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Review

Two follicle-stimulating hormone receptor polymorphisms and polycystic ovary syndrome risk: a meta-analysis

Dao-Jun Chen [a], Rui Ding [a], Ji-Yu Cao [a,b], Jin-Xia Zhai [a], Jia-Xiang Zhang [a], Dong-Qing Ye [c,*]

[a] Department of Occupational and Environmental, School of Public Health, Anhui Medical University, Meishan Road, Hefei, Anhui, China
[b] The Teaching Center for Preventive Medicine, School of Public Health, Anhui Medical University, Meishan Road, Hefei, Anhui, China
[c] Department of Epidemiology and Biostatistics, School of Public Health, Anhui Medical University, Meishan Road, Hefei, Anhui, China

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ABSTRACT

The aim of this study was to explore the association between follicle stimulating hormone receptor (FSHR) Thr307Ala and Asn680Ser polymorphisms and susceptibility to polycystic ovary syndrome (PCOS). A comprehensive literature search for relevant studies was conducted on Google Scholar, PubMed, the Chinese National Knowledge Infrastructure (CNKI) and the Chinese Biomedical Literature Database (CBM). This meta-analysis was performed using the STATA 11.0 software and the pooled odds ratio (OR) with 95% confidence interval (CI) was calculated. Ten case-control studies were included in this meta-analysis. However, meta-analysis results showed no association between both FSHR Thr307Ala polymorphism and Asn680Ser polymorphism and susceptibility to PCOS. Stratified analysis of ethnicities also showed no association. In conclusion, the present study suggested that the FSHR polymorphisms were not associated with an increased risk of PCOS and larger-scale studies of populations are needed to explore the roles played by FSHR polymorphisms during the pathogenesis of PCOS.

Contents

* Corresponding author. Tel.: +0086 0551 3869179; fax: +0086 0551 3869179.
E-mail address: ydqahmu@gmail.com (D.-Q. Ye).

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Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders among women of reproductive age. The prevalence of PCOS is nearly 5–10% and the clinical manifestation of the disease varies [1]. According to the 2003 Rotterdam criteria, the characteristics of PCOS mainly include hyperandrogenism, oligomenorrhea or amenorrhea, and polycystic ovary morphology [2]. The exact cellular and molecular mechanisms of PCOS remain elusive. However, the impact of environment and heredity is considered to be the potential causative factors for the disease. Recent epidemiological studies suggested that there are several susceptibility genes associated with PCOS, including INS VNTR, TCF7L2, and PPARG [3–5].

Follicle stimulating hormone (FSH) is a pituitary glycoprotein which has an important role during folliculogenesis by accelerating the proliferation and differentiation of granulosa cells and the maturation and development of follicles [6]. The effect of FSH is mediated by binding of the hormone with a specific receptor (namely FSHR) that is specifically located on the granulosa cells of the ovary [7]. FSHR belongs to the G-protein coupled receptor family and consists of 10 exons, 9 introns, and the promoter region at chromosome 2p21 [8]. Via the cascade effect, FSHR transfers the biological signals of FSH to the downstream network.

Previous investigations revealed a low incidence of gene polymorphisms for the FSHR gene in nature. Single nucleotide polymorphisms (SNPs) were identified in the FSHR gene, such as Thr307Ala and Asn680Ser polymorphisms in exon 10, which have drawn increasing attention [9,10]. Due to the alteration of nucleotides at 307 and 680 loci, which result in changes of corresponding amino acids, FSHR varies in its biological effects [11]. Several studies revealed that the polymorphisms may be related to clinical practice by regulating the ovarian reaction to the hormone, changing the menstrual cycle, controlling ovarian hyperstimulation, and causing PCOS.

Recently, several studies have indicated that FSHR polymorphisms might significantly relate to the increased risk of PCOS. However, the results are inconsistent and controversial. Therefore, we attempted to perform this meta-analysis of all eligible studies to provide a more comprehensive and reliable conclusion by reevaluating the association between FSHR Thr307Ala and Asn680Ser polymorphisms and PCOS risk.

Methods

Search strategy

Studies which evaluated the link between FSHR polymorphisms and PCOS risk were searched in the databases of Google Scholar, PubMed, the Chinese National Knowledge Infrastructure (CNKI) and the Chinese Biomedical Literature Database (CBM) with the following terms: follicle stimulating hormone receptor, FSH, FSHR, polymorphism, polymorphisms, mutation, variant, variants, polycystic ovary syndrome, and PCOS. There was no limitation on languages. In addition, all references cited were also reviewed to identify additional studies.

Inclusion criteria

Regarding PCOS susceptibility and the polymorphisms, studies which met the following criteria were identified: (1) Clinical case-control or cohort studies concentrated on the role of FSHR Thr307Ala and Asn680Ser polymorphisms in the pathogenesis of PCOS. (2) All patients should meet the PCOS definition specified in the 1990 National Institute of Health-National Institute of Child Health and Human Development conference or in 2003 Rotterdam conference by the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM). (3) The specific numbers or genotype frequency in case and control groups must be shown in the articles. (4) The genotype frequency distribution of the controls should be consistent with Hardy–Weinberg equilibrium (HWE), which was performed for evaluating the qualities of the studies. Studies were excluded if they did not confirm to all the inclusion criteria.

Data extraction

Two authors independently extracted data from each included study independently according to the selection criteria. We compared the data and made decisions by consensus of all members of our group. For included studies, data on first author, year of publication, study design, ethnicity of the study, number of cases and controls, mean age of participants, diagnostic standards of cases in each study, and the number of cases and controls for the two variants were extracted.

Statistical analysis

Crude ORs with their 95% CIs were used to estimate the strength of association between the two polymorphisms and PCOS susceptibility. The pooled ORs were calculated for the allele contrasts, recessive genetic model, dominant genetic model, and additive comparison. Subgroup analyses were also performed by ethnicity.

A random or fixed effect model was employed based on the heterogeneity assumption [12,13]. Heterogeneity assumption was examined by the chi-square based Q test [14]. The random effect model was used as the pooling method in the presence of substantial heterogeneity ($I^2 > 50\%$), otherwise the fixed effect was performed to assess the pooled OR. The genotypic frequency distribution in the controls was checked for consistence with the Hardy-Weinberg equilibrium (HWE) in all the included studies. Potential publication bias was estimated by Begg's test or Egger's linear regression test by visual examination of the funnel plot, and $p < 0.05$ was regarded as representative of statistically significant publication bias. To assess the stability of the results of the meta-analysis, case definition influence on the pooled evaluation, one-way sensitivity analyses were performed. All statistical tests were used with STATA version 11.0 (Stata Corporation, College station, TX, USA). All p-values tested were two-tailed.

Results

Fig. 1 illustrates the study selection process. There were altogether 648 relevant papers under the search words (PubMed 47, Google scholar 300, CBM 125, and CNKI 176. However, 47 articles searched in PubMed can be found in Google Scholar and 125 articles searched in CBM can also be identified in CNKI, of which 603 were excluded and a total of 43 articles were identified through literature search and screening of title and/or abstract. Of these, 9 articles were not concentrated on the FSHR gene, 10 articles were not related to FSHR gene polymorphism, 1 meta-analysis and 2 studies were without clear data. During the extraction of data, 2 articles were excluded owing to omission of control data, 1 article was excluded as the distribution of genotypes deviated from HWE, and 9 studies did not have clear data. Ten studies met all inclusion criteria and were included in the meta-analysis. Selected details of the individual studies are listed in Table 1.