Myotonic Dystrophy

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KEYWORDS

• Myotonic dystrophy • Electrophysiology • Myopathy • Expanded DNA repeat

KEY POINTS

- 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′ noncoding region of *DMPK*, the gene encoding the DM protein kinase.
- More recently, a second form of the disease, myotonic dystrophy type 2, 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.

EPIDEMIOLOGY

A population-based screen to determine the genetic frequency of myotonic dystrophy (DM) is technically feasible but has not yet been performed on a large scale. The most ambitious screen to date showed a DM gene frequency of 1 in 1100 among Finnish blood donors, equally divided between myotonic dystrophy type 1 (DM1) and type 2 (DM2).[1] However, the 95% confidence intervals were broad (1 in 500 to 1 in 3700) because the sample size was small (n = 4520). 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 9400 was considered conservative because at-risk relatives were not systematically screened. Other DM1 prevalence estimates in Europe ranged from 1 in 8300 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 7400.[5] Studies of non-European populations

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indicated that 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 2 disorders is similar in northern Europe. This observation agrees with the genetic screening studies in Finland cited earlier.[1] In Europeans the DM2 expansion is only found 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 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, ranging from 5 to 37 repeats.[12] Individuals with DM1 have at least 50 and in some cases upwards of 3000 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 more than 1000 CCTG repeats, and the mean expansion size is around 5000 repeats.[15]

The clinical features of DM1 are shaped by 2 characteristics of the CTG expansion: (1) the expansion is highly unstable so that new alleles with different repeat sizes are frequently generated and (2) there is a bias for further expansion, rather than contraction, in the generation of 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 process 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 nondividing 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 2000 repeats by 20 years of age,[20] and in patients older than 40 years the average repeat length in skeletal muscle was greater than 4000 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 likely that the 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 to 70 repeats may have normal neurologic examinations even into the sixth decade.[23] Most commonly these individuals