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The tip of the iceberg: what is hidden under the fragile X

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The case report published in this issue by Floriani *et al.* (2017)⁽¹⁾, describing a fragile X syndrome (FXS) unexpectedly detected by G-banding karyotype (G-bands after trypsin and Giemsa), seems like the view of the tip of the iceberg.

The karyotype was the only available diagnostic test until 1990, when the *FMR1* gene located at Xq27.3 was described. The deoxyribonucleic acid (DNA) test replaced the karyotype and became the gold standard as it detects more the 99% of cases.

Fragile X is a constriction, gap or break detected on metaphase chromosome obtained from cultures with acid folic depleted medium. Probably the methotrexate, an anti-folate drug, used to obtain high-resolution chromosomes explains the fragile site fortuitous detection in this case. The aberration was then confirmed with appropriate medium culture, allowing the diagnosis.

Diagnosis with a preliminary test like karyotype means a shortcut and the reduction of costs with additional tests besides the early reference of the family to genetic counselling. However, the molecular test must still be performed in the mother.

In fact, FXS is the most common inherited genetic syndrome causing mental retardation and autism spectrum in boys. Its prevalence in males is around 1:4000 and in females up to 1:6000. The higher frequency in males is because all men with the *FMR1* gene full mutation will present the disease, while some females will not have the physical, behavioral and cognitive features.

The genetic cause is a mutation of the *FMR1* gene: a trinucleotide repeat expansion [cytosine-guanine-guanine (CGG), or triplets] to more than 200 repeats [detected by polymerase chain reaction (PCR)] and abnormal methylation. The hypermethylation (detected by Southern blot test) silences the fragile X mental retardation protein (FMRP) synthesis.

In normal individuals, the triplets are between 6 and 45. However, when an allele size from 55 to 200 is detected, it is named premutation. Females with premutation are at risk of having children (male and female) with FXS according to the size of the triplets: the larger the number, the higher the risk of expansion to full mutation.

Premutation are unmethylated, so male with premutation do not present FXS, but suffer a neurodegenerative disorder: the fragile X tremor ataxia syndrome (FXTAS), manifested later in life. Around 25% of female with premutation present primary ovarian failure (POF) (menopause before 40 years) and present infertility (FXPOI).

Besides that, around 2% of the individuals present an intermediate allele size or grey area with 45-54 repeats that do not cause disease. Intermediate allele may rarely expand to premutation in future generation.

Therefore, the genetic counselling of the family is of fundamental importance in order to avoid new cases, to orient the female relatives about infertility or early menopause, to detect adult neurological symptoms of FXTAS and to detect male and female relatives with developmental, cognitive and learning disabilities.

Moreover, a FXS child is eligible for special education including speech and language, behavior and cognition, among others.

Fortunately, the karyotype provided the view of tip of the iceberg, now its size and move require to be monitored by additional medical attention.

REFERENCES

1. Floriani MA, Vilas Boas MR, Rosa RFM, et al. Report of a patient with fragile X syndrome unexpected identified by karyotype analysis. J Bras Patol Med Lab. 2017; 53(2): 108-9.