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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

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Table 1 Polycystic ovary syndrome genes showing sex-related associations.

Gene	*Features*		
	Female	*Male*	*Both sexes*
DENND1A	Hyperandrogenism Menstrual cycle irregularity PCOS Tumours (endometrioid adenocarcinoma)		
THADA	Hyperandrogenism PCOS		
LHCGR	Anovulation PCOS Primary amenorrhoea Tumours (endometrioid adenocarcinoma, mammary gland)	Azoospermia Hypogonadism Pseudohermaphroditism Tumours (Leydig cells)	Infertility Tumours (adrenal aldosterone-producing) Virilization
FSHR	Anovulation Endometriosis PCOS Polycystic ovaries Primary amenorrhoea Tumours (ovarian epthelial)	Azoospermia	Infertility Precocious puberty
YAP1	PCOS		
RAB5	PCOS		
SUOX	PCOS		Sulphite oxidase deficiency
INSR	Hyperandrogenism PCOS Tumours (ovarian epthelial, pancreatic beta-cell)		Acanthosis nigricans Autoimmunity Diabetes mellitus Dyslipidaemia Fatty liver Hypertension Insulin sensitivity, insulin resistance Myotonic dystrophy Obesity Rabson–Mendenhall syndrome Retinopathy Skin lesion Werner syndrome
AR	Primary amenorrhoea Preeclampsia Tumours (breast, ovarian epithelial, endometrium, extramammary Paget disease, multiple metastatic,	Androgen insensitivity syndrome Androgenetic alopecia Azoospermia and oligozoospermia Bone mineral density Kennedy disease Pseudoermaphroditism Spermatogenesis impairment Tumours (prostate, urothelial, bladder)	Infertility Obesity Tumours (skin appendage, salivary gland and duct, sebaceous gland, benign pleomorphic adenomas) Virilization

PCOS, polycystic ovary syndrome.

Smitz, 2014; Lee et al., 2015). Moreover, a *LHCGR* SNP (rs4073366) is associated with a higher response to gonadotrophins in women undergoing assisted reproduction techniques, resulting in increased risk of ovarian hyperstimulation syndrome (O'Brien et al., 2013). Also, inactivating mutations or deletions of the *LHCGR* gene give rise to infertile or subfertile phenotypes in both sexes, such as Leydig cell hypoplasia in men (Gromoll et al., 2000; Segaloff, 2009) and oligomenorrhoea, amenorrhoea and empty follicle syndrome in women (Arnhold et al., 2009; Bentov et al., 2012; Yariz et al., 2011). Moreover, activating mutations of the *LHCGR* gene cause gonadotrophin-independent precocious puberty in men (Segaloff, 2009), but have no detectable effects in women. If the early sexual development is considered as a precocious start of fertile age, it could represent an evolutionary advantage in men rather than in women. Therefore, the *LHCGR* genotype could have a modulatory effect on the reproductive features of both sexes.

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FSHR gene

The *FSH receptor (FHSR)* belongs to the superfamily of the rhodopsine-like G protein-coupled receptors, together with the LHCGR. It is a mediator of follicle maturation by regulating the proliferation and differentiation of the ovarian cells (Simoni et al., 1997), although in-vitro studies have demonstrated the apoptotic potential of FSH exerted through its receptor in granulosa cells (Amsterdam et al., 1999). In men, FSHR mediates the FSH-dependent maturation of germ cells. *FSHR* gene carries the common SNPs c.2039A>G (rs6166) and c.919A>G (rs6165), which are in strong linkage disequilibrium, resulting in two discrete isoforms largely widespread among human populations (Simoni and Casarini, 2014). Several studies have suggested that *FSHR* c.2039A>G is a modulator of the ovarian response to FSH in women (Perez-Mayorga et al., 2000) and spermatogenesis, testis volume and testosterone levels in men (Grigorova et al., 2013; Lazaros et al., 2013; Lindgren et al., 2012), affecting the FSH, inhibin B and anti-Müllerian hormone serum levels (Grigorova et al., 2014; Hagen et al., 2013). A recent in-vitro study confirmed that this polymorphism results in the modulation of steroidogenesis in granulosa cells (Casarini and Brigante, 2014). Also, a SNP located in the promoter region of the *FSHR* gene (c-29G>A; rs1394205) may cause altered receptor expression (Desai et al., 2011). It may result in cumulative effects, together with other *FSHR*, *FSHB* and *follistatin* gene variants (Urbanek et al., 1999), modulating reproductive parameters (Grigorova et al., 2014; Simoni and Casarini, 2014). In fact, the SNP -211G>T located within the *FSHB* promoter negatively influences reproductive parameters in men but not in women, suggesting gender-specific regulation of gonadotrophin secretion and, as a consequence, of progesterone and testosterone production (Schüring et al., 2012). Indeed the *FSHB* gene was found to be associated with PCOS (Hayes et al., 2015). Because of their role in the modulation of gonadal functions, *FSHR* common SNPs are also involved in PCOS pathogenesis in women (Du et al., 2010; Mutharasan et al., 2013), and are associated with hyperandrogenic phenotypes (Valkenburg et al., 2009), preterm birth (Chun et al., 2013) and ovarian cancer risk (Qin et al., 2014). The same SNPs are linked to testicular germ cell tumours (Ferlin et al., 2008), and infertility (Shimoda et al., 2009) in men. Interestingly, *FSHR* SNPs may be associated with longevity and lower risk of developing Alzheimer's disease in women but not in men (Corbo et al., 2011, 2013), leading to the speculation that it may have played a role in prolonging the life span of women.

