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EVALUATING THE CONTRIBUTION OF X-CHROMOSOME MUTATIONS TO MENTAL RETARDATION BASED ON THE PATTERN OF X INACTIVATION IN MOTHERS OF AFFECTED BOYS

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In normal women carrying X-linked mutations significant deviations from the expected 50:50 random pattern of X inactivation have been documented. About 30% of obligate carriers of mutations causing X-linked mental retardation have been reported to have X-inactivation skewing $\geq 90:10$ in peripheral blood cells, compared to about 2% of their non-carrier relatives. (Plenge et al. 2002; Am J Hum Genet 71:168). Selective advantage of cells with the non-mutated allele on the active X chromosome would explain this skewing. We used the pattern of X-inactivation in mothers of mentally retarded boys as a parameter to evaluate the frequency of mental retardation caused by mutations on the X chromosome, among isolated cases. We selected 85 boys with mental retardation of unknown cause, who had normal karyotypes and tested negative for fragile X syndrome; their mothers were heterozygous for the polymorphic CAG repeat of the *AR* gene. To determine the X-inactivation pattern in these women, we investigated the methylation status of the *AR* alleles in blood cells. Eleven women (12.9%) had completely skewed X-inactivation (100:0), a frequency highly above that reported for women in the general population (~2%). Assuming that every mother with completely skewed X-inactivation is a carrier of an X-chromosome mutation causative of mental retardation in her son, the frequency of X-linked mental retardation in our sample of 85 boys is 12.9% (CI 95% = 6.6%-22.0%), the fragile X syndrome being excluded. Although these figures are quite in agreement with previous estimations of the frequency of X-linked mental retardation, they might be an underestimation, considering the observation that only 30% of obligate carriers of mutations causing X-linked mental retardation in males have highly skewed X inactivation.

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