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Association of insulin gene variable number of tandem repeats regulatory polymorphism with polycystic ovary syndrome

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ABSTRACT

The present meta-analysis aimed to investigate the association between insulin gene variable number of tandem repeats (INS VNTR) and polycystic ovary syndrome (PCOS). Systematic searches of electronic databases, reference lists of included articles, and the abstracts presented at related scientific societies meetings were performed. Statistical analyses were conducted using software Stata 11.0. The pooled odds ratios (ORs) with 95% confidence intervals (95% CIs) were applied. Publication bias was tested by Begg's funnel plot and Egger's regression test. A total of 9 studies including 1075 PCOS patients and 2878 controls were included in the meta-analysis. There were evidence of statistical significant association between INS VNTR and PCOS in allelic model (OR = 1.25, 95% CI = 1.08–1.43, $P = 0.002$) and dominant model (OR = 1.34, 95% CI = 1.11–1.63, $P = 0.003$) but not in additive model (OR = 1.38, 95% CI = 0.93–2.04, $P = 0.11$) and recessive model (OR = 1.26, 95% CI = 0.96–1.65, $P = 0.09$). No significant publication bias was shown by funnel plots and Egger's regression tests. In conclusion, our meta-analysis suggests that the III allele of INS VNTR is associated with increased risk of PCOS.

1. Introduction

Polycystic ovary syndrome (PCOS), a heterogeneous endocrine disorder, is a leading cause of female infertility [1]. It was reported that up to 10% of reproductive women were diagnosed as PCOS [2,3]. By now, the pathogenesis of PCOS has not been completely elucidated. Insulin signaling pathway dysfunction may be one candidate as a large amount of women with PCOS were accompanied with insulin resistance, β-cell dysfunction, impaired glucose tolerance and/or type 2 diabetes [4,5]. In addition, evidence from different familial and monozygotic twins' studies indicated that the genetic factors played a key role in the development of PCOS [6,7]. Taken the above into consideration, it is reasonable that the genes regulating insulin secretion and action may contribute to the development of PCOS.

Insulin gene is localized on chromosome 11p15.5 [8]. About 596 bp upstream of the insulin gene translation initiation site is the promoter element, by binding to which the transcription factor Pur1 initiates transcription. This promoter element is known to have a variable number of tandem repeat regions. Alleles of Insulin gene variable number of tandem repeats (INS VNTR) are designated I, II, and III depending on the number of repeats: 26–63 repeats (I); 80 repeats (II); and 140–200 repeats (III) [9]. The first evidence showing linkage of INS VNTR and PCOS was from a family-based study. The study showed that the III alleles were only associated with women who were anovulatory and hyperinsulinaemic [10]. Another family-based study also showed that PCOS was associated with the III alleles [11]. In addition, numerous genetic associated studies with case-control design have focused on the association of INS VNTR and POCS [10,12–18]. However, results of different studies have been inconsistent, suggesting that it is unclear whether INS VNTR is associated with PCOS or not. We therefore performed this meta-analysis by combining current data to assess the association between INS VNTR and POCS.

2. Materials and methods

2.1. Literature search

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) criteria [19]. Using the combination of the following terms: insulin gene, variable number of tandem repeat and polycystic ovary syndrome,

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we collected all published studies on humans up to Feb. 21 2014 by searching three electronic databases (PubMed, Embase and Web of Science), reference lists of included articles, and the abstracts presented at related scientific societies meetings. The language was limited to English and Chinese.

2.2. Inclusion criteria

Two investigators (Yan MS and Liang GY) screened each of the titles, abstracts, and full texts to determine inclusion according to the following inclusion criteria independently: (1) studies reporting the relationship between INS VNTR and PCOS; (2) studies with case-control design; (3) studies with sufficient data for estimating an odds ratio (OR) with 95% confidence interval (CI).

2.3. Data extraction

Information was carefully extracted from all included publications independently by the same two authors (Yan MS and Liang GY) according to the inclusion criteria listed above. Disagreement was resolved by consensus. If these two authors could not reach a consensus, another author (Jin XM) was consulted. The following data were collected from each study: first author's name, publication date, country, ethnicity, study design (source of controls), and evidence of HWE ($P < 0.05$ of HWE was considered significant), respectively. Different ethnicities were categorized as Caucasian, Asian, African, Amerindian, and mixed. Study design was stratified to population-based (PB) studies and hospital-based (HB) studies. As INS-VNTR polymorphism is highly linked with −23/Hph I A/T single nucleotide polymorphism, the Hph I was used as a surrogate marker for INS-VNTR length polymorphism. We extracted the data of A allele for calculating III allele and T allele for I allele.

