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ORIGINAL ARTICLE

Are *FSHR* polymorphisms risk factors to premature ovarian insufficiency?

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Abstract

Premature ovarian insufficiency (POI) is an ovarian dysfunction characterized by increased FSH levels and amenorrhea before 40 years old. In recent years, the search for genetic causes of POI intensified and studies have been published relating the presence of mutations and polymorphisms in genes associated with development, recruitment and oocyte atresia. The aim of this study was to evaluate the presence of *FSHR* polymorphisms in our population and contribute with the elucidation of POI etiology. To achieve it, we have studied 100 patients with POI (G1), 60 patients with border line levels of FSH (G2) and 123 controls with regular menopause onset. Cytogenetic analysis of patients' samples and genotyping of Asn680Ser and Ala307Thr polymorphisms were performed in cases and controls. Cytogenetic analysis showed that 92% of G1 patients had normal karyotype, 4% presented polymorphic variants, 3% presented mosaic karyotype involving X chromosome. In G2, 91.6% had normal karyotype results, 3.2% displayed polymorphic variants, and 3.3% presented a mosaic karyotype involving X chromosome. Statistical comparison showed that the polymorphic allele of Ala307Thr polymorphism is more frequent in patients than in controls (G1: $p < 0.001$ and G2: $p = 0.0259$). This association has not been previously reported. We concluded that Ala307Thr polymorphism in *FSHR* can be potentially associated to POI development and can be considered as a screening marker in patients with ovarian failure signals.

Keywords

Follicle stimulating hormone, *FSHR*, infertility, premature ovarian insufficiency, X chromosome

History

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Introduction

The premature ovarian failure, recently renamed primary premature ovarian insufficiency (POI), is an ovarian dysfunction featured by secondary oligomenorrhea or amenorrhea of more than 3 months' duration and/or follicle-stimulating hormone (FSH) levels above 40 UI/L in women under 40 years old [1]. In 2013, ESHRE POI Consensus (Utrecht, the Netherlands) determined a new cut-off level for FSH (25 mUI/mL), above which, patients can be classified with POI. The condition affects about 1 in every 100 women between 30 and 39 years [2].

The main characteristic of POI is the absence of functional follicles, but the dysfunction may be characterized by primary amenorrhea or ovarian follicles premature depletion before 40 years of age. The etiology of this condition is complex and the dysfunction may be secondary to autoimmune diseases, infections, iatrogenic exposure and genetic alterations [3–6].

Cytogenetic abnormalities linked to the X chromosome, usually, lead to POI, suggesting that the genes located on the X chromosome are essential for normal ovarian function [7]. These abnormalities include total or partial deletion of chromosome, the presence of an additional X, mosaicism and translocation [2]. However, a large number of patients show normal karyotypes, suggesting that not only karyotype aberrations, but mutations in specific genes related with ovarian function and located in other chromosomes can be correlated with POI as well.

Follicle-stimulating hormone is a glycoprotein that coordinates normal ovarian function and regulates follicle growth, differentiation and proper gametogenesis. The hormone performs these functions through the perfect binding to the FSH receptor, encoded by *FSHR* gene [8,9]. Point mutations can cause variations in the amino acid sequence of the receptor protein. Some of these structural changes affect the receptor functional properties that may be enhanced or impaired (activating or inactivating mutations). Activating mutations confer to FSHR a higher responsiveness to FSH, making it constitutively active even in the absence of the ligand, or render it able to non-specifically respond to other tropic hormones (e.g. TSH). Inactivating mutations reduce the receptor's function up to a total block, altering either the formation of the receptor–ligand complex, or FSH signal transduction. FSHR inactivating mutations may cause primary or secondary amenorrhea, infertility and POI [10].

Two polymorphisms in *FSHR* have been extensively studied, both located in exon 10 of *FSHR*, impacting in the protein

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