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REVIEW ARTICLE

Androgen receptor gene polymorphism and polycystic ovary syndrome

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is characterized by ovulatory dysfunction and hyperandrogenism. Its etiopathology is not well understood but genetic factors seem to have a role. Polymorphism of the androgen receptor (AR) gene has been associated with different androgen pattern diseases. *Objective:* To review the association between AR gene polymorphism and PCOS. *Search strategy:* A systematic review was performed via PUBMED, EMBASE, and LILACS (up to May 31, 2011). *Selection criteria:* Studies assessing the presence of the $(CAG)_n$ polymorphism of the AR gene in at least 2 comparison groups (PCOS and control). Studies that did not contain adequate information were excluded. *Data collection and analysis:* Study characteristics and results were analyzed. Meta-analysis could not be performed because only 2 articles provided odds ratios. *Main results:* Ten studies met the inclusion criteria. Three studies reported a correlation between the polymorphism and PCOS; 2 studies linked the disorder to shorter repeats, whereas the other associated it with longer repeats. *Conclusion:* Polymorphism of the AR gene seems to be a promising biomarker for PCOS because shorter repeats may be linked to the disorder. However, further studies are needed to understand the association fully.

1. Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies in young women [1]; it is characterized by chronic anovulation, clinical and laboratory evidence of hyperandrogenism, and ultrasound detection of micropolycystic ovaries [2]. It is a heterogeneous disorder of unclear etiopathogenesis but there is evidence of the participation of a genetic component [3].

Hyperandrogenism is the hallmark of PCOS. Clinically, it is possible to observe hirsutism, acne, androgenetic alopecia, and signs of virilization. Laboratory examination reveals increased androgen levels [2], which are associated with inhibition of follicle development, anovulation, menstrual changes, and microcysts in the ovaries [4]. Evidence from experimental models indicates that exposure to intrauterine androgens leads to the development of a phenotype similar to PCOS in animals [5]. Thus, excessive androgen has an important role in the pathophysiology of PCOS.

Androgen action is mediated by the androgen receptor (AR). The gene encoding the AR is located in the Xq11–q12 region and has a polymorphic region in exon 1 typified by a CAG trinucleotide repeat encoding polyglutamine residues [6]. A gene is considered polymorphic when it has 2 or more allele variants, of which at least 2 occur in more than 1% of the population. Some polymorphic loci have been associated with diseases, as markers or as genetic susceptibility factors, because they can alter the production and expression of their products [7].

It has been reported that the number of CAG repeats negatively correlates with AR activity [8]. Whereas abnormal trinucleotide expansion (>40 CAGs) results in spinobulbar muscular atrophy (a fatal neuromuscular disorder), polymorphic variations within the normal range (8–35 CAGs) have been associated with disorders of high or low androgen pattern [9,10].

Shorter polymorphic repeats $(CAG)_n$ of the AR gene correlate with the seriousness and aggressiveness of prostate tumors [11,12], hirsutism [13], and precocious pubarche [14]. Longer polymorphic repeats are associated with male infertility [15] and precocious development of breast cancer both in female carriers of the BRCA1 mutation [16] and in men [17]—the latter probably because of the inhibitory effect of androgens on the proliferation of mammary tissue [18].

Considering the hyperandrogenic pattern of PCOS, the defective AR function in the presence of polymorphism $(CAG)_n$, and the conflicting results in the literature, the aim of the present study was to evaluate the association between AR polymorphism and PCOS via a systematic review of the literature.

2. Materials and methods

PUBMED, EMBASE, and LILACS were searched for articles published up to May 31, 2011, with no bars on foreign languages. The following keywords, taken from the Medical Subject Headings, were used: polycystic ovary syndrome AND androgens AND genetic polymorphism. References from the original articles were also analyzed. Studies involving at least 2 comparison groups (PCOS and control) were included if they assessed the presence of the $(CAG)_n$ polymorphism of the AR gene in patients with PCOS.

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Studies not containing adequate information about the control group (clinical data about comorbidities and menstrual cycle) or the PCOS group (no exclusion of other causes of hyperandrogenism or diagnostic criteria) were excluded. Diagnostic criteria were considered valid if they conformed to the Androgen Excess and PCOS (AE-PCOS) Society [2], 2003 Rotterdam [19], or 1990 National Institutes of Health (NIH) [20] criteria. Case series or reports, clinical trials, and reviews were excluded. The MOOSE statement was consulted to improve study quality.

3. Results

In total, 187 articles were found, 16 of which evaluated AR polymorphism in PCOS patients. Five studies were excluded because they did not meet the objective of the present systematic review. The study by Diaz et al. [21] evaluated the $(CAG)_n$ polymorphism function only in patients with PCOS after metformin use. Sanders et al. [22] and Urbanek et al. [23] used family samples in their studies. The studies by Mohlig et al. [24] and Van Nieuwerburgh et al. [25] limited assessment of the effect of polymorphism to insulin resistance and hyperandrogenic parameters of PCOS patients, respectively. The study by Laisk et al. [26] was also excluded because the authors did not list the inclusion criteria for the patients in the control group.

The 10 studies that were selected were published between 2000 and 2010, all of them in English (Table 1). Five included women of Asian ethnicity (Indian, Chinese, and Korean) [27–31] and 3 studied white European populations (Greek, Slovenian, and Finnish) [32–34]. Hickey et al. [35] evaluated white Australian populations descended from Europeans, and Shah et al. [36] included white and black populations in the USA.

