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Mini Review

The Role of Mutations on Gene FMR1 in Fragile X-Associated Primary Ovarian Insufficiency Syndrome

Narjes Arshia, Zahra Gholizadeh, Shahin Asadi and Elaheh Fayyazian*

Division of Medical Genetics and Molecular Pathology Research, Harvard University, Boston Children's Hospital, USA

Abstract

FXPOI syndrome is a genetic disorder that affects women and is characterized by decreased ovarian function. FXPOI syndrome can cause irregular menstrual cycles, premature menopause, infertility, and increased levels of a hormone called Follicle-Stimulating Hormone (FSH) in women. FSH is produced in both men and women and helps regulate reproductive cells (eggs in women and sperm in men). FXPOI syndrome is caused by a mutation in the *FMR1 gene*, which is located on the long arm of the sex X chromosome as Xq27.3.

Keywords: FXPOI syndrome; FMR1 gene; Genetic mutation; Infertility

Introduction

FXPOI syndrome is a genetic disorder that affects women and is characterized by decreased ovarian function. FXPOI syndrome can cause irregular menstrual cycles, premature menopause, infertility, and increased levels of a hormone called Follicle-Stimulating Hormone (FSH) in women. FSH is produced in both men and women and helps regulate reproductive cells (eggs in women and sperm in men). FXPOI syndrome is caused by a mutation in the *FMR1 gene*, which is located on the long arm of the sex X chromosome as Xq27.3.

Overview of Fragile X Syndrome with Primary Ovarian Failure (FXPOI)

FXPOI syndrome is a genetic disorder that affects women and is characterized by decreased ovarian function. The ovaries are the female reproductive organs in which egg cells are produced [1].

Clinical signs and symptoms of Fragile X Syndrome with Primary Ovarian Failure (FXPOI)

FXPOI syndrome can cause irregular menstrual cycles, premature menopause, infertility, and increased levels of a hormone called Follicle-Stimulating Hormone (FSH) in women. FSH is produced in both men and women and helps regulate reproductive cells (eggs in women and sperm in men). In women, FSH levels increase and decrease, but in general, as women get older, FSH levels also increases. In young women, high levels of the hormone FSH can cause premature menopause and fertility problems [1,2].

The severity of the symptoms of FXPOI syndrome varies among women. Women with severe FXPOI syndrome have irregular or no menstrual cycles and increase FSH levels before the age of 40. POI disorder often causes infertility. Some women have latent POIs that have a normal menstrual cycle but reduce fertility and may have higher FSH levels, known as biochemical POIs [1,2].

Decreased ovarian function due to FXPOI leads to decreased estrogen levels, which in turn leads to many of the signs and symptoms of menopause, such as hot flashes, insomnia, and osteoporosis. It is worth noting that women with FXPOI syndrome are on average 5 years earlier in menopause than women without FXPOI [1,3].

Etiology of Fragile X Syndrome with Primary Ovarian Failure (FXPOI)

FXPOI syndrome is caused by a mutation in the *FMR1 gene*, which is located on the long arm of the sex X chromosome as Xq27.3. This gene provides the instructions for the synthesis of a protein called FMRP, which helps regulate the production of other proteins. This protein plays an important role in the function of nerve cells (neurons). In addition, the FMRP protein is important for normal ovarian function, although its mechanism of action is not yet well understood (Figure 1) [1,4].

Women with FXPOI syndrome have a mutation in the *FMR1 gene*, in which three CGG nucleotide repeats occur. Normally, this part of the DNA is repeated 5 to 40 times. In women with FXPOI syndrome, the three-nucleotide segment of CGG is repeated up to 200 times. This mutation is known as a permutation of the *FMR1 gene*. Some studies suggest that women with replication of 44 to 54 of the three CGG nucleotides, also known as the "gray zone" mutation, may also have the characteristics of FXPOI syndrome. Proliferation of more than 200 replicates of three CGG nucleotides is known as a

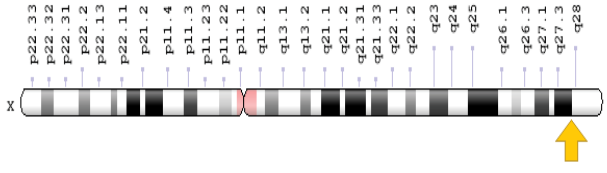

Figure 1: Schematic of the sex X chromosome where the FMR1 gene is located in the long arm of this chromosome as Xq27.3 [1].

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***Corresponding author:** Shahin Asadi, Division of Medical Genetics and Molecular Optogenetic Research, Medical Genetics-Harvard University, USA, Tel: +1-857-600-7921; E-mail: shahin.asadi1985@gmail.com

complete mutation and causes a more serious disorder called Fragile X Syndrome, which is characterized by mental disabilities, learning disabilities, and some specific physical features of this syndrome [1,5].

