding region of *DMPK*, the gene encoding the DM protein kinase.

-More recently a second form of the disease, myotonic dystrophy type 2 (DM2) was recognized, which results from repeat expansion in a different gene.

-Both disorders have autosomal dominant inheritance and multisystem features, including myotonic myopathy, cataract, and cardiac conduction disease.