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# The significance of polymorphism and expression of oestrogen metabolism-related genes in Chinese women with premature ovarian insufficiency

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**KEY MESSAGE**

The frequency of expression of the *CYP17* T/C variant tended to be higher and the A allele of *COMT* polymorphism together with down-regulation of its mRNA expression may be more frequent in Chinese patients with idiopathic primary ovarian insufficiency.

ABSTRACT

The aim of this study was to investigate whether polymorphism and expression of *CYP17*, *CYP1A1*, *COMT* and *SULT1A1* affected the risk of idiopathic primary ovarian insufficiency (POI) in Chinese women. DNA sequencing and real-time PCR were used to detect these genes in 132 cases of idiopathic POI and 132 normal women. A significant increase in the C allele of *CYP17* (rs743572) polymorphism was observed in women with POI compared with controls ($P_{FDR}$ = 0.046). A significant decrease was observed in the C allele of *CYP1A1* (rs4646903) in women with POI compared with controls ($P_{FDR}$ = 0.004). The A allele of *COMT* (rs4680) polymorphism was more frequent in women with POI compared with controls ($P_{FDR}$ = 0.029). The genotypic frequency of *SULT1A1* (rs9282861) was not significantly different between the two groups. For the relative expression of *CYP17* and *COMT* were statistically significant (both $P_{FDR}$ = 0.066), with false discovery rate controlled at 0.1. No significant difference was observed in the RNA levels of *CYP1A1* and *SULT1A1* between the two groups. The frequency of expression of the *CYP17* T/C variant tended to be higher and the A allele of *COMT* polymorphism together with down-regulation of its mRNA expression may be more frequent in Chinese women with idiopathic POI.

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http://dx.doi.org/10.1016/j.rbmo.2017.07.007
1472-6483/© 2017 Published by Elsevier Ltd on behalf of Reproductive Healthcare Ltd.

Please cite this article in press as: Chunrong Qin, et al., The significance of polymorphism and expression of oestrogen metabolism-related genes in Chinese women with premature ovarian insufficiency, Reproductive BioMedicine Online (2017), doi: 10.1016/j.rbmo.2017.07.007

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## Introduction

Premature ovarian insufficiency (POI) is the preferred term for the condition previously referred to as premature menopause or premature ovarian failure. According to the new European Society of Human Reproduction and Embryology guideline, POI is a clinical syndrome defined by the loss of ovarian activity in a woman before the age of 40 years (Webber et al., 2016).

Despite extensive research in this field, the cause of POI still has not been elucidated. Familial studies have indicated that POI may be genetically linked, and it has been suggested that POI has a genetic basis. The most common genes observed for this condition are *FMR1*, inhibin, *BMP15*, *LHR*, *FSHR* and *AMH* (Cordts et al., 2011; Goswami and Conway, 2005; Qin et al., 2014).

Oestrogen has an important effect in adjusting the development and function of granulosa cells and follicular development. The appropriate levels of oestrogen within the follicle are known to be crucial for many ovarian functions, such as promoting FSH activity, inducing LH receptors, inhibiting apoptosis, and follicular growth. Ireland et al. (2009) summarized the importance of oestradiol concentration in the follicles for follicular function in cows, a mono-ovulatory species resembling humans, because the concentration of oestradiol in the follicle up-regulates many genes involved in endocrine receptor activity, steroidogenesis, determinants of oocyte quality in the cells of the cumulus oophorous, and thecal and granulosa cell differentiation. In addition, the difference of oestradiol concentration in the follicles was related to the antral follicle count and the total fertility potential of the animals. Furthermore, compared with women with more severe POI, higher levels of oestradiol in the circulation are currently diagnosed as a milder form of POI (Bachelot et al., 2009).

On the basis of these observations, functional polymorphism of genes related to oestrogen metabolic pathways have been proposed as candidates for association studies on POI risk. A previous study has also investigated the association between polymorphism of gene encoding enzymes (catechol-O-methyltransferase *COMT*) involved in oestrogen metabolism and the risk of POI (Cordts et al., 2014).