2.4. Quality score assessment

Quality score assessment was performed using Newcastle-Ottawa Scale (NOS) as previous described [20]. Briefly, two authors (Yan MS and Liang GY) of this article independently assessed the qualities based on and scored the studies from 0 to 9 points. Studies with a score of seven stars or greater were considered to be of high quality. Disagreement was settled as described above.

2.5. Statistical analysis

According to previous studies, we considered the I alleles as the referred allele. Combined OR with their 95% CI were calculated respectively for allelic model (III allele vs. I allele), additive model (III/III vs. I/I), dominant model (I/III + III/III vs. I/I), and recessive model (III/III vs. I/III + I/I) [21]. Between-study heterogeneity was assessed by the Q-test and I^2 statistic, $P < 0.10$ and $I^2 > 50\%$ indicated evidence of heterogeneity [22,23]. If there was no heterogeneity, a fixed effects model was used [24]. Otherwise, a random effects model was adopted [25]. Strength of agreement between reviewers regarding study selection was evaluated by Kappa statistic. Subgroup analyses were performed according to ethnicity (Asian and Caucasian) and source of control (PB and HB). Sensitivity analysis was conducted by limiting the meta-analysis to the high quality studies (NOS score $\geqslant 7$) and to studies in agreement with HWE. Publication bias was analyzed by Begg's funnel plot and Egger's test ($P < 0.05$ was considered representative of statistically significant publication bias) [26]. All above statistical analyses were performed using Stata 11.0.

3. Results

3.1. Study characteristics

The study selection process is detailed in Fig. 1. Our initial search identified a total of 476 potentially eligible articles. Based on our inclusion criteria, a total of 8 articles were involved in this meta-analysis [10,12–18]. There was perfect inter-rater reliability for the selection of studies to be included in the meta-analysis, with Kappa values of 0.834 based on titles and abstracts and 0.857 based on full texts. Table 1 lists the studies identified and their main characteristics. There were two independent case-control studies in the study of Powell et al. [13]. They were therefore analyzed separately. The NOS results showed that the average score was 7.33 (range 6–9), which indicated that the methodological quality was generally good.

3.2. Quantitative synthesis

Table 2 lists the main results of the meta-analysis. When all 9 studies were pooled into the meta-analysis, there were evidence of statistical significant association between INS VNTR and PCOS in allelic model (OR = 1.25, 95% CI = 1.08–1.43, $P = 0.002$) and dominant model (OR = 1.34, 95% CI = 1.11–1.63, $P = 0.003$) but not in additive model (OR = 1.38, 95% CI = 0.93–2.04, $P = 0.11$) and recessive model (OR = 1.26, 95% CI = 0.96–1.65, $P = 0.09$) (Fig. 2). When stratified by study design, significant associations were found in PB subgroup but not HB subgroup (Table 2).

3.3. Sensitivity analysis

Sensitivity analyses were conducted to determine whether modification of the inclusion criteria of the meta-analysis affected the final results. The included studies were limited to those conforming to HWE and those with high NOS score ($\geqslant 7$). Three studies [10,14,18] with relatively low NOS score (<7) and one study [10] being not in agreement with HWE ($P < 0.05$) were excluded. The corresponding pooled ORs were not materially altered indicating that our results were robust (Table 2).

3.4. Publication bias

Visual inspection of the funnel plot did not reveal any evidence of obvious asymmetry for all genetic models (Fig. 3). In addition, there was no evidence of publication bias among studies in all genetic models using Egger's regression test ($P = 0.587$ for allelic model, $P = 0.298$ for additive model, $P = 0.799$ for dominant model, $P = 0.839$ for recessive model, respectively).

4. Discussion

Recently, increasing studies have evaluated the association between INS VNTR and PCOS. However, the observed associations of these studies were inconclusive. Moreover, due to the relatively small sample size, single study may be too underpowered to detect a possible small effect of the gene polymorphism on PCOS. By combining samples from different studies, meta-analysis has been applied widely to detect the relationship between a specific gene and diseases [27,28]. Therefore, we conducted this meta-analysis to explore the association between INS VNTR and PCOS.

The underlying pathogen of PCOS is complicated. Burghen et al. showed that women with PCOS had increased insulin responses during oral glucose tolerance testing and acanthosis nigricans, suggesting a possible linkage of insulin resistant and PCOS [29]. Insulin was considered to participate in the regulation of ovarian