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FRAGILE X SYNDROME MOSAIC CASES PRESENTING NORMAL-SIZED ALLELES: HOW MANY ARE WE MISSING?

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Fragile X syndrome (FXS) is the most common form of inherited intellectual disability. It is caused by an expansion of a CGG repeat in the 5'UTR region of the *FMR1* gene that expands to over 200 triplets. In typical FXS cases, silencing of the *FMR1* gene due to methylation of its promoter precludes protein expression. Loss of the FMR1 protein leads to the physical, neurocognitive and behavioural FXS features. Somatic mosaics in the FMR1 locus are uncommon and can be due either to the presence of alleles with various CGG repeat sizes or epigenetic differences in the extent of methylation. Mosaicism for more than two alleles is a particularly rare finding, although it has been previously described. These phenomena hamper prediction of the disease prognosis.

Herein, we report four cases of unrelated males with a phenotype compatible with FXS who show atypical mosaic patterns for CGG repeat number; three are mosaic for a full mutation/normal allele and the fourth for a full mutation/ premutation/normal allele. In all cases, the mothers were carriers of a premutation. A methylation-based PCR methodology enabled the characterization of these four cases and respective maternal alleles that led us to propose a hypothesis for the origin of these normal sized alleles in mosaic cases. According to our experience methylation mosaics in the *FMR1* locus are not uncommon, particularly premutation/full mutation. On the other hand, normal/mutated size-mosaics are either very rare or are missed in routine PCR based methodologies. In light of the implications for FXS diagnosis, we propose that complementary technical approaches be used in cases with a highly suggestive phenotype.

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15Q13.3 DELETION SYNDROME: A CASE REPORT

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The 15q13.3 deletion syndrome was first described in 2008 and is characterized by intellectual disability, seizures, autism spectrum disorders and behavioural problems, among others. The microdeletions typically involve loss of 1.5 to 2 Mb in the region 15q13.2q13.3, which contain seven genes. Although recent studies indicate that the *CHRNA7* gene is responsible for the neurodevelopmental phenotype, it is not yet entirely clear what or which genes are responsible for the characteristic features of the syndrome.

We report a case of a child with a microdeletion on 15q13.3 chromosome region detected by array Comparative Genomic Hybridization (aCGH). A deletion of 494Kbp segment was found, involving the *CHRNA7* gene. The child has moderate cognitive impairment, hyperactivity, impulsive behaviour and minor dysmorphic features (down-slating palpebral fissures, prominent nasal tip, large ears, short neck and pigmented naevi in the nuchae).

In the present case, the features described are consistent with phenotypic 15q13.3 deletion syndrome, like moderate cognitive disability, hyperactivity and impulsive behaviour, corroborate the recently proposed for *CHRNA7* gene.

Every new case of a rare chromosomal alteration should be reported in order to obtain a more precise genotype/ phenotype correlation, improving risk evaluation and genetic counselling.