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COMT polymorphism influences decrease of ovarian follicles and emerges as a predictive factor for premature ovarian insufficiency

Emerson Barchi Cordts[1], Monise Castro Santos[1], Carla Peluso[1], Erika Azuma Kayaki[1], Bianca Bianco[1,2*], Caio Parente Barbosa[1] and Denise Maria Christofolini[1]

Abstract

Background: Estrogens are important factors in the female reproductive functions and are processed by a number of enzymes along their metabolic pathway. The *COMT* gene constitutes a crucial element in estrogen metabolism and is assumed to be involved in the development of Premature Ovarian Insufficiency (POI). This study aimed to determine whether the presence of the *COMT* Val/Met polymorphism (rs4680) is associated to the risk of developing POI.

Findings: In this case–control study, we evaluated 96 infertile women with POI and 120 fertile women as controls, after obtaining a detailed history of the disease and follicle-stimulating hormone measurements, besides karyotype determination and fragile-X premutation syndrome investigation. *COMT* (Val/Met) genotypes were identified by real time PCR (genotyping *TaqMan* assay), and the results were statistically analyzed. A statistically significant difference was found in the distribution of *COMT* genotypes ($p = 0.003$) and alleles ($p = 0.015$) between the POI patients and the control group.

Conclusion: We were able to demonstrate a strong association between the *COMT* Val/Met polymorphism and the risk of premature ovarian insufficiency in the Brazilian women evaluated. However, further studies in larger populations are necessary to confirm these findings.

Keywords: *COMT*, Estrogen metabolism, Infertility, POI, Polymorphism

Background

Premature ovarian failure (POF) is a disorder with a complicated clinical presentation and course that is poorly defined by its name. POF is classically defined as a process in which the gradual decline of ovarian function results in failure of folliculogenesis before the age of 40 years, elevated FSH and low estradiol levels [1-3]. However, this definition does not take into account the longitudinal progression towards the final menstrual cycle. A scientifically more accurate term for the disorder is "primary ovarian insufficiency" (POI), which can be appropriately modified to describe the state of the ovarian function [4]. Indeed, the process of ovarian senescence in this condition may resemble that of natural menopause, which is preceded by several years by elevated FSH levels and menstrual irregularity [4].

The most common etiologies observed for this condition are chromosomal abnormalities, fragile X premutations and autoimmune causes. Once these were ruled out, we can think that a non-obvious genetic pathway could be implicated in the disease. Several genes have been identified as being expressed in the ovary and are postulated to play a role in ovarian physiology and in maintaining normal homeostasis in the ovarian cycle. Alterations in these genes can be associated with the development of POI [5]. A recently demonstrated example of that is that mutations in estrogen receptors can affect regulatory pathways and have been reported to be positively associated with the development of POI [6-8].

* Correspondence: bianca.bianco@hotmail.com
[1]Center of Human Reproduction and Genetics – Faculdade de Medicina do ABC, Santo André/SP CEP 09060-650, Brazil
[2]Faculdade de Medicina do ABC, Avenida Príncipe de Gales, 821, Santo André/SP CEP: 09060-650, Brasil