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REVIEW

Is polycystic ovary syndrome a sexual conflict? A review

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Abstract Several studies have attempted to explain the high overall prevalence of polycystic ovary syndrome among women worldwide (about 4–10%) despite its link to subfertile phenotypes. For this reason, it is considered an evolutionary paradox. In this review, we show that several genetic loci associated with the disease differently modulate the reproductive parameters of men and women. This observation suggests that such genetic variants lead to opposite effects in the two sexes in reproductive success. Intralocus sexual conflict as a cause of the persistence polycystic ovary syndrome genotypes among humans is supported.

KEYWORDS: evolution, gender, hyperandrogenic, metabolic, PCOS, sex-specific

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age (Conway et al., 2014; Dumesic et al., 2015). The high prevalence worldwide and the large negative effect on female fertility have focused attention on this multifaceted disease. Even if the disease impairs female fertility, its high global prevalence is still increasing, representing an evolutionary paradox.

The complexity of PCOS is demonstrated by the absence of agreement on the definition of the disease itself, as a consequence of its heterogeneity and uncertain cause. It is mainly characterized by ovulatory disturbances, hyperandrogenism and polycystic ovarian changes (Dumesic et al., 2015). It is also associated with defects in glucose homeostasis caused by insulin resistance, which confers a significantly increased risk for type 2 diabetes (Hayes et al., 2015). The resulting hyperinsulinaemia seems to contribute to ovulatory disfunction

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(Hayes et al., 2015). These clinical features in fact generate different phenotypes with ethnic variations.

We recently demonstrated that ethnic variations in women with PCOS are linked to a genetic background derived from genetic drift (Casarini and Brigante, 2014). Familial aggregation and twin studies (Vink et al., 2006) has also shown a significant role of genetics in PCOS. Further genome-wide association studies (GWAS) have identified some susceptibility regions associated with PCOS (Chen et al., 2011; Shi et al., 2012; Welt and Duran, 2014), which need to be deepened. Moreover, PCOS GWAS loci contain extensive alterations in methylation, resulting in different gene expression profiles, with differences between clinical subtypes based on presence or absence of obesity (Jones et al., 2015).

As PCOS is a disease affecting only women, all the studies cited above were conducted among women. Men, however, should have a role in the maintenance of the genetic trait predisposing to PCOS. The male sex hormone, testosterone, regulates libido, genital organ development and secondary sexual characteristics, such as muscles, beard, hair and voice timbre. For this reason, androgenization of men increases their reproductive potential and can be considered favourable from an evolutionary point of view. The pro-fertility role of testosterone is not primarily related to an increase of spermatogenesis. In fact, germ cells do not express androgen receptor and the testosterone effect on them is mediated by Sertoli, Leydig and interstitial cells (O'Hara and Smith, 2015). Therefore, fertility is preserved as normal in oligozoospermic mice lacking the androgen receptor in testis peritubular myoid cells (Zhang et al., 2006). An important reproductive role of androgenized phenotypes could, therefore, depend on higher chances of finding a partner and having sexual intercourse.

Besides androgenization, women with PCOS have a worse metabolic profile, but the opposite is the case in men: androgens seem to protect the male from metabolic disorders (Grossmann, 2011). Indeed, low testosterone levels, together with low LH, are strongly associated with obesity and the risk of developing metabolic syndrome in men (Antonio et al., 2015).

With this in mind, we might explain why the human species tends to preserve a genetic trait that impairs female fertility but improves the chances of male reproduction.

In this review the genetics behind PCOS is analysed from an innovative perspective, looking for a different modulation on reproductive parameters in men and women.

Disease's genetic hot spot

Several genetic *loci* were found in association with PCOS in women of Han Chinese ancestry (Chen et al., 2011; Shi et al., 2012), but only a few of them were confirmed in Caucasian (Welt and Duran, 2014). This might be a result of the different diagnostic criteria used, but does reveal the ethnicity-related nature of the disease. The most significant loci and the phenotypical consequences linked to their most significant variants, in women and men, are briefly described. The online database PCOSKB (http://www.pcoskb.bicnirrh.res.in), a collection of genes, diseases, and biochemical pathways associated with the disease (Joseph et al., 2016) (**Table 1**), was used to further confirm the relationship between PCOS genes and phenotype, and their sex-related differences. As the large volume of data do not permit extensive quotation of the original papers, we refer to the database for the specific references supporting the informations provided in the table.

DENND1A gene

DENND1A is a member of the connecdenn family and binds to clathrin and clathrin adaptor protein-2, acting as guanine nucleotide exchange factors for the early endosomal small GTPase RAB35 (Marat and McPherson, 2010). Some single nucleotide polymorphisms (SNPs) in this gene were associated with PCOS, at least in women of Chinese and European ancestry (Chen et al., 2011; Goodarzi et al., 2012; Shi et al., 2012; Welt et al., 2012). *DENND1A* overexpression results in a PCOS-like phenotype of theca cells, characterized by increased androgen biosynthesis (McAllister et al., 2014), revealing that this gene may give a strong contribution to the establishment of hyperandrogenic PCOS phenotypes. In Han Chinese women with PCOS, *DENND1A* SNPs are also associated with endocrine and metabolic disturbances (Cui et al., 2013). These studies suggest that *DENND1A* gene is a candidate marker for the disease, although some contradictory data exist. In fact, no association was found between *DENND1A* and PCOS in Bahraini Arab women (Gammoh et al., 2015), most likely because compensatory metabolic mechanisms depend on the genetic background. Moreover, no studies investigating the role of *DENND1A* gene SNPs in men have ben conducted, so it is not possible to draw any conclusions about the role of SNPs within this gene.

THADA gene

Some aberrations in the *thyroid adenoma-associated* (*THADA*) gene were found in thyroid tumours (Drieschner et al., 2006; Rippe et al., 2003). SNPs within the *THADA* gene were associated with body-mass index (BMI), weight, type 2 diabetes, obesity and metabolic syndrome in both men and women of different ethnicity (Almawi et al., 2013; DeMenna et al., 2014; Gupta et al., 2013). This is most likely caused by thyroid hormones in the metabolic regulation. As metabolic disturbances are frequent in women with PCOS, SNPs in the *THADA* gene were associated with the disease in Asians and Europeans (Cui et al., 2013; Goodarzi et al., 2012). A possible link between this gene and the phenotypic metabolic features of the disease should be mediated by the alteration of pancreatic beta-cell function (Simonis-Bik et al., 2010).

LHCGR gene

The LH chorionic and gonadotropin receptor (LHCGR) plays a key role in the control of development and reproduction, regulating oestrogen production, progesterone synthesis and ovulation in women, and testosterone production in men (Ascoli et al., 2002). Several *LHCGR* SNPs were largely studied in association with PCOS (Mutharasan et al., 2013; Welt and Duran, 2014; Hayes et al., 2015) and other diseases, including abnormal sexual differentiation and ovarian cancer (Choi and