

Premature ovarian insufficiency caused by *FMR1* premutations may be underdiagnosed

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The *FMR1* gene [Xq27.3; MIM*309550] has an unstable region comprised of CGG triplets located the 5' untranslated region. Based on the number of those repeats alleles are classified as normal, intermediate, premutation or full mutation, respectively from triplet numbers between 5 to 49, 50 to 58, 59-200 or over 200 CGG triplets. Full mutation-size expansions are associated with the fragile X phenotype. The Fragile X Syndrome [FXS; MIM#300624] is the most common cause of inherited intellectual disability. In contrast, Premutation carriers do not have manifestations of FXS in cognitive deficits, but are at increased risk for development of the "Fragile X-associated disorders". Examples are the Fragile X tremor ataxia syndrome [FXTAS; MIM#300623] and Fragile X Primary Ovarian Insufficiency [FXPOI; MIM#311360] (Figure 1).

The FXTAS affects predominantly older males and includes gait ataxia, intention tremor and cognitive impairment, FXPOI affects approximately 20% of females with *FMR1* premutations and is characterized by onset of menopause before age 40. Interestingly, the repeat size alleles that have the highest risk of developing FXPOI are in the range of 80-99 CGGs and result in a reduction of 7 years in the menopause appearance. Studies show that women who have idiopathic POI have a 1/50 chance of being a *FMR1* carrier, whereas affected women with a family history of POI, have a 1/15 chance of carrying this premutation ^[1, 2, 3].

In this work we present the transmission of the *FMR1* allele within a family, where an early menopause was clinically diagnosed. Both the index female and her sister were found to have a *FMR1*-CGG number within the premutation range. Additionally, one of the premutation carriers was pregnant and consequently prenatal diagnosis for FXS was performed.