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THE ORIGIN OF TRISOMY 21 IN THE OFFSPRING OF *FMR1* PREMUTATION CARRIERS

Juliana F. Mazzeu^{1,2}, Adriano Bonaldi², Valter Della-Rosa³; Angela M. Vianna-Morgante²

¹Departamento de Genética e Morfologia, Universidade de Brasília, Brasília, Brasil;

²Departamento de Genética e Biologia Evolutiva, Universidade de São Paulo, São Paulo, Brasil; ³Departamento de Biologia Celular e Genética, Universidade Estadual de Maringá, Maringá, Brasil.

Down syndrome is the most common cause of mental retardation and more than 95% of the cases are caused by nondisjunction of chromosome 21. The additional chromosome is maternal in approximately 90% of the affected individuals, and 70% of these errors occur at maternal meiosis I. The second most frequent cause of mental retardation is the fragile X syndrome. A few instances of concurrence of the two syndromes have been reported, all girls with predominant physical signs of Down syndrome, the mental retardation being severe to profound. We ascertained three girls with trisomy 21 and *FMR1* full mutations in unrelated fragile X families, and investigated the origin of the extra chromosome 21. Microsatellite loci mapped throughout chromosome 21 were genotyped in the patients and their parents. In one case, the 30-year-old mother carried a full mutation, and the non-disjunction could be ascribed to maternal meiosis I or II, as the most centromeric markers were not informative. In the other two cases, maternal ages at conception were 26 and 30 years, and both mothers carried *FMR1* premutations. We did not identify any recombination event and this reduction to parental homozygosity along the chromosomes that underwent non-disjunction suggested a mitotic error. Although the number of investigated patients is too small, it is an unexpected finding, since mitotic non-disjunction is estimated to account for only 5% of all chromosome 21 trisomies. However, in these two cases, we cannot rule out meiotic II non-disjunction in the absence of crossing over in meiosis I, in either parent, which is also an uncommon event. Chromosomal disjunction is affected by ovarian ageing, a condition that is premature in premutation carriers, and thus could make them prone to meiotic non-disjunction at an early age. In the past, anecdotal findings suggested that aneuploidy could be more frequent than expected in the offspring of female carriers, and at least one study in the 1980s (Watson et al, Am J Med Genet 1988;30:115) showed that the rate of Down syndrome was significantly higher among the children of carriers. This possibility deserves further investigation, as well as the non-disjunction mechanisms originating aneuploidy in the offspring of carriers.

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