

GENETIC VARIATIONS IN POLYCYSTIC OVARIAN SYNDROME DISEASE

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ABSTRACT

Objective: Polycystic ovary syndrome (PCOS) is one of the common endocrine disorders among women of reproductive age with a prevalence of approximately 5-10% worldwide. PCOS is a complex genetic disorder caused by several genes and environmental factors. The aim of this study is to provide an overview on variations in PCOS-associated genes based on underlying genetics

Methods: Detailed literature screening was performed in PubMed. Manual curation process was adopted to extract the information on PCOS, associated genes, mechanism of association, details of the association, significance of association mentioned in the papers were carefully captured according to the authors' interpretation of the results.

Results: The detailed literature study revealed several genes and the genetic variations in PCOS and its critical effects, such as ovarian failure, obesity, spontaneous abortion, recurrent pregnancy loss, insulin resistance, and hyperandrogenism. The causal genetic variants were assembled at various levels, including mutation, single nucleotide polymorphism, etc., in PCOS and the associated phenotypic effects.

Conclusion: The genetic variations play an important role in the pathogenesis of PCOS across different ethnicities, as it is associated with various other endocrine disorders including diabetes, insulin resistance, cardiovascular diseases, hyperandrogenism, reproductive disorders, etc. The underlying mechanism and the network help in identifying the candidate genes or biomarkers in the disease conditions.

Keywords: Polycystic ovary syndrome, Gene, Mutation, Polymorphism, Single nucleotide polymorphism.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a complex disorder affecting approximately 5-10% of all women of reproductive age [1]. It is a multifactorial endocrine disorder, which demonstrates menstrual disturbance, infertility, anovulation, hirsutism, and hyperandrogenemia/hyperandrogenism [2]. PCOS is a common reproductive disorder characterized by arrested follicular development prior to selection of a dominant follicle. The increase in the secretion of androgens by the ovaries and the adrenal glands is one of the pathological effects observed in PCOS [3]. PCOS is also associated with an increased risk of developing Type 2 diabetes, dyslipidemia, and cardiovascular diseases [4]. Insulin resistance, a common disorder associated with PCOS, is as high as up to 70% in PCOS condition [3]. The etiology of the disease has been difficult to determine because of its heterogeneity. The cause of PCOS is still unclear; however, it has been observed that various environmental and genetic factors, such as genetic variations, differential regulation of genes, and affected pathways, may contribute to the pathogenesis of PCOS [4]. Women with PCOS are also at an increased risk of developing gestational diabetes and pre-term birth (PTB) [5,6]. It has also been observed that the pregnant women diagnosed with PCOS are likely to give birth to premature babies [5]. Although various studies have been performed on PCOS, the information is scattered in the literature, which is the most specific challenge for researchers. Our earlier study presented an overview of the differential regulation of genes in PCOS including miRNAs and its influence in causing various phenotypic changes associated with PCOS [7].

In this paper, we have assembled the information on genetic variations in PCOS and its uniqueness to different population or ethnicities, through comprehensive literature study. Based on the detailed literature curation, we have collected information on several susceptible genes and its variations in PCOS condition. Both significant and non-significant association of variations in PCOS, along with conflicting data and negative correlation, have been covered in this paper. We have

underpinned the critical genetic variations in PCOS across different ethnicities and its associated effects, such as endometrial receptivity, implantation failure, recurrent pregnancy loss (RPL), early pregnancy loss, PTB, insulin resistance, and hyperandrogenism in women with PCOS [8].

METHODS

Search strategy

"PCOS" or "polycystic ovary syndrome" and "gene" and "mutation or polymorphism or variation or single nucleotide polymorphisms (SNP)" were used as keywords in PubMed Medline database to search for the research papers. References were screened at the abstract level to segregate the false positive papers from the hit list. All potential published studies on candidate genes and PCOS were identified through different databases and evaluated. The true positive papers were collected to perform the manual data extraction process.

Data extraction

Manual curation process was adopted to extract the information. All papers were read, and specific information on PCOS, associated genes, mechanism of association, details of the association, significance of association mentioned in the papers were carefully captured according to the authors' interpretation of the results.

RESULTS AND DISCUSSION

Genetic variations in PCOS

AdiponectinQ (ADIPOQ)

ADIPOQ (adiponectin, C1Q, and collagen domain containing) is a protein-coding gene. Research based on the relationship between the variation of the two SNPs (rs2241766 and rs1501299) in the adiponectin gene and PCOS has revealed ADIPOQ rs2241766 polymorphism as a marker for high susceptibility to PCOS [9], and additional study has concluded that adiponectin gene variant SNP rs1501299 is considerably linked

to the threat for PCOS in the Chinese Han population [10]. T45G polymorphisms in the adiponectin gene are of high prevalence in PCOS patients compared to controls [11]. The variation of the SNP 45T/G and 276G/T in the adiponectin gene is linked to susceptibility to PCOS and may be associated with high blood pressure in PCOS [12]. The variation of the two SNPs in exon 2 and intron 2 in the adiponectin gene is associated with the susceptibility to PCOS in Caucasian women [13]. There are studies that did not reveal a strong association of the SNP 45T/G and 276G/T to PCOS; however, an interaction between the ADIPOQ and steroid action was observed by Xian [14].

