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Association of the CAG repeat polymorphisms in androgen receptor gene with polycystic ovary syndrome: A systemic review and meta-analysis

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ABSTRACT

Background: Many studies have reported the associations of polymorphic CAG repeats in androgen receptor (AR) gene with PCOS risk, but with inconsistent results. So, the aim of present meta-analysis was to clarify such inconsistence, so as to provide more conclusive results.
Methods: PubMed was searched for the eligible reports published until February 2012 without language limitation. The studies reporting the relationship between CAG repeat length and PCOS were selected for the meta-analysis according to the inclusion criteria. Two reviewers independently extracted the data and evaluated the study quality.
Principal findings: As for the relationship between CAG repeat length and PCOS risk, the pooled results showed that the biallelic mean was not significantly different between PCOS and controls (SMD −0.03, 95% CI −0.16–0.10, P = 0.603), and that the ORs of PCOS were not demonstrated for the individuals with the biallelic mean less than median (OR 0.96, 95% CI 0.68–1.35, P = 0.794), with the short CAG allele (OR 0.94, 95% CI 0.80–1.10, P = 0.424), or with the X-weighted biallelic mean (OR 0.81, 95% CI 0.46–1.41, P = 0.447). Further, as for the relationship between CAG repeat length and T levels in PCOS patients, the biallelic mean was not significantly different between PCOS patients with high T and those with low T (SMD 0.79, 95% CI −0.12–1.70, P = 0.088), while the summary correlation r indicated that the CAG biallelic mean appeared to be positively associated with T levels in PCOS (r 0.20, 95% CI 0.11–0.30, p = 0.000).
Conclusions: This meta-analysis demonstrates no evident association between the CAG length variations in AR gene and PCOS risk, while the CAG length appears to be positively associated with T levels in PCOS patients.

1. Introduction

Polycystic ovary syndrome (PCOS), a common endocrine disorder in the women of reproductive age, is characterized by a spectrum of clinical and biochemical manifestations mainly including hyperandrogenism, chronic anovulation and polycystic ovaries (Azziz et al., 2006; ESHRE/ASRM, 2004; Goodarzi et al., 2011). Although the pathogenesis of PCOS remains largely unclear, increasing evidences have indicated that the genetic defects may contribute to the development of this disorder (Diamanti-Kandarakis and Piperi, 2005; Urbanek, 2007). Since hyperandrogenism has been taken as one of the most important features of PCOS (Azziz et al., 2006), the genetic variants in some candidate genes that result in abnormal androgen activity may predispose an individual to the development of PCOS. However, no definitive genetic association with PCOS has been established with consistency up to now, even with a variety of genetic variants reported in literature (Simoni et al., 2008).

Androgen receptor (AR) gene is found in the first exon a polymorphic region of CAG trinucleotide repeats that ranges normally from 6 to 39 length in healthy individuals and encodes a polyglutamine chain related to the DNA transcriptional activity by AR (Edwards et al., 1992). Functional studies in vitro have demonstrated an inverse correlation between the CAG repeat length and AR activity, with the shorter CAG repeats having a higher receptor sensitivity to androgen response (Beilin et al., 2000; Chamberlain et al., 1994; Palazzolo et al., 2008). Additionally, clinical studies have also indicated that the CAG repeat polymorphisms might lead to an increased risk for many diseases due to aberrant androgenic sensitivity. For example, the shorter CAG repeat was reported to be associated with increased risk for prostate cancer (Giovannucci et al., 1997; Stanford et al., 1997), hirsutism and ovarian hyperandrogenism (Calvo et al., 2000; Ibanez et al., 2003; Legro et al., 1994), while the longer CAG repeat appeared to result in spinal and bulbar muscular atrophy, abnormal sperm production and thus male infertility (Davis-Dao et al., 2007; Dowsing et al., 1999; Mhatre et al., 1993; Tut et al., 1997; Yong et al., 2003).

Abbreviations: AR, Androgen receptor; PCOS, Polycystic ovary syndrome; MeSH, Medical Subject Headings; SNPs, Single nucleotide polymorphisms; HWE, Hardy–Weinberg equilibrium; ORs, Odds ratios; CIs, Confidence intervals; SMD, Standardized mean difference.

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Based on the above findings, it is plausible for the hypothesis that the CAG length variants may be involved in the pathogenesis of hyperandrogensim in women and thus lead to the PCOS development. However, recent clinical studies that attempted to testify such hypothesis have produced conflicting results. Some studies reported evident association between the short CAG repeats and high PCOS susceptibility, and such causal relationship was presumably related to the hyperandrogenic activity of the short CAG variants (Schuring et al., 2012; Shah et al., 2008), while others could not confirm it (Dasgupta et al., 2010; Ferk et al., 2008; Jaaskelainen et al., 2005; Liu et al., 2008; Skrgatic et al., 2012). Contrary to most other studies, one study by Hickey et al. (2002), paradoxically reported that the longer CAG repeats were associated with an increased PCOS risk. Moreover, since X-chromosome inactivation might lead to preferential activation of the shorter CAG allele and thus increase androgen receptor activity, such epigenetic modification of CAG allele has been proposed to be implicated in the pathogenesis of PCOS as well (Vottero et al., 1999). Similarly, subsequent clinical studies on such issue have yielded inconsistent results (Dasgupta et al., 2010; Hickey et al., 2002; Shah et al., 2008). Finally, another question remains controversial regarding the relationship between CAG polymorphisms and T concentrations (a parameter of hyperandrogensim) in PCOS women (Jaaskelainen et al., 2005; Kim et al., 2008; Liu et al., 2008; Mifsud et al., 2000; Schuring et al., 2012; Skrgatic et al., 2012).

