RESEARCH ARTICLE

Genetic Polymorphisms of TCF7L2 Lack Influence on Risk of the Polycystic Ovary Syndrome - a Systemic Analysis

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Abstract

Background: The results of previous researches that analyzed the association between genetic polymorphisms of transcription factor-7-like 2 (TCF7L2, rs7903146) and polycystic ovary syndrome (PCOS) were conflicting. Current systematic analysis was conducted to re-explore this association using updated materials. Materials and Methods: The PubMed database was used for data collection and the final search was conducted on January 3, 2014. For TCF7L2 rs7903146, a non-signficiant slight increase in risk of PCOS development was observed under three genetic models (dominant model: OR=1.06, 95%CI: 0.93-1.21, *p*>0.05; recessive model: OR=1.12, 95%CI: 0.87-1.43, *p*> 0.05; homozygous model: OR=1.14, 95%CI: 0.87-1.47, *p*>0.05). In the subgroup analyses in Asian group, allele susceptibility of PCOS was calculated (allele model: OR=1.00, 95%CI: 0.74-1.35, *p*>0.05; dominant model: OR=0.98, 95%CI: 0.71-1.35, *p*>0.05; recessive model: OR=1.79, 95%CI: 0.33-9.84, *p*>0.05; homozygous model: OR=1.78, 95%CI: 0.32-9.80, *p*>0.05), the differences were again not statistically significant. Conclusions: The findings of this systemic analysis suggest that the polymorphism of TCF7L2 rs7903146 may not be associated with the susceptibility to PCOS.

Keywords: Transcription factor-7-like 2 - genetic polymorphism - polycystic ovary syndrome

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Introduction

Polycystic ovary syndrome (PCOS) is a proliferative disorder among women of reproductive age, and currently considered a predominantly hyperandrogenic syndrome (Azziz et al., 2009; Bilici et al., 2013; , Haroon et al., 2014; Liu et al., 2013; Takiar et al., 2014a; 2014b). The three main diagnostic guidelines are the 1990 National Institutes of Health (NIH) criteria (Dunaif, 1992), the 2003 European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) (i.e. ESHRE/ASRM or Rotterdam) criteria (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). Several characteristics of PCOS are hyperandrogenemia, clinical hyperandrogenism (generally hirsutism), oligo-anovulation and polycystic ovaries. The underlying etiology of PCOS is unknown. However, cumulative evidence demonstrates that genetics plays an important role.

On the other hand, insulin resistance (IR) is a notable characteristic of PCOS. About 50-70% women with PCOS also develop IR. IR and hyperinsulinaemia could be a factor in the development of PCOS, as weight loss and insulin sensitizing drugs improve the clinical manifestations such as hyperandrogenaemia and restoring ovulation. The PCOS patients who develop IR could also be obese and also have impaired glucose tolerance. If the patients are not treated, they will likely develop type 2 diabetes (T2DM) in the future.

T2DM is a disease characterized by impaired insulin sensitivity. Candidate gene mapping suggests that many putative susceptibility variants, but only a few genetic variants leading to T2DM have been clearly identified including transcription-factor-7-like 2 (TCF7L2). A study on T2DM progression also suggests that TCF7L2 might be associated with beta-cell dysfunction on insulin secretion but not with insulin resistance. The TCF7L2 gene product is a high mobility group box-containing transcription factor implicated in blood glucose homeostasis. Previous study suggests that TCF7L2 acts on regulation of proglucagon through repression of the proglucagon gene in enteroendocrine cells via the Wnt signaling pathway. Now it has been definitively identified as the most important T2DM susceptibility gene. The single nucleotide polymorphism (SNP) rs7903146 is in strong linkage disequilibrium with the microsatellite and strongly associated with an increased risk of T2DM, and the T allele is identified as the variant which most strongly determines the T2DM. Thus, genotyping the SNP rs7903146 is probably the best way to evaluate the risk effect of the TCF7L2 on PCOS.

On this background, to further clarify the association between SNP rs7903146 genetic variation and PCOS, and to explore potential sources of heterogeneity that may have influenced the results, we conducted this systematic analysis.

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Materials and Methods

Search strategy

The searches were performed by two investigators and the final search strategies were performed with agreement. Electronic literature searches were conducted in PubMed/MEDLINE, till the beginning of January, 2014, using both free words and index terms specific to search platform (PubMed). The search strategies were based on combinations of the keywords 'PCOS', and 'transcription factor-7-like 2' as well as the abbreviations and synonyms of each terms. Only manuscript written in English was considered qualified. We also reviewed the reference lists of retrieved articles to identify other relevant publications.

Eligibility of relevant studies

Eligibility criteria included the following: (1) independent case-control or cohort studies; (2) inclusion of both PCOS cases and non-PCOS controls; (3) inclusion of adequate data to calculate the effect size: (a) biallelic mean and corresponding SD or (b) allele or genotype frequencies.

When the populations of several publications overlapped, we used the article with the most extensive data. If an article presented data of different groups of research subjects, the results of those analyses were handled as separate studies. The studies published in conference proceedings or as abstracts were included if they met the aforementioned criteria. Pedigree and family based studies were excluded because such studies are generally linkage studies or family based transmission disequilibrium studies.

Data extraction

Data extraction from the included studies was carried out by two authors independently and disagreements were resolved by consensus. All relevant articles identified through the search were scanned on the basis of title and abstract, and were rejected in the initial screening if the article clearly did not meet the inclusion criteria. If an article could not be rejected with certainty on the basis of its title and abstract, we obtained the full text of the article for further evaluation.

