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Polycystic ovary syndrome and genetic factors influencing its development: A review article

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Abstract:

Polycystic ovary syndrome (PCOS) is a common infertility disorder, affecting a significant proportion of the global population. This syndrome has been one of the most controversial entities in gynecological endocrinology for many years. Both genes and the environment contribute to PCOS. Obesity, exacerbated by poor dietary choices, and physical inactivity, worsens PCOS in susceptible individuals. PCOS is a complex and heterogeneous disorder characterized by hyperandrogenemia, hyperinsulinemia, insulin resistance, and chronic anovulation. Many candidate genes have been identified to be one of the causes of PCOS. Different studies have been carried out to find the genetic correlation of PCOS. It is essential to carry out such studies that identify the clear cause of PCOS and its genetic association and hormonal disbalance. Currently, PCOS is considered a polygenic trait that might result from the interaction of susceptible and protective genomic variants and environmental factors, during either prenatal or postnatal life.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrine disorder in females; especially in women of reproductive age (1). The worldwide prevalence of PCOS is estimated to be 5–10%. One in every 5–6 females is facing serious complications regarding infertility and irregularity in their menstrual cycles (2). Stress, obesity, fluctuation in hormonal level are the major causes worldwide. This endocrine disorder affects females in the age of 18–44 (3). PCOS could be diagnosed by infertility, acne, amenorrhea or oligomenorrhea, hirsutism, insulin resistance, obesity, hyperandrogenism, and polycystic ovaries by ultrasonography (4). The definition of PCOS has been an issue of great and continuous debate among experts in the field since 1990 when the National Institutes of Health (NIH) sponsored a conference on PCOS and put forward as diagnostic criteria of chronic anovulation and hyperandrogenemia (2, 5). Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder which is considered to be the commonest cause of anovulatory infertility and hirsutism (6). It is now clear that the majority of hirsute women with regular menses have polycystic ovaries (7). The normal functioning of hormones plays an important role in the ovary functioning and regulation of the menstrual cycle that maintains fertility. If there is a constant disturbance of hormonal level in females, then it will disturb ovary functioning which leads to the formation of a cyst inside the sac of an ovary (8). PCOS is a multifactorial disorder where individual genes, gene–gene interaction, or gene–environment interactions have been reported to influence predisposition to PCOS development. Familial clustering of cases suggests that genetic factors play an important part in its aetiology (4, 9). A number of studies of families with several cases of PCOS have produced results suggesting an autosomal dominant trait. Although clustering of cases in families strongly supports the role of genetic factors in the development of PCOS, heterogeneity of phenotypic features in different families and even within the same family underscores the importance of the environmental contribution (10). Unhealthy lifestyle, diet or any infectious mediators increase the risk of PCOS. Due to insulin resistance and its elevated level, the ovaries function disturbs the androgen level which leads to anovulation (11). Apart from the environmental factors, there are genetic factors that are responsible for the etiology of PCOS. It›s cause involves candidate genes, SNP's.

Polymorphism or any nucleotide change cause a defect in the transcriptional activity of a gene that leads to PCOS (12). Mostly genes that encode for the androgen receptor, Luteinizing Hormone receptors, Follicular Stimulating Hormone receptors, Leptin receptors are responsible. Two possible approaches are used to identify a genetic locus for PCOS genes: (i) association studies where a predisposing allele is expected to be found more frequently in the affected population than the normal individuals and (ii) linkage studies where the probands and their families are investigated to determine if particular genomic landmarks are distributed independently or in linkage with the phenotype (13, 14). Risk factors causing multiple aberrations in steroidogenesis, folliculogenesis, and metabolic pathways, are continuously recognized but the key abnormality escapes detection (15).