For unknown reasons, premutation leads to abnormal overproduction of *FMR1* mRNA that contains an extended replication region. *FMR1* mRNA is the genetic design of FMRP. Researchers believe that high levels of mRNA cause the signs and symptoms of FXPOI. MRNA is thought to bind to other proteins and keep them from performing their functions. In addition, replication makes FMRP production more difficult than mRNA, and as a result, people with *FMR1 gene* premutation may have lower than normal FMRP. Deficiency of this protein does not appear to be involved in FXPOI syndrome. However, there may be mild versions of the features seen in Fragile X Syndrome, such as prominent ears, anxiety, and behavioral fluctuations (Figure 2) [1,5].

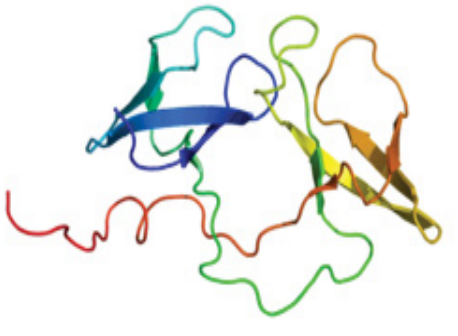

Figure 2: Schematic of the closed structure of the FMR1 protein [1].

FXPOI syndrome follows a dominant X-linked hereditary pattern. The *FMR1 gene* is located on the X chromosome, which is one of two sex chromosomes. (The Y chromosome is a chromosome of the opposite sex.) The dominant X-linked inheritance means that one copy of the altered gene in each cell is sufficient to increase the risk of FXPOI syndrome. In women (who have two X chromosomes) mutations in one of the two gene copies per cell can lead to a disorder. However, not all women who inherit permutation of the *FMR1 gene* develop FXPOI. Because men do not have ovaries, they are not affected by this syndrome [1,6].

Frequency of Fragile X Syndrome with Primary Ovarian Failure (FXPOI)

FXPOI syndrome is a genetic disorder that has an estimated prevalence of about 1 in 200 women worldwide, although only about a quarter of them develop FXPOI syndrome. FXPOI syndrome accounts for about 4% to 6% of primary ovarian failure cases [1,6].

Diagnosis of Fragile X Syndrome with Primary Ovarian Failure (FXPOI)

FXPOI syndrome is diagnosed based on the clinical findings of some patients and some pathological tests and infertility. The most accurate way to diagnose this syndrome is a molecular genetic test for the *FMR1 gene* to check for possible mutations (Figure 3) [1,7].

Treatment options for Fragile X Syndrome with Primary Ovarian Failure (FXPOI)

The treatment and management strategy for FXPOI syndrome is symptomatic and supportive. Treatment may be performed with the efforts and coordination of a team of specialists including

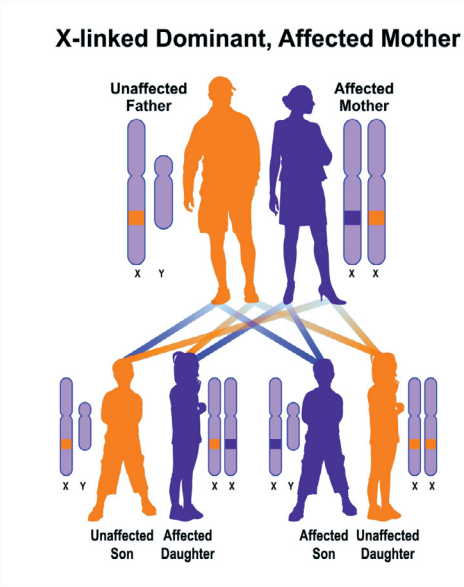

Figure 3: Schematic of the dominant X-dependent hereditary pattern (patient's mother) that FXPOI syndrome follows [1].

gynecologists, hormone therapists, reproductive biologists, and other health care professionals. There is no standard treatment for this syndrome and all clinical measures are to reduce the suffering of patients. Genetic counseling is also very important for all parents who want a healthy child (Figure 4) [1,7].

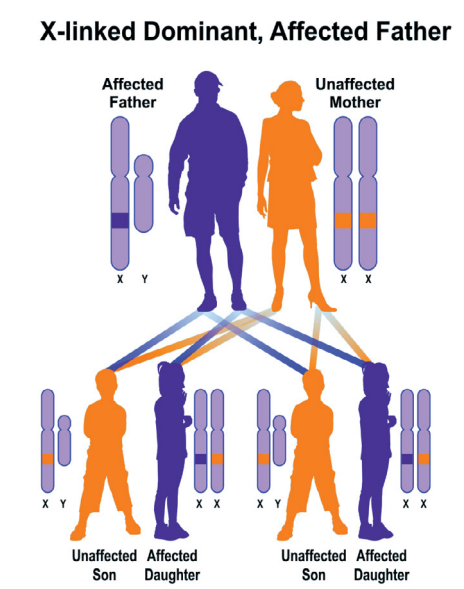

Figure 4: Schematic of the dominant X-linked hereditary pattern (patient father) that FXPOI syndrome also follows [1].

Discussion and Conclusion

The severity of the symptoms of FXPOI syndrome varies among women. Women with severe FXPOI syndrome have irregular or no menstrual cycles and increase FSH levels before the age of 40. POI disorder often causes infertility. There is no standard treatment for this syndrome and all clinical measures are to reduce the suffering of patients.

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