The following information was extracted from each study: the first author's name, year of publication, the country of origin, ethnicity and geographical location of the study population, number of cases and controls, definitions of cases and controls and method used to test the polymorphism.

Statistical analysis

We performed both continuous and dichotomous data analysis. Mean differences with 95% confidence intervals (CIs) were calculated. Dichotomous data are presented as numbers of different genotypes or alleles for each group in the form of 2×2 tables by using cut-off points. If a 2×2 table contained a 'zero cell', we added 0.5 to each cell of the 2×2 table for the study to deal with this problem. Odds ratios (ORs) and 95% CIs were reported by the article or calculated as the metrics of effect size.

Statistical analysis was carried out by using STATA (version SE 11.2; Stata Corporation, College Station, TX, USA). Meta-analysis was performed to assess pooled estimates of the effect. When heterogeneity was significant, data were analyzed by using a random-effects model (DerSimonian and Laird method). Otherwise, a fixed-effects model (Mantel-Haenszel method) was used. p values of <0.05 were considered to be statistically significant.

The following characters were investigated by subgroup analysis and meta-regression to identify whether they were sources of heterogeneity: geographic location, ethnicity, definition of PCOS and sample size of cases. In meta-regression analysis, these four factors were considered as covariates to find potential sources of heterogeneity. Covariates with $p<0.05$ were considered as sources of heterogeneity between studies

Results

Characteristics of studies: eligible studies were selected according to the inclusion and exclusion criteria. Seven eligible studies were retrieved from the PubMed databases, according to the inclusion and exclusion criteria, and were analyzed in this meta-analysis on evaluating the relationship between TCF7L2 SNP rs7903146 and risk of PCOS. There were 2 studies on Asian population and 5 on European population.

Characteristics of eligible studies are presented (Pei Xu et al., 2010; Barber et al., 2007; Kim et al., 2012; Ramos et al., 2013). These included studies were published from year 2011 to 2013 in different countries (China, Korea, UK, Finland, and Tunisia). Ethnicity was categorized as Asian population and Caucasian population. Several genotyping methods were employed in the studies including polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), etc.

The association between TCF7L2 SNP rs7903146 and PCOS susceptibility was assessed in seven studies among which 2 studies were in Asian population and 5 in Caucasian populations. Since heterogeneity was observed in all genetic models, so the random effects model was used to pool the results. An increased risk of PCOS development was observed under three genetic models (dominant model: OR=1.06, 95%CI: 0.93-1.21, $p>0.05$; recessive model: OR=1.12, 95%CI: 0.87-1.43, $p>0.05$; homozygous model: OR=1.14, 95%CI: 0.87-1.47, $p>0.05$), however, was not statistically significant. In the subgroup analyses in Asian group, allele susceptibility of PCOS was calculated (allele model: OR=1.00, 95%CI: 0.74-1.35, $p>0.05$; dominant model: OR=0.98, 95%CI: 0.71-1.35, $p>0.05$; recessive model: OR=1.79, 95%CI: 0.33-9.84, $p>0.05$; homozygous model: OR=1.78, 95%CI: 0.32-9.80, $p>0.05$), the differences were not statistically significant.

Discussion

To date, a number of genes have been reported to be associated with PCOS. Most of these genes are investigated due to relevant pathogenesis of PCOS based on their functions. However, the conclusion of the

pathogenesis of PCOS is still controversial.

The present systematic analysis on the association between TCF7L2 SNP rs7903146 and risk of PCOS did not provide evidence for this association. Some limitations of this systematic analysis should be taken into consideration, eg., the overall ORs were calculated on the basis of unadjusted estimates. Some confounding factors, including environmental factors and phenotypic characteristics of cases and controls, might exist in the included studies. However, such confounding factors could not be extracted from all the eligible studies because of different reporting strategies. As a result, adjusted estimates could not be used to perform a more precise evaluation and between-study heterogeneity existed. We performed subgroup analysis and meta-regression analysis, as well as random-effect modeling to solve the problem. To address this issue, individual patient data meta-analysis should be performed and confounding factors could be standardized.

Further, the sample sizes of cases and controls were limited. Although 2038 cases and 2519 controls were included in the analysis, for continuous and dichotomous data analysis, <2000 subjects were analyzed in each group respectively because of different reporting strategies. Fewer subjects were included in subgroups. Of the included studies, 5 studies (Pei Xu et al., 2010; Barber et al., 2010; Barber et al., 2010; Kim et al., 2010; Ramos et al., 2010) had over 200 case subjects; the rest studies had relatively small sample sizes. Therefore, owing to a limited number of individuals, some studies were underpowered to detect an association with PCOS. It is necessary to collect more samples in order to have enough statistical power to explore real association. In addition, potential biases may still exist. In order to avoid selection bias and publication bias, we did not perform study quality assessment, or excluded any non-English articles or conference abstracts. Owing to lack of necessary data, we still excluded several studies, which might result in the potential selection bias and be a source of heterogeneity.

Future genetic association studies should still be designed on the basis of new discoveries of such in vitro studies. The first genome-wide association study (GWAS) in PCOS was published in early 2011, and three genetic susceptibility loci were mapped in Han Chinese women with PCOS (Chen et al., 2011). We should advocate more effective studies to explore the association between TCF7L2 SNP rs7903146 and PCOS.

In conclusion, the findings of this systemic analysis suggest that the polymorphism of TCF7L2 rs7903146 may not be associated with the susceptibility of PCOS.

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