Myotonic Dystrophy
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Myotonic Dystrophy is an autosomal-dominant inherited disease affecting individuals of all ages. It’s prevalence among Caucasians is estimated at 35 per 100,000 individuals in the population. (1) The age of onset allows for specific classification of the disease into one of four categories: congenital, which appears at birth; juvenile, appearing up through teenage years; adult, symptoms start in the late twenties to early forties; and late onset, where patients present after their forties. The severity of the disease has been found to be directly related to the age of onset, with congenital myotonic dystrophy being the most severe.

Genetics
Myotonic Dystrophy is caused by an expanded CTG trinucleotide repeat in the 3’ untranslated region of chromosome 19. The involved gene, named dystrophia myotonica-protein kinase (DMPK) has been mapped to the 19q13.3 locus. Although the exact function of the kinase is still unknown, we do know that it is a serine threonine protein kinase that plays an important regulatory role in muscle, heart and brain cells. (1) Unaffected individuals have only 5-35 CTG repeats in the gene whereas individuals with myotonic dystrophy range from 35-49 in the premutation state to greater than 2000 repeats in the most severe cases. (2) Repeats of greater than 35 have been shown to be very unstable and are very likely to expand during meiosis. Accordingly, this disease exhibits anticipation and has a tendency to increase in severity with successive generations and growing number of repeats. Because of the unstable nature of the repeats, myotonic dystrophy results in less than 100 percent penetrance in affected tissues. This type of somatic mosaicism makes establishing a correlation between repeat size and overall phenotypic severity more difficult.

There is a less common form of the disease, myotonic dystrophy 2, also called proximal myotonic myopathy, which has been traced to a 4 nucleotide repeat. The CCTG expansion has been mapped to chromosome 3q21 in the first intron of a gene encoding a zinc-finger protein called ZNF9. The number of repeats in extremely variable and ranges from 75 to over 10,000 and this mutation has been shown to display an even greater instability than the DM1 mutation. (1)

Homozygosity is not seen frequently with DM, although it does occur. Studies of patients who are homozygous for DM have usually shown that these people are either classically affected or only mildly affected. The failure of homozygosity to dramatically increase the disease phenotype puts DM in the category of true-dominant disorders (3).

Disease Risk for Other Family Members:
Owing to the fact that Myotonic Dystrophy’s penetrance is highly variable, many abnormal gene carriers are asymptomatic and may be unaware of their potential for passing the gene on to offspring. The majority of congenital cases of DM are transmitted by the mother; it is only very rarely transmitted by the father. The risk that a woman who is heterozygous for DM will have a congenitally affected child is 3%-9%. However, once one affected offspring has been born, the risk raises to 10%-41% for future offspring. Usually a woman who shows multisystem effects of the disorder at the time of
childbirth is considered at risk for having a congenitally affected child, but anecdotal cases of affected children born to asymptomatic parents show that more research needs to be done about how DM is inherited (4).

**Biochemistry and Molecular Biology:**

While it has been known that Myotonic Dystrophy 1 (DM 1) arises from a mutation in the Myotonic Dystrophy Protein Kinase (DMPK) gene and that Myotonic Dystrophy 2 (DM 2) develops from a mutation of the Zinc Finger Protein 9 (ZNF9) gene, the mechanism of disease has only recently begun to be elucidated (5). Although the simplest conclusion would be to infer haploinsufficiency of the affected genes, an article in the NEJM this October concluded that the molecular biology of the disease has nothing to do with abnormal gene products. Rather, RNAs transcribed by the genes have unusually long repeats of either CUG (DM 1) or CCUG (DM 2). The nucleotide repeats cause the RNA strands to develop abnormal hairpin folds. These misshaped RNA structures then accumulate within cell nuclei and interfere with the mechanism that allows splicing of pre-mRNA into mature messenger RNA (5). They can also disrupt RNA processing in the cytoplasm (6).

Pre-mRNA splicing, or alternative splicing, can be regulated by a variety of methods, though only one of them is involved in DM. Thirteen alternative splicing events are misregulated in patients with DM, all of which are normally developmentally regulated. With developmental regulation, varying splice sites allow different protein isoforms to be expressed at different stages in life. Patients with DM fail to express the adult splicing pattern in adult tissue but still express fetal isoforms. Problems result when at least two of these fetal protein isoforms are non-functional in adult tissue (6).

