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NO EVIDENCE FOR SKEWED X-CHROMOSOME INACTIVATION IN FRAGILE X SYNDROME PREMUTATION CARRIERS

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It has been estimated that 20% of female premutation carriers present premature ovarian insufficiency (POI), which occurs in only 1% of the general population. The association between FMR1 premutation and POI has been widely studied. Many factors such as the repeat tract size, the sequence organization of the CGG repeat tract, the parental origin of the premutation, and the FMR1 mRNA levels have been examined. X-chromosome inactivation has also been studied as a risk factor, but the reported results are inconclusive. Although some authors have not found an association with the POI manifestation, others suggest that the severity of FMR1 premutation-associated phenotypes may be related to this X-inactivation ratio. To evaluate the significance of skewed X-inactivation patterns among female premutated carriers, we examined and compared the X-inactivation ratios of 220 female samples from the general population and 220 female premutation carriers phenotypically unaffected and 40 premutation carriers affected by POI. The results show the incidence of skewed XCI (90:10) to be 9.5% in controls, 10.5% in phenotypically unaffected premutation carriers and 7.5% in premutation carriers affected by POI. These results failed to show a direct effect of X-inactivation in the manifestation of POI among FMR1 premutation carriers. However, a negative correlation has been found between X-chromosome inactivation and low-medium CGG repeat size alleles. The manifestation of POI cannot be merely explained by the X-chromosome inactivation patterns; however, we speculate it may contribute to POI together with other genetic factors.

Acknowledgements: Marató TV3 (U-2006-TV060810-0)