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Additive Influence of Maternal and Offspring DM-Kinase Gene CTG Repeat Lengths in the Genesis of Congenital Myotonic Dystrophy

To the Editor:

Myotonic dystrophy (DM) is an autosomal dominant multisystemic genetic disorder affecting ~1 in 8,000 individuals. The mutation consists of an unstable trinucleotide CTG repeat sequence in the 3′ UTR of a gene encoding a putative member of the serine-threonine protein kinase family (Brook at al. 1992; Fu et al. 1992; Mahadevan et al. 1992). The trinucleotide repeat sequence is amplified in DM individuals, the severity of the disease being positively correlated with the number of repeats. The congenital form of the disease (CDM) is more severe, with different phenotypic features, and is maternally inherited. The number of repeats seen in CDM is generally higher than that seen in non-CDM cases (Tsilfidis et al. 1992).

The intergenerational amplification of this repeat is influenced by the sex of the parent transmitting the mutant allele (Harley et al. 1993; Lavedan et al. 1993; Redman et al. 1993), in that, overall, a greater average intergenerational amplification (addition of CTG repeats) is seen on maternal transmission. Moreover, paternal transmission of DM demonstrates a higher frequency of reductions (loss of repeats) than does maternal transmission. As a result of these observations it has been proposed (Lavedan et al. 1993; Mulley et al. 1993) that the exclusive maternal origin of CDM derives from the parent-of-origin differences in behavior of the mutant allele when transmitted to the next generation.

Our analysis of the dynamics of the mutation in >300 transmissions (174 maternal and 127 paternal) indicates that this explanation is incomplete. We have found that, while a high number of repeats seems to be a necessary condition for CDM, this alone cannot explain its exclusive maternal inheritance. This is most clearly reflected in the fact that, in our study group, approximately one-quarter of DM cases inherited from affected fathers have repeat numbers equal to or greater than those found in the CDM cases with the lowest number of repeats (~700 repeats).

Furthermore, the following two significant correlations need to be considered: First, although only very few CDM cases had DM mothers with a very low number of CTG repeats, these CDM cases generally presented with a number of repeats in the upper end of the CDM range (fig. 1). Second, although mothers with a higher number of repeats tended to have a higher percentage of CDM offspring, the number of repeats in these offspring was, in general, at the lower end of the CDM cases (fig. 1).

These two observations, together with previous studies on maternal phenotypes of CDM offspring (Koch et al. 1991), suggest that CDM arises from an "additive" pathology comprising both maternal and offspring components; it may be that CDM is the result of metabolic disturbances of a DM mother on a developing DM fetus with a sufficiently high number of CTG repeats. The DM mother must make some contribution to the phenotype of the CDM fetus, in addition to having

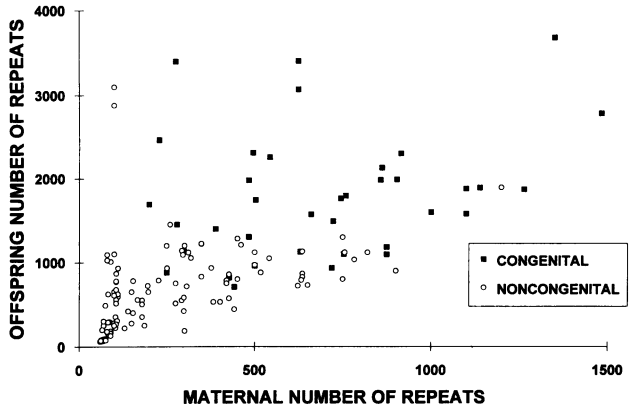

Figure 1 Relationship between maternal and offspring number of repeats and CDM.

transmitted a large mutant allele—since DM fathers can transmit large alleles without giving rise to CDM.

The data that we are presenting are based on the mutation status found in peripheral lymphocytes. Since there is tissue heterogeneity for this mutation (Anvret et al. 1993), tests done on different tissues may have shown a slightly different pattern. Nevertheless, we believe that, because tissue differences are correlated, no patterns radically different from the one seen in figure 1 would emerge. An understanding of the maternal inheritance of CDM may have to await further delineation of the mutation status in other tissues, such as uterus and placenta, that are relevant to fetal development.

We do not yet have an explanation for the exclusive maternal inheritance of CDM, and we do not expect that it will be a simple one. The explanation may be found when the pathophysiology of the disease is better understood in terms of gene expression and metabolic pathways associated with the adult form of DM and CDM.

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