

## Abstract 77

### DIFFERENT SIDES OF THE SAME COIN? REPEAT EXPANSION AND CHROMOSOME FRAGILITY IN FRAGILE X SYNDROME.

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Increasing numbers of CCG•CCG-repeats in the *FMR1* gene are associated with an increased propensity of the repeat to undergo further expansion. In humans, small expansions predominate when the repeat number is relatively small and these expansions have a paternal bias. In contrast, large expansions occur exclusively from larger premutation alleles and only when they are maternally transmitted. The resulting alleles are responsible for Fragile X syndrome. Increasing repeat numbers are also associated with the increased expression of the folate-sensitive fragile site that is coincident with the expanded repeat on the X chromosome. Using a Fragile X premutation mouse model we have generated, we have shown that there are at least 2 types of repeat expansion in these animals, one that occurs in both males and females, but more frequently in males, and a second that occurs exclusively when the premutation allele is maternally transmitted. We have shown that a deficiency of the Ataxia telangiectasia mutated (ATM) kinase that is involved in the cellular response to DNA damage, increases the frequency of expansions with a paternal bias. In contrast, a deficiency in the related kinase, Ataxia telangiectasia and rad3 related (ATR), increases the incidence of the maternal-specific expansions. Other experiments provide clues as to the molecular mechanisms responsible and suggest environmental factors that may affect expansion risk. ATM and ATR deficiencies also affect the incidence of chromosome fragility in cells from individuals with Fragile X syndrome. This suggests that parallels may exist between the mechanisms responsible for repeat expansion and chromosome fragility.