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# Repeats revisited

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Cathy Holding
**Email**: cholding@hgmp.mrc.ac.uk

The mechanisms by which triplet repeat expansions cause the neurological and muscular defects seen in diseases such as myotonic dystrophy (DM) or fragile X syndrome have been unclear. In the December 12 Science, Rahul N. Kanadia and colleagues at the University of Florida College of Medicine report a hypothesis to explain the occurrence of triplet repeat expansions in different genomic regions - producing two different transcripts, DM1 and DM2 - that result in the same disease. In addition, the authors describe the accumulation of mutant transcripts in muscle nuclei together with proteins in the muscleblind-like (MBNL) family and suggest that normal Mbnl1 binds abnormally to triplet-expanded DM transcripts, interfering with highly specific aspects of pre-mRNA splicing (*Science* 2003, **302:**1978-1980).

Kanadia *et al*. generated mice homozygous for Mbnl1 deleted for exon 3, previously shown to be required for binding CUG triplet repeats, which developed overt myotonia around 6 weeks of age. Previous observations that skeletal muscle chloride (ClC-1) channel transcripts are aberrantly spliced in transgenic mice exhibiting a DM-like phenotype were examined in the Mbnl1-mutant mice, which also showed abnormal splice variants. Another transcript, fast skeletal muscle troponin, Tnnt2, was also found to be aberrantly spliced.

"These studies confirm a key prediction of the MBNL protein sequestration hypothesis for DM pathogenesis... Although muscleblind-like proteins may influence gene expression at multiple levels, our results raise the possibility that these proteins play a direct role in splice site selection," conclude the authors.

# References

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