As of yet, the mechanism by which the mutated “hairpin RNAs” affect splicing regulation is unclear although a recent hypothesis is gaining credence and acceptance. It suggests that one or more of the regulators of alternative splicing are sequestered on repeat-containing RNA, which results in nuclear depletion and a loss of function of these regulators. Two families of regulators that will bind to CUG-repeats have been identified which makes them likely candidates for implication in DM. These are the CELF and MBNL families. It is thought that loss of function of one or both of these alternative splicing regulators occurs by the binding, and therefore sequestration, of the proteins to the CUG-rich sequences in the mutant hairpin-RNA. (6)

The RNA-binding proteins that regulate alternative splicing within the nuclei often also regulate splicing in the cytoplasm. Sequestration of CELF and MBNL within the nucleus would also explain why RNA processing is disrupted in the cytoplasm of cells of patients with DM.

**Diagnostic criteria**

The diagnostic tests required for accurate determination of myotonic dystrophy begin with a physical examination and the observation of muscle weakness, especially of the distal leg, hand, neck and face, and sustained muscle contraction specifically in the inability to let go of a hand once shaken. This can also be observed by tapping the thenar muscle with a reflex hammer. Cataracts may also be detected in a patient with myotonic dystrophy during slit lamp examination. However, many of the muscle tone based
observations can be difficult to determine due to pseudohypertrophy – the phenomenon of fat and connective tissue build up that may make the muscle appear larger.

Therefore, additional tests must also be done, namely electromyography and electrocardiography, where myotonic discharges are observed in affected adults, serum CK concentration, which will be mildly elevated, and a muscle biopsy, where pathological features will be observed. Molecular genetic testing may also be carried out to determine if the patient has a normal allele, a premutation allele or a full penetrance allele. This can be done with PCR and southern blot analysis. (2)

Prognosis

The short-term prognosis for individuals affected with myotonic dystrophy varies with the varying manifestations of the disease. This ranges from more severe mental retardation, respiratory and cardiac conduction abnormalities as well as muscle weakness and wasting and a characteristic “V” shaped upper lip in the most severe, congenital, form, to no mental retardation, and fewer respiratory problems and less muscle wasting in the less severe manifestations. A mild manifestation may only be cataracts, mild myotonia or diabetes mellitus. Myotonic facies are also commonly seen, resulting from weakness of the muscles of facial expression as well as the palpebral muscles. Problems with dexterity of the hands as well as smooth muscle of the intestinal tract can occur, leading to constipation or diarrhea, as well as a higher occurrence of gallstones. Hypersomnia and sleep apnea may also be manifest, as well as endocrinopathies. (7)

Long-term prognosis of patients affected with myotonic dystrophy varies as the disease itself does. Many individuals with myotonic dystrophy must use ankle-foot orthoses, wheelchairs or other devices for mobility. It may also affect using tools and household equipment such as doorknobs. Usually no mental retardation is manifest in patients who are affected by the less severe variation, and they are able to live a normal or only slightly shortened lifespan. However, those affected with the more severe variation have a lifespan that ranges between 48 and 55 years. The most severe form of myotonic dystrophy, the congenital form, has an average lifespan of 45 years. Personality traits such as obsessive-compulsive and passive-aggressive behavior have also been reported (2).

Women who have myotonic dystrophy are at higher risk for pregnancy complications, and fetuses that have congenital myotonic dystrophy are at a higher risk for polyhydramnios. Individuals with myotonic dystrophy will have to be monitored long-term by cardiologists for their cardiac conduction, and their hormone levels may need monitoring as well. Since they are at high risk for diabetes mellitus, testing for fasting serum glucose and glycosylated hemoglobin are generally repeated on a yearly basis.

The most frequent causes of death for myotonic dystrophy patients are pneumonia/respiratory failure, cardiovascular sudden death/arrhythmia and neoplasms. (7)

Possible Treatment

Until recently, no treatment for myotonic dystrophy existed, and only the individual symptoms were treated. However, new experimental research has shown that a possible treatment by increasing the activity of MBNL1 (muscleblind-like 1) and
decreasing the activity of CUG-BP1 (CUG-binding protein 1), both of which are RNA binding proteins, have reversed splicing defects in myotonic mice. This is accomplished through increased expression of MBNL. (However, over expression of MBNL can also have potential downsides, namely expressing MBNL that has only RNA binding capabilities without splice-regulating domains.) However, this treatment does not reverse the major skeletal muscle histological abnormalities. This treatment has the potential to reverse many other expansion disorders similar to myotonic dystrophy. (5)

The symptoms of myotonic dystrophy are generally treated on an individual basis. Muscle weakness associated with hypothyroidism and low cholesterol can be reversed with elimination of these factors. Pain management is generally accomplished through the combination of medications specific to each individual, though no specific combination has been shown to be effective routinely. These medications include mexilitene, gabapentin, non-steroidal anti-inflammatory drugs, low-dose thyroid replacement, low-dose steroids, and antidepressants, as well as low-dose analgesics. Cataracts may need to be removed, and physical therapy may be necessary if beneficial. (7)

References
7. Gene Reviews