Anticipation

Because expansion of the CTG repeats commonly occurs during meiosis, the repeat count tends to increase over successive generations. As a result, children of affected individuals (including those with the pre-mutation) tend to experience more severe symptoms at an earlier age than their parent. This parent-to-child amplification of repeat count is termed anticipation.

The molecular cause of anticipation is based on the instability of long stretches of repeated nucleotide sequences. These repeats occur naturally, but are present in greater copy numbers in individuals with myotonic dystrophy. Once repeat counts reach a predictable threshold (>38 repeats for DM1 and >75 repeats in DM2), the sequences become highly unstable. The cellular machinery for DNA replication begins to slip across the expanded region, generating extra copies of the repeated sequence. The length changes caused by this slippage are relatively large, often with gains of 100 repeats or more.

These expansions occur in both somatic and germline tissues. Because the expanded repeats are particularly unstable in meiotic cells, slippage during gametogenesis is common. The resulting eggs or sperm have dramatically higher repeat counts than somatic parental cells. Repeat count tends to increase over successive generations as a result. Nearly all pedigrees show this progressive expansion, although decreases in copy number have been reported in rare cases.

The few reported decreases are due at least in part to the fact that the number of repeats changes, is different in different cells, and increases in number throughout the lifetime of the individual. Thus, the number of repeats reported in a diagnostic test will depend on how old the individual was when sampled, which tissue was tested and then will only measure the average number of repeats.

Symptomatic Consequences of Anticipation

- DM1. The repeat length shows a positive correlation with the severity of the disease. In addition, the number of repeats shows a negative correlation with the age of onset. As repeat counts increase over successive generations, the progeny tend to experience more severe symptoms at an earlier age. However, these correlations are not very precise, and it is not possible to accurately predict how severely and when an individual will be affected.

  Therefore, the use of pre-symptomatic testing in this disorder should be carefully considered. The size of repeat expansions (measured by the standard method) in white blood cells should not be considered predictive of the age of onset and severity of symptoms. New assays that can measure age-independent repeat expansions are required and are being developed.

- DM2. Repeat expansions tend to be more extensive than those seen in DM1. However, anticipation is less pronounced as repeat length does not correlate strongly with increased severity or earlier onset of disease symptoms. The degree of anticipation may be underestimated, however, as the extensive somatic mosaicism seen in DM2 patients confounds assessment of the phenomenon.

Maternal transmission of congenital DM1

Anticipation occurs differently in males and females. Extreme amplifications are seen during gametogenesis in females with DM1, elevating their risk of having a child with congenital DM1. These large increases in repeat count are only rarely seen in males. It is hypothesized that maternal imprinting plays a role in the difference seen, although minimal methylation evidence exists to support this conclusion.

As a result of this anticipation bias, newborns with the severe congenital form of myotonic dystrophy are almost always the offspring of affected mothers. Because the increase in repeat count can be dramatic, the mothers may be asymptomatic or have symptoms so mild that they are unaware they have the disease. In such cases, the child is often the index case in the extended family and other relatives may be subsequently identified as having the disease.