Given that the conflicting results have been reported in literature regarding associations of CAG repeat length with PCOS risk and testosterone concentration in PCOS, we conducted a comprehensive meta-analysis of the published data to clarify such inconsistence and identify potential sources of heterogeneity that might confound the conclusions.

2. Materials and methods

2.1. Literature search

We performed a full search in PubMed database for the eligible articles published until February 2012, without language limitation. The search terms covered Medical Subject Headings (MeSH) and/or text words relating to androgen receptor and PCOS. Of the retrieved papers, the abstracts and titles, as well as the full-text if needed, were screened for fulfillment of the inclusion criteria. Additional relevant articles were identified by further manual searches of the reference lists of the retrieved papers and reviews.

2.2. Study selection and data abstraction

Only those original studies that reported genetic associations of CAG variants in AR gene with PCOS were included. Additionally, it should fulfill the following criteria: PCOS diagnosed according to one of the three accepted criteria by the National Institutes of Health (NIH)(Zawadzki JK, 1992), the Rotterdam (ESHRE/ASRM) (ESHRE/ASRM, 2004) and the Androgen Excess Society (AES) (Azziz et al., 2006); healthy women with proven fertility selected as controls; with genotyping details and sufficient data for meta-analysis. In cases of duplicate publication and/or overlapping data, the primary authors were contacted for clarification, and if confirmed, only the largest or most recent publication was included as recommended previously (Little et al., 2002).

The variables were abstracted from each eligible study according to the MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines. Quantitative data were either extracted directly from articles or calculated using original information provided in the tables and figures in case of lacking direct data (Parmar et al., 1998). Study selection and data abstraction were performed by two independent authors (T Zhang and WQ Liang), and any disagreement was resolved by consensus.

2.3. Data synthesis

The present meta-analysis aimed to define two questions, i.e., the influences of CAG length polymorphisms on PCOS risk and T concentrations in PCOS patients respectively. As for the first question, the primary outcome measures included SMD (standardized mean difference) of the CAG biallelic mean between PCOS patients and normal controls, and the OR (Odd ratio) of PCOS for individuals with different CAG allele patterns (the CGA biallelic mean length less than median, the short CAG allele and the X-weighted biallelic mean less than median). As for the second question, the primary outcome measures included SMD of the CAG biallelic mean between PCOS with high T and PCOS with low T, and correlation r of the CAG biallelic mean with T levels in PCOS patients. The summary SMD, OR and r were calculated with their 95% confidence interval (CI), and the outcomes in each study were weighted. These outcomes were pooled by random effect model or fixed effect model according to the between-study heterogeneity. Forrest plot was employed to display graphically the outcomes and their 95% CIs. We calculated the power for each pooled outcome to show the probability of detecting a true effect, assuming the significance level at 0.05 and the PCOS prevalence at 6% (Hedges and Pigott, 2001, 2004).

2.4. Bias and heterogeneity

For each outcome pooled, the bias and heterogeneity were assessed with appropriate methods among included studies. First, the Begg's funnel plot was created with the effect size (on a logarithmic scale) against its standard error for each study, and visual confirmation of any plot asymmetry indicates bias presentation. Further, a test for funnel plot asymmetry, described by Egger et al., was also performed to statistically assess the presence of publication bias (Egger et al., 1997). Heterogeneity was assessed by Cochran's Q test and I^2 statistic (Higgins et al., 2003).

2.5. Analysis software

All statistical analyses were carried out in Stata 11.0 (StataCorp, College Station, TX).

3. Results

3.1. Search results

A total of 209 articles were identified by the PubMed search, of which 20 were selected as the potentially relevant studies after screening of the titles and abstracts, and reviewed subsequently in full text for a more detailed evaluation. As a result, 11 studies met the inclusion criteria and were involved in the meta-analysis. The main reasons for exclusion are as follows: 4 papers not reporting PCOS risk as main outcomes (Diaz et al., 2010; Ibanez et al., 2003; Mohlig et al., 2006; Tong et al., 2010), 2 studies not related to the genetic variants CAG of AR (Goodarzi et al., 2008; Peng et al., 2010), one without normal controls(Van Nieuwerburgh et al., 2008) and two without sufficient data (Ramos Cirilo et al., 2012; Xita et al., 2008). A hand-searching reference lists produced no other eligible publications. Fig. 1 provides an overview of the flow chart for study selection.

3.2. Study characteristics

The eligible studies were conducted in populations from a wide range of geographical settings and different ethnic origins. PCOS patients were diagnosed according to the Rotterdam criteria or alike in most studies, and the remaining two used the NIH criteria (Hickey et al., 2002; Shah et al., 2008). The normal controls in most studies were selected from hospital-based fertile women, while in 2 studies selected from