Sample sizes varied; taking into account all of the studies, the total number of patients was 1508, with 1623 controls. The Rotterdam diagnostic criteria were used in half of the studies [27–30,33]; the NIH criteria were used in 3 studies [32,33,36]. In the other 2 studies [31,34], the authors applied their own diagnostic criteria; however, the patients also met the Rotterdam criteria.

The methods used to evaluate polymorphism were fairly heterogeneous. Three studies [29,31,33] used the biallelic mean and the mean repeat number of the long and short alleles. Liu et al. [30] used only the biallelic mean. The other 6 studies grouped the patients in classes according to the number of repeats using the biallelic mean [28,35,36] or a pre-established number of repeats based on the literature [27,32,34]. Of the 10 studies, 3 found an association between polymorphism and PCOS, whereas 7 found no association. The results of Shah et al. [36] and Tong et al. [27] corroborated the assumption that shorter repeats are linked to PCOS, whereas the study by Hickey et al. [35] associated the disorder with longer repeats.

A meta-analysis could not be performed because only 2 articles [28,36] provided data regarding odds ratios and calculated the risk for PCOS in relation to the $(CAG)_n$ polymorphism of the AR gene.

4. Discussion

Polycystic ovary syndrome is a multifactorial disorder of unclear etiopathogenesis. Dysfunctions of gonadotropin secretion, folliculogenesis and ovulation, androgen production and action, and insulin resistance and adipose tissue have been reported [37]. Of the PCOS abnormalities, hyperandrogenism stands out because it is an item included in all of the diagnostic criteria adopted worldwide and is deemed a *sine qua non* by researchers in the field [2]. Hence, the present study systematically reviewed articles relating the $(CAG)_n$ polymorphism of the AR gene to the occurrence of PCOS.

One of the factors making it difficult to study PCOS is the heterogeneity of clinical presentations. Currently, 3 sets of diagnostic criteria (1990 NIH, 2003 Rotterdam, and 2009 AE-PCOS Society) are well established and accepted worldwide. In the articles included in the present review, the authors used NIH, Rotterdam, or their own criteria. Although it is arguable not to use well-defined diagnostic criteria in a scientific publication, the 2 research groups [31,34] that applied their own criteria stipulated parameters for the syndrome that met the Rotterdam criteria. The problem with using the Rotterdam criteria for defining PCOS is the inclusion of a phenotype characterized by ovulatory dysfunction (anovulation and polycystic ovaries) alone, without the presence of hyperandrogenism. Thus, it would not be adequate to evaluate the presence of a genetic variation that has an influence on the androgen pattern, as was the case in most of the studies [27–31,33,34].

Table 1
Characteristics of studies evaluating the presence of the $(CAG)_n$ polymorphism in the androgen receptor gene as a risk factor for polycystic ovary syndrome.

Author and year of publication	Ethnicity	Country	Diagnostic criteria for PCOS	No. of cases	No. of controls	Evaluation method for polymorphism	Association
Tong et al. 2010 [27]	Asian	China	2003 Rotterdam	50	141	Stratification in groups: <20; 20–25;and >25 repeats (evaluation of total number of repeats)	Yes
Dasgupta et al. 2010 [28]	Asian	India	2003 Rotterdam	250	299	Stratification in groups: <19; 19; and >19 repeats (evaluation of total number of repeats and biallelic mean)	No
Kim et al. 2008 [29]	Asian	Korea	2003 Rotterdam	114	205	Biallelic mean, and long and short allele mean	No
Liu et al. 2008 [30]	Asian	China	2003 Rotterdam	148	104	Biallelic mean	No
Mifsud et al. 2000 [31]	Asian	Singapore	Changes in menstrual cycle, polycystic ovaries, infertility, and exclusion of other diseases	91	112	Biallelic mean and long and short allele mean	No
Xita et al. 2008 [32]	White	Greece	1990 NIH	180	168	Stratification in groups: ≤20 and >20 repeats (total number of repeats)	No
Ferk et al. 2008 [33]	White	Slovenia	2003 Rotterdam	117	114	Biallelic mean and long and short allele mean	No
Jääskeläinen et al. 2005 [34]	White	Finland	Anovulation, polycystic ovaries, exclusion of other diseases, and one of the following: hirsutism; infertility; rise in androgen levels; elevated LH/FSH ratio at the luteal phase	106	112	Stratification in groups: <19; 19–24; and >24 repeats (total number of repeats)	No
Hickey et al. 2002 [35]	White	Australia	1990 NIH	122	83	Stratification in groups: ≤22 and >22 repeats (evaluation of the biallelic mean and total number of repeats); ≤21 and >21 repeats (evaluation of the shortest allele); ≤23 and >23 repeats (evaluation of the longest allele)	Yes
Shah et al. 2008 [36]	White and black	USA	1990 NIH	330	289	Stratification in groups: repeats below and above the biallelic mean (22 for white women and 20 for black women)	Yes

Abbreviations: AR, androgen receptor; FSH, follicle-stimulating hormone; LH, luteinizing hormone; NIH, National Institutes of Health; PCOS, polycystic ovary syndrome.

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