The Environment and PCOS

An overemphasis on genes is a simplistic explanation of the PCOS epidemic. The rise in PCOS in populations where the gene pool has been relatively constant, confirms that environmental factors are assuming an ever more important role (16). The development of obesity is linked to the development of PCOS in susceptible individuals (17). The modern living environment in developed countries is characterized by low daily energy expenditure and an abundant and inexpensive food supply, making positive energy balance common. The main environmental factors we consider, includes environmental toxins, diet and nutrition, socioeconomic status, and geography. There is some evidence that environmental toxins play a role in disrupting reproductive health, but there is limited research as to how these toxins may affect the development of PCOS (18, 19).

Genetics of Polycystic Ovary Syndrome

PCOS is an extremely heterogeneous and complex disease. The genetic basis of PCOS is different between families and within families, but it is related to a common pathway (20). Due to complexity and heritability single gene or related genes in a single family have not been reported. Cases of PCOS cluster in families and there is evidence for hereditability of both hyperandrogenaemia and hyperinsulinaemia in affected siblings. The mode of inheritance of PCOS is not yet certain (21). An autosomal dominant mechanism (i.e. representing a single gene defect) is possible but it is much more likely to be oligogenic or perhaps even polygenic. Molecular defects in gonadotropins and their receptors, in enzymes involved in steroidogenesis, as well as those underlying insulin action and secretion pathways, have been under continuous and intense investigation with variable results (22). Genome screening to search for a candidate gene in a complex disease like PCOS is unrealistic. PCOS is a multifactorial disease and is caused by a number of abnormalities. All genes/mutations that affect ovaries directly or indirectly are associated with PCOS (23).

Genes Involved in PCOS

The most common endocrine disorder associated with PCOS is an elevated androgen level. Hence, in uncovering the reason for the elevated level of androgen, several genes have been reported to be associated with PCOS, as follows.

CYP11A

CYP11A1 named as Cytochrome P450, family 11, subfamily A, member 1. It encodes the superfamily of cytochrome p450 (24). It is present in the mitochondrial inner membrane. The main function is in the catalysis of cholesterol to pregnenolone. It also plays a vital role in the steroid synthesis pathway (25). Gharani et al. reported polymorphs and variation as associated factors in a study of 97 infertile women (23).

Two other studies from China and Greece replicated the finding and reported CYP11a to be an association factor with PCOS (26).

CYP17

Cytochrome P450, Family 17, subfamily A, member 1, is another steroidogenesis enzyme that is monooxygenases (27). Its cytogenic location is on chromosome 10q24.32 and has 8 exon count. CYP17 is reported as a causative gene in the pathogenesis of PCOS (28). Rosenfield et al. reported elevated androgen levels in PCOS patients (29). Wickenheisser et al. reported increased expression of CYP17 in theca cells (30). A study conducted on the Chilean population concluded that polymorphism C > T in the CYP17 is responsible for PCOS progression (31).

Androgen Receptor Gene (AR)

This gene is present on chromosome Xq12 and has 11 exons, it codes for a more than 90 kb long protein that has a total of three functional domains (32). Mutations and structural disruption of the gene are reported to cause PCOS. As the AR gene is located on the X chromosome, a change in a single copy of the gene is sufficient to cause pathology (33, 34). GWAS also reported a novel variation in the gene to be the cause of PCOS. Urbanek et al studied 150 families and failed to find evidence for an association of the trinucleotide (CAG) repeat polymorphism in the X-linked androgen receptor gene and PCOS. However, this short CAG repeat length has been shown to be inversely associated with androgen levels (35).

Sex Hormone-Binding Globulin Gene

The SHBG gene is localized to chromosome

17p13-p12. SHBG synthesizes a protein of 373 amino acids. The protein product of SHBG controls the level of sex hormones in the body by binding to androgens, predominantly with estrogens and testosterone (36). Hogenveen et al 131 identified a polymorphism in the coding region of SHBG that encodes a missense mutation, P156L, in 4 of 482 women with PCOS, hirsutism or ovarian dysfunction (37). Single nucleotide polymorphism in the SHBG gene was described to be significantly associated with PCOS in numerous studies (38). A pentanucleotide repeat polymorphism, at the promoter of SHBG gene has been described to influence the transcriptional activity of SHBG gene. A significant association was found between this polymorphism and PCOS (39).