YAP1 gene

The *YES associated protein* 1 (*YAP1*) gene is highly expressed in placenta, prostate, testis, ovary and small intestine (Sudol et al., 1995). It is a nuclear factor downstream to the Hippo signalling pathway, involved in anti-apoptotic processes related to cell fate during development, cell proliferation, DNA repair, homeostasis and oncogenesis (Basu et al., 2003; Zhang et al., 2011; Fu et al., 2014). *YAP1* acts as an oestrogen and progesterone receptor co-activator (Dhananjayan et al., 2006), potentially modulating the activity of steroid hormones. In the ovary, Hippo signalling stimulates follicle growth via activation of *YAP1* (Hsueh et al., 2015), and it has been indicated as a possible target for infertility treatments in PCOS or primary ovarian insufficiency affected women (Kawamura et al., 2013). Therefore, *YAP1* is a candidate gene for PCOS pathogenesis (Louwers et al., 2013); in particular, *YAP1* SNPs are associated with different oral glucose tolerance and LH levels in Han Chinese PCOS patients (Li et al., 2012), contributing to modulate phenotypic features of the disease. On the contrary, no studies have demonstrated a significant role of YAP in the modulation of reproductive parameters in males, suggesting that this gene might be involved in sex-dependent regulatory mechanisms of metabolism and gonadal functions.

RAB5B/SUOX genetic locus

RAB5B is a Rab-GTPase, which regulates membrane trafficking, endocytosis and receptor recycling (Stenmark, 2009). It was speculated that, in women, this protein contributes to the establishment of PCOS hyperandrogenic phenotype by modulating the gonadotropic action via protein kinase B (AKT) pathway (McAllister et al., 2015). *SUOX* gene encodes for a sulphite oxidase (Garrett et al., 1995), and its genetic variants were mainly associated with sulphite oxidase deficiency (Garrett et al., 1998; Johnson et al., 2002; Kisker et al., 1997; Seidahmed et al., 2005). The intergenic region *RAB5B/SUOX* was reported as a susceptibility locus for type 1 diabetes (Wellcome Trust Case Control Consortium, 2007), suggesting that SNPs within this region may be implicated in glucose tolerance in women with PCOS (Saxena et al., 2015). Little, however, is known about the molecular mechanisms underlying the involvement of this genomic region in the pathogenesis of the disease.

INSR gene

The *insulin receptor (INSR)* is fundamental for insulin metabolism and its genetic variants are associated with hyperandrogenism, insulin resistance, *achantosis nigricans*, obesity and anovulation in women with PCOS (Cui et al., 2013; Grasso et al., 2013; Højlund et al., 2004; Jiang et al., 2011; Mukherjee et al., 2009; Tucci et al., 2001). It reflects the role of insulin resistance in the modulation of PCOS features (Chen et al., 2011) and ovarian function (Sirotkin, 2011). Although testosterone excess is linked to insulin resistance in women with PCOS (Alpañés et al., 2015; Münzker et al., 2015), high androgen levels are linked to weight loss in males (Traish, 2014). Moreover, androgen deficiency may result in metabolic syndrome in men (Yu et al., 2014). Taken together, an inverse, sex-dependent relationship between testosterone and metabolism homeostasis among PCOS women and men has been suggested (Navarro et al., 2015).

