GENETIC CAUSES OF MYOTONIC DYSTROPHY

Myotonic dystrophy (DM) was the first autosomal dominant disease found to be caused by a repeat expansion that is transcribed into RNA, but is not translated into protein. Transcriptions of the repeat expansion accumulate and, as toxic RNAs, disrupt the function of up to twenty other genes, causing the multiple symptoms of the disorder.

Although the two types of myotonic dystrophy present with similar symptoms, they have fundamentally different origins. The two forms (DM1 and DM2) are caused by distinct microsatellite expansions that occur in the non-coding regions of different genes. (The existence of other forms, caused by mutations at different sites, is currently being investigated.)

Causes of DM1

The genetic defect for this form of the disorder results in an expanded and unstable (CTG) trinucleotide repeat, localized to the 3’ untranslated region of the dystrophia myotonica-protein kinase (DMPK) gene on chromosome 19q13.3. Once there are more than 37 triplet repeats in the DMPK gene, the expanded sequence becomes unstable and slippage is more frequent. Disease symptoms are apparent in individuals once the CTG expansion exceeds 50 repeats. Disease severity roughly correlates with the number of repeats:

- Individuals with 5 to 37 repeats in the 3’ UTR region are unaffected.
- Individuals with 38-50 repeats are said to carry the pre-mutation. These individuals are asymptomatic and are unlikely ever to show symptoms. However, these repeats are unstable and very likely to expand during meiosis. As a result, such individuals are at risk of having affected children.
- Individuals with >50 repeats to 4000 repeats have myotonic dystrophy. These individuals are symptomatic or likely to develop symptoms in later life. A looser correlation is seen between the form of the disease and repeat count in these individuals:
  - 50 to 150 repeats are consistent with the mild adult-onset form of myotonic dystrophy.
  - 100 to 1000 repeats are consistent with the classic adult or childhood onset form of myotonic dystrophy.
  - 750 repeats or greater are consistent with the congenital form of myotonic dystrophy and often result in severe neonatal complications.
The figure below presents a visual explanation of the cause of DM1.

Causes of DM2

Also known as proximal myotonic myopathy (PROMM), this form is caused by an expanded and unstable (CCTG)n tetranucleotide repeat in the first intron of the zinc finger 9 (Znf9 also known as Cnbp) gene on chromosome 3. The repeat structure in DM2 is more complex than the triplet repeat seen in DM1.

- The normal repeat structure is approximately 10-20 repeats of a complex motif that is 104 to 176 nucleotides long ((TG)12-26(TCTG)7-12(CCTG)3-9(g/tCTG)0-4(CCTG)4-15).

- Individuals with 22-33 uninterrupted CCTG repeats are said to carry a pre-mutation. These individuals are asymptomatic and are unlikely ever to show symptoms. However, these repeats are unstable and very likely to expand during meiosis. As a result, such individuals are at risk of having affected children.

- Unaffected individuals typically have less than 75 repeats. Once the repeat number exceeds 75, the expanded sequence becomes unstable and slippage is more frequent. Affected individuals can have between 75 and 11,000 copies of the repeat sequence.

- The minimum pathogenic length of the expanded region appears to be 75 uninterrupted CCTG repeats. Repeat counts can increase to over 11,000 in affected individuals, with a mean repeat length of ~5000 repeats. The expanded region has been shown to display an even greater instability than the DM1 mutation.

- Unlike DM1, the length of the DM2 repeated DNA expansion does not appear to correlate significantly with the age of onset or severity of disease symptoms.
The figure below presents a visual explanation of the cause of DM2.

Other forms

Additional forms (DM3, DM4) have been suggested, as a small number of individuals have been seen who have the characteristic symptoms of myotonic dystrophy, but who do not have the genetic mutations which cause these disorders. Considerable debate exists as to whether these individuals truly represent a new form of myotonic dystrophy or whether they simply present unique diagnostic challenges.

Origins of DM

The mutation involved in DM1 does not arise spontaneously. It appears that all affected individuals share a common ancestor. With the exception of one sub-Saharan family, the presence of DM1 has been associated with a single haplotype within and flanking the DMPK gene. This suggests predisposition for CTG instability has resulted from a single mutation event, which occurred after the migration from Africa to Europe.

A second alternative exists, where predisposition to CTG instability is due to elements within the haplotype. Individuals who do not possess this specific set of genetic alleles would have a stable number of repeats and not develop the disease.