Journées Klotz

Premature ovarian failure and \textit{FMR1} gene mutations: An update

\textit{Insuffisance ovarienne prématuérée et mutations du gène \textit{FMR1}: avancées récentes}

G.S. Conway

\textit{Institute for Women's Health, UCLH NHS Foundation Trust, 250, Easton Road, London NW1 2PQ, United Kingdom}

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Résumé

La recherche de prémutations exposant au risque de syndrome de l’X fragile est recommandée en routine chez toutes les femmes présentant une insuffisance ovarienne prématuérée (IOP). En effet, ces femmes avec IOP ont quand même une chance de conception de 5\% et cette possibilité est encore accrue dans les prémutations FRAXA. Les femmes doivent savoir si elles sont à risque de donner naissance à un enfant porteur du syndrome de l’X fragile. De plus, l’identification d’une famille au sein de laquelle le site de répétition de l’X fragile est amplifié peut conduire à la reconnaissance d’autres femmes de la famille à risque de transmettre ce syndrome de l’X fragile. L’identification d’un cas index doit donc déclencher un conseil génétique de toute la famille en fonction du souhait de ses membres.

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Mots clés : Prémutations de l’X fragile ; Insuffisance ovarienne prématuérée ; Prémutation FRAXA

Abstract

Screening for fragile X premutations is recommended for the routine work-up for any woman presenting with premature ovarian failure (POF). The reason for this is that women with POF have an approximate 5\% chance of conceiving and this possibility may be increased further in the FRAXA premutation subgroup. Women need to be informed if they are at risk of having a child with fragile X syndrome. In addition, the identification of a family in which the fragile X repeat site is expanded can lead to the identification of other female family members at risk of transmitting fragile X syndrome. The identification of an index case should therefore trigger genetic counseling throughout the pedigree according to the wishes of the family.

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Keywords: Fragile X premutations; Premature ovarian failure; FRAXA premutation

1. Introduction

Ever since the first report of an association between fragile X syndrome and ovarian failure in three pedigrees \cite{1}, evidence has grown to strengthen the connection using large cohorts from several countries. Fragile X syndrome (FRAXA) screening has become the single most informative marker for premature ovarian failure (POF), yet the pathogenic mechanism has so far eluded precise definition.

E-mail address: g.conway@ucl.ac.uk.

2. Molecular genetics of the FRAXA site on the X chromosome

The gene for fragile X syndrome (\textit{FMR1}) is located at locus Xq27.3. The syndrome is one of a group of conditions that is caused by expansion of a trinucleotide repeat that is located in the untranslated first exon of the gene \cite{2}. In a normal situation, a few are then 55 repeats of a CGG sequence occurred in this exon and the protein is transcribed in a normal fashion. Fragile X syndrome occurs when the repeat sequence occurs more than 200 times forming the full mutation which results in hypermethylation and failure of transcription so that no \textit{FMR1} mRNA is generated \cite{2,3}.
An intermediate number of repeats varying between 55 and 200 are designated a “premutation” and in this instance gene transcription is thought to be normal. Interestingly, ovarian failure is associated only with the premutation and not with trinucleotide repeat numbers less than 55 or greater than 200.

Over generations, the number of repeats of the CGG sequence can increase so that women are carrying at the premutation may well have children with repeat numbers greater than 200 therefore have the full mutation and fragile X syndrome. This increase in risk for fragile X syndrome with each generation is known as “anticipation”.

3. Fragile X syndrome and other related clinical conditions

Fragile X syndrome is the most common cause of inherited mental impairment occurring in 1:4000 males [4]. The clinical profile is variable comprising autistic behaviour patterns, delayed development of speech and language and characteristic physical features including prominent ears, a long face and forehead with high arched palate and macroorchidism (enlarged testes) in men [5,6].

Females generally have a lesser phenotype because of X chromosome inactivation and the full syndrome is estimated to occur in 1:8000 women. Males who carry the premutation are prone to develop tremor and ataxia over the age of 50 – fragile X associated tremor/ataxia syndrome (FXTAS) [7] again with women exhibiting a lesser form. Women with a premutation, however, have an increased risk of developing ovarian failure as outlined below.

The protein encoded by the FMR1 gene is designated the fragile X mental retardation protein (FMRP). FMRP is an RNA binding protein that acts to suppress translation of messenger RNA within the brain [8]. The protein is found in association with ribosomes which translate the genetic message to protein and it moves between the cytoplasm and the nucleus within neurons. A lack of FMRP is thought to lead to an accumulation of mRNA particularly within dendrites which in turn leads to impaired development of neural circuits. The FMR1 is also expressed within the ovary where less is known about its function [9].

4. FRAXA premutation and premature ovarian failure

The association between fragile X premutations and ovarian failure was first recognised in families where boys with fragile X syndrome was born in a generation after women with POF [1]. Subsequent screening confirmed to the association in both sporadic and familial forms of POF [10–14]. In women without a positive family history for ovarian failure, the premutation has been identified in 0.8 to 7.5%. In women with a positive family history for ovarian failure, up to 13% are carriers of the FRAXA premutation [10]. Compared to other markers for ovarian failure, this genetic test has the highest pickup rate [15].

Women who present with ovarian failure and who are found to have a FRAXA premutation frequently have relatively well-preserved ovarian function [16] as determined by normal or only modestly reduced ovarian volume as measured by ultrasound with active ovarian follicles commonly identified. A return of ovarian function and a random ovulation is therefore a sufficiently common event to make genetic screening and important procedure for women of childbearing age. Several women with ovarian failure have been reported to give birth to boys with fragile X syndrome some years later [17].

5. Ovarian function in FRAXA premutation carriers

From collections of individuals with fragile X syndrome, it has been possible to study ovarian function in female relatives carrying fragile X premutations [18]. Impaired ovarian function as determined by raised FSH or reduced inhibin B or antimullerian hormone concentrations is commonly found in female premutation carriers [19–21]. In addition, menopause occurs approximately 5 years earlier than average in this group of women [22].

There is some disagreement as to whether trinucleotide repeat numbers towards the lower end of the premutation range or even into the normal range also have impaired ovarian function. There seems to be no difference in the risk of ovarian failure depending on whether the premutation is inherited from the father or mother [23]. In addition, skewed X inactivation does not appear to have an effect on the ovarian phenotype [24].

6. Implications for genetic screening

Screening for fragile X premutations is recommended for the routine work-up for any woman presenting with POF [25]. The reason for this is that women with POF have an approximate 5% chance of conceiving and this possibility may be increased further in the FRAXA premutation subgroup. Women need to be informed if they are at risk of having a child with fragile X syndrome. In addition, the identification of a family in which the fragile X repeat site is expanded can lead to the identification of other female family members at risk of transmitting fragile X syndrome.

The identification of an index case should therefore trigger genetic counseling throughout the pedigree according to the wishes of the family.

Conflict of interest

The author has not declared any conflict of interest.

References