X-linked PCOS phenotypes

Although PCOS is particular to women, an association has been found between genes within the X chromosome and the

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disease. A candidate locus may be the cytosine-adenine-guanine (CAG) repeats within the exon 1 of the *AR* gene, which confers differential receptor activity and androgen sensitivity; different lengths of the CAG and GGN repeats (where 'N' indicates "any nucleotide") are present in white women and Han Chinese women with PCOS compared with healthy controls, resulting in high testosterone levels and metabolic consequences (Hickey et al., 2006; Peng et al., 2014; Schüring et al., 2012; Skrgatic et al., 2012; Yuan et al., 2015). Other studies and a meta-analysis, however, failed to find such association (Zhang et al., 2013), suggesting that several factors modulate the disease, most likely polygenic regulation of the trait. GGN and CAG trinucleotide repeats in the *AR* gene are more strongly associated with central obesity in white adult women rather than men (Gustafson et al., 2003), suggesting a sex-related relationship between androgens and metabolism. In particular, the length of *AR* CAG repeats is associated with testosterone levels and fat accumulation in men (De Naeyer et al., 2014; Fietz et al., 2011; Mouritsen et al., 2013; Simmons and Roney, 2011; Zitzmann, 2009), providing a putative evolutionary advantage for men with high androgen levels. This leads to the evolutionary speculation that testosterone may have played a role in the choice of the male partner but with a detrimental effect in female progeny that inherited high androgen sensitivity (Howard, 2001; Roney et al., 2010).

Clinical features of women with PCOS may also be modulated via X-linked epigenetic modification (Hickey et al., 2006), but further studies should be conducted to better address this issue.

Evolutionary theories

Several theories attempting to explain the maintenance of PCOS in humans, rely on the paradox that the disease results in a sub-fertile female phenotype, which should be evolutionarily disadvantageous (Corbett and Morin-Papunen, 2013). The concept of "subfertility", however, requires clarification. Women with PCOS encounter infertility problems more frequently than healthy women, at least in a general population sample considered within a time window excluding late fertile age (Koivunen et al., 2008). In fact, the percentage of women with PCOS who seek assisted reproduction techniques is higher than in the general population (Koivunen et al., 2008). The overall number of conceived children per woman seems not to be affected by the disease (Hudecova et al., 2009), perhaps owing to a higher success rate after ART (Kalra et al., 2013) and in spite of increased risk of pregnancy complications (Palomba et al., 2015).

As the overall prevalence of PCOS is constant among human populations worldwide, the disorder seems to be subjected to balancing selection, suggesting its appearance before the rise of different human ethnic groups (Azziz et al., 2011). Some evolutionary advantages may have occurred from PCOS phenotypical features, especially hyperandrogenicity and propensity to high fat storage as energy reserve.

Women characterized by high androgen levels, especially testosterone, should benefit from increased muscle and bone strength, useful in ancient hunter gatherer societies (Azziz et al., 2011; Holte et al., 1994), in spite of subsequent decreased fertility and mating success (Abbott et al., 2002; Kirchengast, 2005). An evolutionary study proposed that subfertile women may have played an important role as "allomothers" (Eggers et al., 2007), a phenomenon well described in mammals, including primates (Kumar et al., 2005), helping to raise children and contributing to the kin selection and human geographical expansion. Moreover, the fetal exposure to maternal androgens may confer benefit, increasing fat storage during low food conditions (Shaw and Elton, 2008). Finally, a genetic predisposition to functional hyperandrogenism may be linked to advantageous proinflammatory genotypes conferring protection against infectious diseases (Escobar-Morreale et al., 2005).

Insulin resistance, metabolic thrift, fat storage and type-2 diabetes may be the result of adaptation to starvation, providing energy supply for ovarian functions and pregnancy (Azziz et al., 2011; Corbett et al., 2009; Franks et al., 1996; Holte et al., 1994; Robinson and Johnston, 1995; Shaw and Elton, 2008). Finally, an interesting theory has attempted to explain the increase of immature follicles in women with PCOS, which may serve as oocyte reserve for lean times; moreover, the later menopausal age may have prolonged the reproductive window in women, providing a "fertility storage" for a longer period of time (Gleicher and Barad, 2006). As the reproductive advantage of women with PCOS was recently proposed to be the higher chance of live birth in the late fertile age rather than the duration of the reproductive window, this issue merits further debate (Kalra et al., 2013).

