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Review

Gene variation and premature ovarian failure: a meta-analysis

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ABSTRACT

Objective: Premature ovarian failure (POF) is a complex, heterogeneous disorder that is influenced by multiple genetic components. This meta-analysis aimed to investigate the association between gene variants and susceptibility to POF.
Study design: MEDLINE and CNKI were searched for studies published from inception (1950) to June 2014. Meta-analysis was performed when three or more studies reported genetic data on the same polymorphism or mutation. Additive and dominant models were analyzed using RevMan Version 5.1.
Results: The literature search yielded 575 articles, of which 59 studies on the association between POF and gene variants were identified for meta-analysis. Five genes were selected for analysis, including 10 common gene polymorphisms [BMP15 (−9C>G, 788insTCT and 852C>T), ESR1 (−351A>G and −397C>T), FMR1 CGG repeat, FSHR (919A>G and 2039A>G), INHA (−16C>T and −124A>G)] and two mutations (BMP15 538G>A and INHA 769G>A). BMP15 538G>A was found to be significantly more common in patients with POF compared with controls. No significant associations were found between the other variants of BMP15 and POF. With respect to ESR1, the accumulative results were not significant, although the findings of the individual studies were controversial. The incidence of FMR1 premutation was significantly higher in patients with POF compared with controls [odds ratio (OR) 9.2, 95% confidence interval (CI) 5.42–15.61; $p < 0.001$] in the overall population, as well as in both Caucasian and Asian subgroups. Stratified analysis was applied for INHA 769G>A by ethnicity; a significant association with POF was only found in the Asian subgroup (allelic frequency: OR 8.89, 95% CI 2.1–5.52; $p = 0.004$). No significant associations were found between the other variants of INHA and POF.
Conclusions: BMP15 538A, FMR1 premutation and INHA 769A (in Asians alone) may indicate susceptibility to POF. Further well-designed studies and larger samples are required to confirm the association between gene variants and POF.

Contents

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Introduction

Premature ovarian failure (POF) is defined as the cessation of ovarian function with follicle-stimulating hormone (FSH) concentrations exceeding 40 IU/l before 40 years of age, resulting in amenorrhoea, infertility and other systemic consequences (e.g. cardiovascular disease, osteoporosis) because of oestrogen deficiency [1]. Recently, the term 'primary ovarian insufficiency' (POI) has been proposed to reflect the continuum of altered ovarian function [2]. POF affects approximately 1% of women under 40 years of age [3]. In addition to environmental and iatrogenic factors, genetic background, auto-immunity and metabolism are thought to contribute to POF/POI. The exact aetiology of POF remains unknown, and various data indicate that POF has a strong genetic component. These data include the existence of several causal genetic defects in human, experimental and natural models. Familial POF research showed that 4–30% of all subjects with POF had a familial form [4], which implied a genetic predisposition to POF.

Genetic causes of POF can be chromosomal or caused by single genes, involving the X chromosome or autosomes. There are many reports of mutations and polymorphisms in genes related to POF. Possible associations between gene polymorphisms and POF/POI have been investigated for several genes [5], including X-linked genes [e.g. fragile X mental retardation 1 (FMR1) and bone morphogenetic protein 15 (BMP15)] and autosomal genes [follicle-stimulating hormone receptor (FSHR), luteinizing hormone receptor, inhibin alpha (INHA), forkhead box L2 and splicing factor 1, oestrogen receptor (ESR)]. Even mitochondrial DNA has been studied, and shown to have a close association with POF/POI [6]. However, these results remain controversial.

The primary aim of this study was to perform a meta-analysis of the association between gene variants and POF in order to integrate the evidence for the risk of POF and genetic factors.

Materials and methods

Search strategy

A literature search was performed to identify studies investigating the potential influence of any gene variant on POF. MEDLINE and CNKI were searched for all relevant published manuscripts from inception (1950) to June 2014 using the following keywords: 'polymorphism', 'mutation', 'variant', 'variation', 'gene', 'premature ovarian failure', 'primary ovarian insufficiency' and 'premature menopause'.

Identification and eligibility of relevant studies

All data were extracted independently by two authors (DP and YX). Studies were included if they analyzed the association between any gene variant and POF/POI. POF was diagnosed as cessation of menstrual cycles for $\geq$4 months in women aged $\leq$40 years, with serum FSH level exceeding 40 IU/l at least twice $\geq$1 month apart. All included studies were peer-reviewed, published articles and there was no language restriction. In addition, studies were identified by a manual search of original publications from review articles.

Studies were included in the meta-analysis if: (1) they were genetic association studies evaluating gene polymorphisms and POF, or gene mutations and POF; (2) patients with POF were diagnosed according to the following criteria [7]: $\geq$4 months of amenorrhoea and serum FSH levels exceeding 40 IU/l obtained twice $\geq$1 month apart in women aged $\leq$40 years; (3) they showed genotypic and/or allelic frequencies; (4) they were published studies; and (5) they were designed as case–control or cohort studies. Studies were excluded if: (1) they did not investigate the relationship between gene variants and POF; (2) they were review articles, animal studies, commentaries, case reports or unpublished reports; and (3) they were duplicate publications.

Data on first author, publication year, location/ethnicity, sample size and genes were extracted for each study (Table 1). In addition, genotype distributions and/or allelic frequencies were extracted (Table 2). In cases where data were missing from published papers, relevant information was obtained by direct communication with the corresponding authors. Meta-analytic calculations were performed when three or more studies reported the same genetic variation.

Statistical analysis

Statistics were analyzed using RevMan Version 5.1 (Cochrane Collaboration, Copenhagen, Denmark). The association between gene variants and the risk of POF was expressed using odds ratios (ORs) and 95% confidence intervals (CIs). The statistical significance of pooled ORs was evaluated using Z-test. Two comparisons were performed: allelic frequency and dominant genetic model between cases and controls. The meta-analysis was stratified by ethnicity if data were available.

A test of heterogeneity between the studies was conducted using a χ^2-based Q-test [8]. Statistical heterogeneity was assessed using I^2. $I^2 > 50\%$ was taken to indicate substantial heterogeneity [9]. If substantial heterogeneity was detected, a random effects model was used instead of a fixed effects model. The significance analysis of intercept was calculated by t-test, and $p < 0.05$ was considered to indicate significance.

Results

Study characteristics

The literature search yielded 575 articles. Review articles (n = 119), studies that were not related to human research (n = 57), studies that did not have a case–control/cohort/randomized design (n = 62), studies that were not related to POF/POI (n = 110), and studies that were not available for meta-analysis because of fewer than three articles on the same gene polymorphism locus (n = 146) were excluded. After reading the full text of the remaining papers, six were excluded because of duplication, 11 were excluded due to lack of data after efforts to contact the authors, and five articles were excluded as they did not present the required single nucleotide polymorphism (SNP)/mutant site. Fifty-nine studies