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FMR1 ASSOCIATED PATHOLOGIES

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Fragile X syndrome is the most common form of inherited mental retardation with a prevalence of approximately 1:2,466 men and 1:8,333 women in the Caucasian population. The molecular basis of the syndrome is predominantly a CGG expansion in the 5'- untranslated region of the *FMR1* gene. In the general population, individuals carry 6 to 55 repeats, and the triplet number is usually stably transmitted. Individuals with alleles between 55 and 200 CGG repeats are called premutated carriers and those with more than 200 CGG are considered to carry full mutations and present classical Fragile X syndrome. In the premutated range, the CGG number is unstable through transmission to the next generation and tends to expand. Diagnosis is based on the determination of the CGG number. *FMR1* premutation is much more frequent than previously thought. The most relevant pathologies associated with premutation have been described to be Fragile X premature ovarian insufficiency (FXPOI) and Fragile X tremor ataxia syndrome (FXTAS). Other clinical manifestations, associated with this premutation, were later identified as thyroid dysfunction, chronic muscle pain or fibromyalgia, among others. While FXPOI and FXTAS are definitively related, the latter manifestations require further studies. Here we revise the current knowledge of the individuals carrying *FMR1* premutation.

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GENETIC COUNSELING

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Genetic counseling is the process by which patients or relatives at risk of an inherited disorder are advised of the nature and consequences of the disorder, the probability of developing or transmitting it, and the options open to them in management and family planning.

This complex process can be separated into diagnostic and supportive aspects.

Establishing a correct diagnosis is crucial, otherwise erroneous information will likely be given with potentially tragic consequences. Reaching a diagnosis involves three fundamental steps: taking a history, carrying out an examination and undertaking appropriate complementary investigations.

An etiological diagnosis allows precise risk estimation. Sometimes, even in the absence of a molecular diagnosis, a pattern of Mendelian inheritance may be clear from the family tree allowing the calculation of a recurrence risk. However, in many instances it is not possible to arrive to an accurate diagnosis and it is necessary to resort to empiric risks, derived from family studies rather than theoretical calculations. In all cases, recurrence risks should not only be quantified but need also to be qualified and placed in context.

The supportive aspects of the counseling process involve both communication and educational skills. Only an appropriately trained professional can help the individual or the family gain enough knowledge of the disorder and the options available for risk management to allow fully informed decisions without undue pressure or stress, in a way that promotes health, minimizes psychological distress and increases personal control.

These concepts will be illustrated with relevant clinical examples.