The association between genetic predisposition with later menopause and higher PCOS risk was recently confirmed by GWAS, suggesting that balancing selection may have favoured the prolongation of the reproductive window in spite of subfertile female phenotypes (Day et al., 2015).

All these theories may explain, at least in part, why genotypes linked to PCOS are still common among human populations worldwide. A limitation, however, exists: even if PCOS is a sex-dependent disease, none of the evolutionary theories mentioned above takes into account the contribution of the male sex as a carrier of PCOS-related genotypes, neither do they consider if these genotypes have consequences in males, including for their reproductive success.

Sexual conflict

A sexual conflict arises when shared traits have a common genetic basis but result in opposite reproductive success between the sexes, leading to a contrasting selection (Bonduriansky and Chenoweth, 2009; Pennell and Morrow, 2013). An example is given by male facial masculinity: genetic factors that increase male facial masculinity decrease facial attractiveness of female relatives, suggesting that the masculine face increases the reproductive success in men but decreases the genetic benefits of female offspring (Lee et al., 2014).

Sexual conflict was experimentally measured in non-humans. In insect models, the optimal balance between reproduction and lifespan is different for the sexes. The best reproductive success of women is achieved with a longer life span, whereas men achieve a higher number of reproductive events in early life at the cost of a reduced life span linked to the high energetic expenses for mating (Berg and Maklakov, 2012).

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Therefore, selection, in terms of life span, differently influences the reproductive success of men and women. As sex hormones regulate reproductive functions, they should be strong candidates as regulators of sexual conflict dynamics. Indeed, testosterone has a contrasting, sex-related effect on reproductive success in rodents and birds: high levels of the hormone were associated with high reproductive success of men compared with their their daughters, who were challenged with reproductive problems related to a masculine phenotype (Mills et al., 2012; Peterson et al., 2014). Therefore, the genetic benefits of selecting males with high testosterone levels are lost in the opposite-sex progeny.

In response to sexually antagonistic selection, sexual dimorphism occurred and sex-related phenotypes evolved seperately. Men have higher testosterone levels, leading to a sex-specific hormonal environment, which may be considered a form of sexual dimorphism (Mokkonen and Crespi, 2015). Nevertheless, it has been hinted that this sexual conflict has not been completely solved, and studies aiming at understanding sexual antagonism in humans and other animals focused on testosterone are needed (Mills et al., 2009; Mokkonen et al., 2012).

Sexual conflict in PCOS

We suggest that intralocus sexual conflict provides an optimal explanation for the PCOS paradox. It should explain the overall constant prevalence of the disease among human populations (Azziz et al., 2011) despite the the loss of PCOS-related genotypes caused by decreased fecundability and increased risk of pregnancy and neonatal complications (Palomba et al., 2015). The hereditary nature of the hyperandrogenic phenotype was previously suggested. For instance, the connection between PCOS and high levels of serum androstenedione and dehydroepiandrosterone-sulphate in women is similar to that between premature baldness and high testosterone levels among male relatives (Govind et al., 1999). Increased male androgenicity and fertility caused by short CAG repeats in the *AR* gene may represent a locus of antagonistic sexual selection, as the genotype linked to a hyperandrogenic phenotype may be disadvantageous for female reproduction (Summers and Crespi, 2008). In fact, the negative effect of high androgen levels on reproductive function, psychology and quality of life of females has been demontrated (Shifren, 2004), despite an evolutionary advantage for men. High androgen levels are linked to aggressiveness and muscular strength (Bardin and Catterall, 1981; Raboch et al., 1987), which may be useful in improving chances of success in finding resources and consequent male survival.

