J Assist Reprod Genet
DOI 10.1007/s10815-012-9884-x

GENETICS

Risk of premature ovarian failure is associated to the *PvuII* polymorphism at estrogen receptor gene *ESR1*

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Received: 8 August 2012 / Accepted: 29 October 2012

Abstract
Purpose Estrogen plays an important role in the human reproductive system and it action is mediated mainly by two specific receptors: α (ERα) and β (ERβ). There were described polymorphic variants in *ESR1 and ESR2* genes and studies showed controversial results regarding their association with premature ovarian failure. We aimed to determine the prevalence of *ESR1 and ESR2* polymorphisms in Brazilian patients and controls. After associate the polymorphisms with premature ovarian failure (POF).
Methods Genetic association study was performed with 70 women with POF and 73 normally menopaused controls. Detection of *ESR1* (*PvuII*/and *XbaI*) and *ESR2* (*AluI* and *RsaI*) gene polymorphisms were performed using TaqMan PCR. The single-nucleotide polymorphism (SNPs) and haplotype effects were analyzed by multivariate logistic regression and haplotype analysis and a p-value<0.05 was considered significant.
Results Individual SNP analysis revealed that *PvuII* polymorphism was statistically associated with POF (p=0.034) under a recessive model. Regarding *XbaI*, *AluI* and *RsaI* SNPs, no statistical difference was observed between POF group and controls (p=0.575, p=0.258 and p=0.483, respectively). Combined genotypes of *ESR1 and ESR2* polymorphisms did not identify a risk haplotype associated with POF.
Conclusion In Brazilian population evaluated results have demonstrated that the genetic variation in *ESR1* gene (*PvuII* polymorphism) is associated to POF risk.

Capsule Estrogen and estrogen receptor play an important role in the reproductive system. Impairment in function of the receptor isoforms has been associated with the development of premature ovarian failure.

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Keywords Premature ovarian failure · Genetic polymorphism · Estrogen · Haplotype study · Association study

Introduction

Premature ovarian failure (POF) is a process by which the gradual decline of ovarian function results in failure of folliculogenesis before age of 40. It is characterized by the absence of menstruation for a period longer than 6 months (secondary amenorrhea), but it can occur before menarche, leading to primary amenorrhea ([1–4]).

Due to the number of familial cases with affected individuals in more than one generation it has been suggested that POF has a genetic basis. Many genes have been implicated on POF development as *FMR1*, *inhibin*, *BMP15*, *LHR*, *FSHR* and others related to ovarian function [5, 6].

It is well known that follicular growth and maturation occurs by the synergic influence of the hormones estrogen, FSH and LH on the ovary [6–8]. Sequence variations in genes that encode hormone receptor and binding protein genes could change their function, affecting follicular pool size or rate of follicular recruitment and thus the increasing the risk for premature menopause [7]. Due to their active role in folliculogenesis, variations in genes related to estrogen metabolism can be considered important risk factors to POF development [9].

The physiological estrogen response on diverse tissue and organ occurs by the hormone binding to estrogen receptor (ER), at the hypothalamus-hypophysis-ovarian axis, which stimulate gonadotropins releasing and consequently foliculogenesis [10]. There are two specific estrogen receptors, differentially distributed in the tissues: estrogen receptor α (ERα) encoded by the *ESR1* gene (MIM 133430/ Genbank ID 2099) on chromosome 6q25 [11] and estrogen

Published online: 13 November 2012