The insulin gene

Insulin also plays a significant role in the production of androgen by receptors present on theca cells (40). This act of insulin is provoked through the pathway (phosphoinositide 3-kinase/protein kinase B), which becomes active in PCOS theca cells (41). A variable number of tandem repeats (VNTR) polymorphism in the promoter region of the insulin gene (INS) regulates its expression. Abnormalities of insulin secretion have been reported in recent studies of women with PCOS, with and without a family history of NIDDM (42). Waterworth et al94 found strong linkage and association between the class III allele of the insulin gene VNTR (variable number tandem repeats) in the 5› region of the insulin gene and PCOS. This allele was preferentially transmitted from heterozygous fathers but not from mothers to affected individuals (43).

The insulin receptor gene

The insulin receptor is a heterotetrameric glycoprotein composed of two α and two β-subunits and is encoded by the insulin receptor gene (INSR) located at the chromosome 19 (44). Several studies were conducted to find the association of infertility in obese women with PCOS, but they did not find any association. The demonstration of impaired sensitivity to insulin action in vivo and in vitro naturally led to the hypothesis that genetic abnormalities of the insulin receptor and/or post-receptor signalling were involved in the pathogenesis of familial PCOS (45). Many researchers have tried to explore whether the mutations of INSR could explain insulin resistance in PCOS (46). A larger part of chromosome 19p13.2 was searched and D19S884 was reported as the strongest association with PCOS. This region of the chromosome also contains the INSR gene (47). In a recent study, Siegel et al. examined an SNP at the tyrosine kinase domain of INSR and found an association in lean patients with PCOS. This SNP could be a susceptible variant for PCOS, or a result of linkage disequilibrium with another INSR polymorphism (48).

Fat Mass Obesity (FTO)

FTO gene is also known as alpha-ketoglutarate dependent dioxygenase, its cytogenic location is 16q12.2 and has 14 exons (49). Different studies have shown that FTO is associated with obesity, BMI and type 2 Diabetes. Polymorphism in the FTO gene among PCOS patients was also identified via a study conducted in Pakistan. Single nucleotide polymorphism (SNP) rs9939609 was significantly associated with diseases. The SNP rs9939609 was significantly higher in affected women as compared to healthy participants of the study (50).

MEDICATIONS

A better example of an “environmental” substance implicated in the development of a PCOS phenotype is valproic acid, which is a short chained fatty acid that is widely used to treat epilepsy and bipolar disorders as well as migraines and generalized mood disorders (51). There are studies to suggest that women with these disorders and treated with valproic acid may develop stigmata of PCOS, including polycystic ovaries, hyperandrogenism, obesity, and anovulation, and that these stigmata may be reversible with discontinuation of the medication (52).

Obesity has been reported in 30% of PCOS patients. The symptoms of PCOS are also considered to be recovered by dietary therapies including resistance to insulin, annulations, and irregular menstrual cycle (53).

A medicine called clomifene is usually the first treatment recommended for women with PCOS who are trying to get pregnant. Clomifene encourages the monthly release of an egg from the ovaries (ovulation). If clomifene is unsuccessful in encouraging ovulation, another medicine called metformin may be recommended (54).

CONCLUSION

PCOS can be considered a complex, heterogeneous metabolic syndrome triggered or maintained by the combined effect of inheritable genetic susceptibilities and environmental risk factors (18). Apart from environmental factors, many candidate genes are involved in the etiology of the PCOS, Alteration in the metabolic pathway due to a defect in the gene leads to the progression of PCOS and ovary dysfunction (55). The severity can only be reduced when following proper precautionary measures i.e. weight loss, healthy diet and recommended medications. Furthermore, studies with lifestyle modifications have shown that in women with PCOS the hormonal, metabolic, and reproductive abnormalities can improve by means of lifestyle modification, suggesting that environmental factors such as food toxins, smoking, pollution,

etc. play a fundamental role in unmasking genetic predisposition (56, 57).

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