Androgen levels are strictly connected with an opposite bidirectional modulation of glucose homeostasis in men and women (Escobar-Morreale et al., 2014), which is linked to metabolic syndrome, insulin resistance and type 2 diabetes (Navarro et al., 2015). Different responses to selection of individual traits, such as weight, total cholesterol and blood glucose, exist between human males and females (Stearns et al., 2012), resulting from diverse physiological adaptations to the energetic demand ancestrally required. Even if lifestyle certainly affects the individual metabolic features (Ekblom et al., 2015), together with epigenetic causes (Kong et al., 2009; Smith and Ryckman, 2015), the genetic background strongly contributes to the development of metabolic syndrome (Aguilar et al., 2015), suggesting a heritable predisposition. It is reasonable, even if speculative, that high blood glucose levels and fat storage may serve as energy reserve to sustain ovarian function, pregnancy and lactation during periods of food shortage. In contrast, a high body mass index phenotype may be disadvantageous for men in hunter gatherer societies, in which athletic performance may be a determinant to achieving food resources and to avoiding predators (**Figure 1**). Also, androgen deficiency in men is related to metabolic problems (Buvat et al., 2013), as demonstrated *in vitro* (Nasiri et al., 2015) and confirmed in *AR* gene knock-out mice (Dubois et al., 2015). Moreover, low androgen levels negatively affect male fertility and longevity (Buvat et al., 2013; Morales, 2011), thereby decreasing the individual reproductive success. On the contrary, low number of pregnancies and late-age conceptions, which may be more frequent in women with high androgen levels, such as in PCOS, were suggested to positively affect longevity (Laufer, 2015). According to this theory, the low energy expended for reproduction may be invested in the maintenance of somatic tissue, resulting in longer life span (Kirkwood and Rose, 1991). Longevous women should be a social source for taking care of other relatives' children, giving an evolutionary and hereditable advantage to the group (Hawkes et al., 1998). This topic is widely debated and opposite opinions raised, recently issued by an interesting series of reviews (Laufer, 2015).

As recently argued (Archer, 2015), the increasing prevalence of obesity in the last century, especially in Western societies, may be worsened by exaggerated maternal energetic resources accumulated by successive generations of metabolically compromised mothers. It results in the loss of competition between maternal and fetal energy demand, which, together with the lack of exercise and the high availability of food, lead to a high propensity of nutrient sequestration in pancreatic beta-cells and adipocytes of children. *THADA* gene SNPs may be involved in this process by modulating pancreatic beta-cell function (Simonis-Bik et al., 2010). The authors reasoned that lack of natural negative selection occurs also via the increment of caesarean sections, allowing highly "storing-energy" fetuses to be born and increasing the risk of a metabolic tipping point among the global population. Moreover, maternal PCOS was associated with increased risk in the offspring to develop metabolic disorders (Doherty et al., 2015; Welt and Carmina, 2013). Although more studies need to be conducted, this hypothesis suggests that the lifestyle in "westernized" societies should compromise the result of metabolic selection occurred during ancient human evolution.

Contribution of genetic drift

We previously showed the contribution of genetic drift to the distribution of the PCOS genetic markers worldwide by an in-silico approach (Casarini and Brigante, 2014). In this evolutionary study, the frequencies of SNPs linked to the disease from both male and female human samples were analysed, to ensure that the "male factor" was not lost. The genotypes linked to the disease were differently represented among continents, resulting in a peculiar distribution matching the main geographic areas. The analysis of genetic diversity

