Study of triple CGG repeats (FMR1 gene) in 157 patients with ovarian failure of unknown origin

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INTRODUCTION:

OBJECTIVES:

The aims of this work were: 1) to determine the frequency of PM and intermediate alleles in our population of women with different types of ovarian failure. 2) to study possible correlations between POI and the number of CGGs and AGGs and their transmissions.

RESULTS (See Table 1):

• Nine (5.73%) of the 157 women studied had FMR1 alleles >44 repeats; five of them (3.18%) with PM and four (2.55%) with intermediate alleles.
• All the PM women had less than 100 repeats.
• Only the PM woman with 98 repeats had her allele entirely composed of CGG repeats, whereas the other eight women showed one or two AGG interruptions.
• No changes were found in the number of AGGs in 3 transmissions studied (Figure 1).
• We found no association between FXPOI manifestation and the number of repeats. In two families in which we studied three women in each, with similar number of repeats, some manifested FXPOI and others (not Figure 2). No differences were found between the presence of FXPOI and the carrier parents.
• It is also interesting to note from the clinical point of view, that three of the women with PM (84, 86 and 98 CGGs) experienced a very early menopause (at 28, 28 and 21 years respectively). The other two women with PM (64 and 56 CGG repeats) had a poor response to ovarian hormone stimulation (Table 1).

CONCLUSIONS:

Intermediate/Premutated alleles in the FMR1 gene are the most frequent genetic cause of any type of ovarian failure and therefore we recommend FMR1-testing in all women with infertility and cessation of menstrual cycles specially if they are doing fertility treatments.
• As we reported before (3,4), having less than 100 repeats represents a significant risk for FXPOI, being the biggest risk for this pathology between 80-100 repeats (1).
• Our results don’t agree with those of other authors (2), because our patients have AGG interruptions, except for the case with 98 repeats.
• Finally, as we have found no association inside the families between ovarian failure and the number of repeats in PM women, nor with the parent’ carriers, we have demonstrated once again (3,4) that other physiologically causes must be at the origin of this pathology.

PATIENTS:

• We studied 157 women with primary ovarian failure (POF), without family history of Intellectual Disability (ID). 67 of them experienced early menopause (EM) and the others still don’t. Among them, 43 were low responders (LR) to ovarian hormone stimulation and the remaining 47 were studied because of primary or secondary infertility. The median age at menopause for the EM group was 34.1. All participants were informed regarding the purpose of the study and signed the written informed consent.

METHODS:

Determination of number of triple CGG repeats and number of AGG interruptions on both alleles of FMR1 gene were analysed on DNA from patients using a commercial triplet CGG assay (AmplideX FMR1 PCR kit from Asuragen), following the manufacturer’s protocols.

Figure 1: CGG repeats and AGG interruptions (fluorescent PCR with Asuragen assay): A) Mother with 64/30 CGG repeats (Patient 8502). Red arrow indicates that PM allele has one AGG; normal allele has two (blue arrows); B) Her sister has the same number of repeats, one AGG. Red arrow indicates the position of this AGG interruption:

Table 1: The nine patients with FMR1 alleles >44 repeats, five of them (in red) with PM and four (in orange) with intermediate alleles. This table shows some clinical details, CGG repeats, AGG interruptions on the parents that are carriers. Nk = Not known. Other initials are in the text.

REFERENCES:


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