The cytochrome P450 17 hydroxylase (*CYP17*) gene is located on chromosome 10q24.3 encoding cytochrome P450c17$\alpha$, which is one of the key enzymes in androgen biosynthesis. The enzyme mediates steroid 17$\alpha$-hydrolase and 17, 20-lyase activity. A change from T to C at the 5'-untranslated region (UTR) of the *CYP17* gene, may create an additional SP-1 site (CCACC box) at 34 base pairs upstream from the translation initiation site. Increased activity of the promoter with an elevated level of *CYP17* mRNA has been reported in this polymorphism. Therefore, this polymorphism may affect the cytochrome P450c17$\alpha$ enzyme activity and sex steroid synthesis, which seems to change the level of sex hormones, such as androgen, progesterone and oestrogen (He et al., 2006).

*CYP1A1* is located on 15q24-q25 and consists of 7 exons and 512 amino acids. The 3'-noncoding region of *CYP1A1* rs4646903, a common single nucleotide substitution (T→C), is thought to be associated with translational efficiency and mRNA stability (Tanguay and Gallie, 1996). It is reported that the rs4646903 (T > C) C variant is associated with *CYP1A1* inducibility (Petersen et al., 1991).

The catechol-O-methyltransferase (*COMT*) gene is located in chromosome 22q11.2. The *COMT* gene encodes catechol-O-methyltransferase, which converts catechol oestrogens into inactive metabolites (Stolk et al., 2007; Tofteng et al., 2004). Previous studies reported that exon 4 of the *COMT* gene contained a G to A transition at codon 158 and showed relevant polymorphism significantly leading to thermolability and lower activity of the enzyme (Raftogianis et al., 1997; Ronkainen et al., 2008). This slows the metabolism of oestradiol and subsequently leads to higher serum levels of estradiol (Stolk et al., 2007).

Sulfotransferase (*SULT1A1*) is located in chromosome 16p11.2 – p12.1. A polymorphism (rs9282861) in exon 7 causes the replacement of G with A at codon 213. The A variant allele is associated with lower levels of enzymatic activity (Raftogianis et al., 1997) and generated *SULT1A1**2 isoform (Nagar et al., 2006). The protein derived from *SULT1A1**2 (213His variant allele) has two times lower catalytic activity and more reduced thermal stability compared with the wild type (*SULT1A1**1) (Koike et al., 2008).

Little information is available on the role of oestrogen metabolism-related gene polymorphisms as risk factors for POI development, and we therefore examined their associations in this study. We focused on several common functional polymorphisms of key genes encoding enzymes involved in oestrogen metabolism, biosynthesis and catabolism (*CYP17*, *CYP1A1*, *COMT* and *SULT1A1*), and also looked for associations between genetic alterations and their mRNA expression levels in Chinese patients with POI.

## Materials and methods

### Patient and control recruitment

This case-control study included a total of 132 patients (mean age, 35.04 ± 4.40 years) with idiopathic POI who were recruited between January 2009 and July 2016 at the Affiliated Shenzhen City Maternity and Child Healthcare Hospital of Southern Medical University, Shenzhen, PR China. The control group included 132 healthy women who had undergone a physical examination around 35 years of age (mean 32.23 ± 5.21 years), with a normal menstrual history, regular menses (every 25–35 days), no personal or family history of premature or early menopause, and no consumption of oral contraceptives or other hormonal medications at the time of recruitment. The study was approved by the University's Institutional Ethics Committee (reference no, 2012020, approved 15 March 2012), and informed consent was obtained from all participants.

The diagnostic criteria (Webber et al., 2016) for POI were as follows: at least 4 months of amenorrhoea before the age of 40 years, with at least two serum FSH concentrations over 25 IU/l on two occasions 4 weeks apart. Patients with associated endocrinopathies, autoimmune disorders, iatrogenic agents such as pelvic surgery, chemotherapy and radiotherapy and infections were excluded. Karyotyping with high-resolution G-banded chromosomes to check for chromosomal anomalies was carried out in all patients and controls. Those with abnormalities were excluded from the study.

### DNA extraction, karyotyping, polymerase chain reaction protocol and DNA sequencing

Peripheral blood was collected in EDTA vacutainers for genomic DNA and RNA isolation (5 ml) and in heparin vacutainers for chromosomal analysis (5 ml). DNA extraction, karyotyping, polymerase chain reaction (PCR) protocol and DNA sequencing were previously described (Qin et al., 2014). Genomic DNA was extracted from

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