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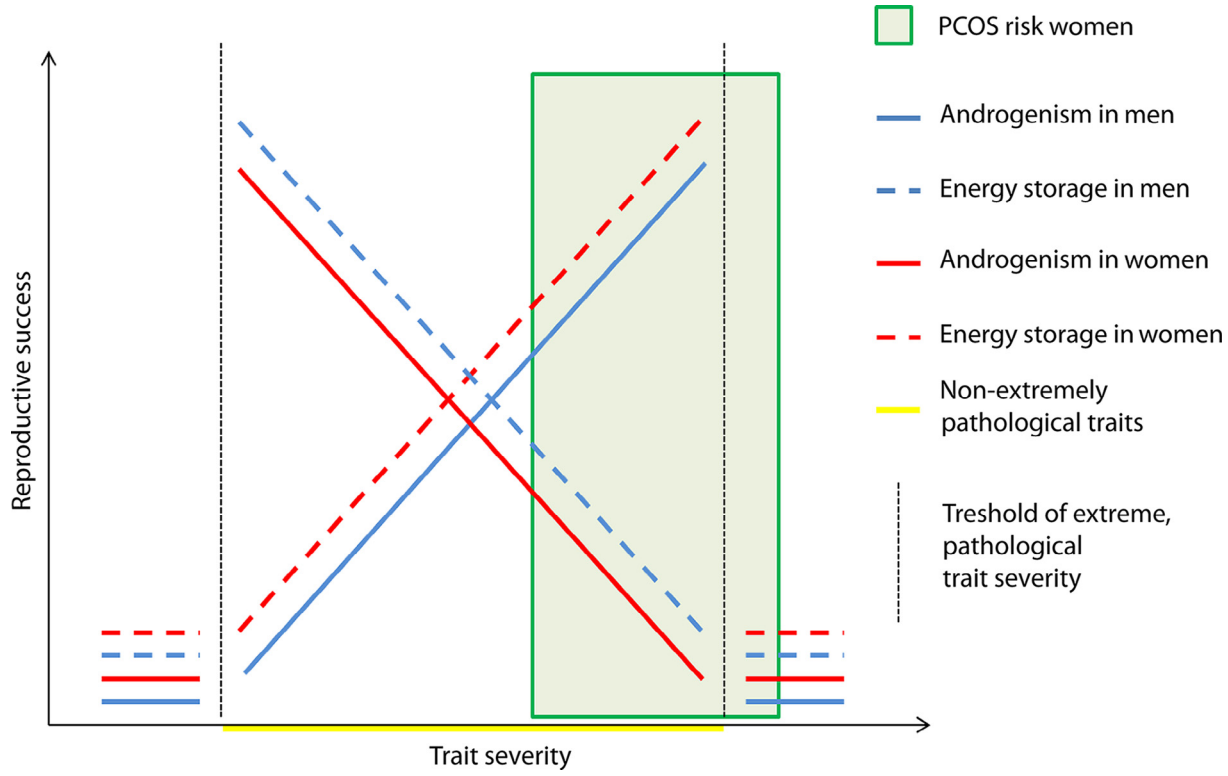

Figure 1 Relationship between phenotypic traits and reproductive success in humans. High androgen levels and energy storage (as result of metabolic disturbances) are classically linked to polycystic ovary syndrome (PCOS) in women and may oppositely affect the reproductive success of both men and women. Sexual conflict occurs as these traits are linked to a common genotype in both sexes. In this model, extremely serious, pathological trait conditions are excluded to best fit the physiological average traits of individuals in ancient societies; for example, anorexia and obesity are pathological conditions affecting the reproductive success differently to that shown. Therefore, in this graph, low and high levels of energy storage are comparable to low and high body mass index, respectively, rather than anorexia and obesity. The scales are exemplificative and expressed in arbitrary units.

(Holsinger and Weir, 2009), calculated using the frequency of PCOS markers, revealed an increase together with the distance from Ethiopia, Africa. As this was assumed to be the putative starting point of ancient human migration (Ramachandran et al., 2005), these data support genetic drift. Interestingly, the heterozygosity calculated using PCOS markers did not decrease, in contrast with the well-known concept of population genetics by which heterozigosity decreases during repeated migrations of some individuals moving from a wider group (Henn et al., 2012; Ramachandran et al., 2005). This suggests that PCOS markers were subjected to a selective pressure that affected the decay of heterozygosity, although genetic drift contributed to its qualitative distribution. Curiously, the disease is constantly prevalent worldwide even if represented by different genotypes (Corbett and Morin-Papunen, 2013). Taken together, these results support the hypothesis that PCOS accompanies humans in their evolution.

In conclusion, a measure of the influence of PCOS-related subfertility on the female reproductive success during human evolution is not available. The antiquity of PCOS was ascertained by documents from the ancient Greek scientist Hippocrate, about 2400 years ago, who described subfertile women characterized by masculine appearance (Hanson, 1975). Therefore, the disease accompanied women for some time and it is still widespread across continents, even if linked to subfertile phenotypes. Overall, its effect on female reproductive success should be better assessed. The mean life expectancy worldwide was overall less than 40 years until the beginning of the previous century (Christensen et al., 2009), because of environmental factors, such as infectious diseases, wars or famines, downsizing the benefit of a long reproductive window in the past (Casarini et al., 2015). On the other hand, motherhood attempts should be reasonably high and constantly repeated during the entire reproductive life span of women. In such a scenario, what is the contribution of hyperandrogenic males to the PCOS-related genotype distribution? Current clinical data, obtained from women with PCOS undergoing assisted reproducton technqiues (often at a late, sub-optimal age for pregnancy), pose the disease as an evolutionary paradox. The presence of genotypes sexually linked to opposite effects on female and male fertility, however, may not affect overall human reproductive success, thus resulting in their heritability and perpetuation through human evolution.

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