Androgen receptor (AR)

ARs (also known as dihydrotestosterone receptors) are nuclear hormone receptors. Studies based on the investigation of the AR encoded by an increasingly polymorphic CAG trinucleotide repeat tract in PCOS revealed that there is an association between short CAG repeat length and the pathological process of polycystic ovaries in PCOS patients of Indian and Chinese population [15]. AR (CAG) n gene and its differential methylation patterns influence the progression of the disease leading to PCOS in Australian Caucasian women [16]; the variation influences the testosterone effects on insulin resistance in PCOS women [17]. It is also found that the CAG trinucleotide repeat polymorphism increases the susceptibility to PCOS, either by increasing the AR activity or by triggering hyperandrogenism [18]. Polymorphism of the AR gene is likely a biomarker for PCOS [19]. In a contradictory note, few studies revealed that the CAG length variations in AR gene were not associated with PCOS, though there was a negligible over-representation of short CAG alleles in some cases [20,21].

Calpain-10 (CAPN10)

CAPN10 is a protein-coding gene. It represents a ubiquitous, well-conserved family of calcium-dependent cysteine proteases. Investigations based on the CAPN10 gene and its association with the etiology of PCOS revealed that the CAPN10 UCSNP-44 allele polymorphism is related to PCOS in the Spanish population [22], linked with the manifestation of PCOS in the South Indian population [23]. In addition, novel candidate risk alleles and genotypes are accredited within CAPN10 gene which could be linked to significant phenotypic and diagnostic differences observed in PCOS patients [24]. The etiology of PCOS revealed that the CAPN10 UCSNP-63 allele polymorphism is related to PCOS; moreover, recessive model and an insertion allele of UCSNP-19 are defensive factors, while deletion allele and heterozygous genotype are threat factors for the development of PCOS [25]. Another study has concluded that UCSNP-19, UCSNP-63, and UCSNP-45 polymorphisms might be the threat factors for PCOS, particularly among the Asian population [26]. A study on the variation of the 112/121-haplotype of the CAPN10 gene has concluded that the 112/121-haplotype combination is linked with the high risk of PCOS in both African American and White population [27]. On a contradictory note, a couple of studies have ruled out the association of SNP-43, 44, 19, 45 of the CAPN10 gene in PCOS [11,28].

Cytochrome P450 genes (CYPs) in PCOS

CYP genes encode the cytochrome P450 superfamily of enzymes. A study on the association of CYP21 gene mutations revealed that the heterozygosity for 21-hydroxylase deficiency (21-OHD) may be related to functional adolescent hyperandrogenism and premature adrenarche; however, further studies are vital to conclude whether heterozygosity for 21-OHD envisages the risk for PCOS [29]. The evaluation of the incidence of heterozygosity for adrenal 21-OHD in patients with true precocious puberty revealed a high incidence of heterozygosity for adrenal steroid 21-OHD; these patients have to be monitored continuously as they might develop PCOS in the later stages [30]. The study involving CYP21 mutation carriers showed that 21-hydroxylase (CYP21) nonsense mutation carriers were non-indicative, whereas the missense mutation carriers that is V281L appeared to mark a PCOS phenotype [31]. Late-onset congenital adrenal hyperplasia (LOCAH) occurs due to 21-hydroxylase (21-OH) deficiency and is found to be associated with the major histocompatibility complex in

hirsutism and polycystic ovary in Turkish women; V281L mutation was the most common mutation found in these patients which confirm that LOCAH is linked to the histocompatibility complex [32]. Mutations in CYP21 gene and insulin receptor substrate-1 (IRS1) gene variant G972R possibly increase the risk of evolving adrenal androgen (AA) excess in PCOS. However, these mutations seem to play a restricted role in the development of PCOS [33]. Investigations have showed that polymorphism in the regulatory region of CYP11a is linked to PCOS [34]. Studies based on the association of the (tttta)_n polymorphism of the promoter region of CYP11A gene and PCOS have inferred that there is an association between CYP11A polymorphism and the pathological process of PCOS in Chinese women [35,36]. There have been various studies that revealed a negative correlation of (tttta)_n repeat polymorphism with PCOS; the results inferred that the (tttta)_n repeat polymorphism in the promoter region of CYP11a does not play a significant role in these diseases in Spanish [37] and Chinese women [38].

Studies based on the association of CYP19(TTTA)_n polymorphism with the hormonal profile of PCOS inferred that there is a possible association of CYP19(TTTA)₇ allele with the abetted reproduction outcome in PCOS patients [39]. SNPs of the aromatase (CYP 19) gene and PCOS have suggested that the variation in this gene is linked to the androgen excess in girls and young women [40]. Contradictory results were published stating that there was no significant association between (TTTA)_n polymorphism in intron 4 of CYP19 gene and PCOS in Chinese women [41].

Studies based on the relationship between T→C substitution (-34 bp) of CYP17 gene promoter and the pathological process of PCOS have suggested that this base pair substitution is not the prime hereditary defect in PCOS, but it might exacerbate hyperandrogenemia, especially when homozygosity exists [42,43]. Investigations based on the association between -344T polymorphism in aldosterone synthetase (CYP11B2) gene promoter region and the pathological process of PCOS have suggested that the -344T polymorphism site of CYP11B2 gene is associated with high risk of PCOS, and that -344CC and -344TC may be the predisposed genotype of PCOS [44]. Studies based on the relationship between CYP1A1 rs4646903 (T>C) polymorphism and the susceptibility to PCOS have inferred that CYP1A1 rs4646903 (T>C) polymorphism may support an increased susceptibility to PCOS, particularly among Turkish and Indian women [45].

Serpin peptidase inhibitor (SERPINE1)

SERPINE1 (clade E [nexin, plasminogen activator inhibitor [PAI] Type 1], member 1) is a protein-coding gene. PAI-Fx is known to be the self-determining risk factor for miscarriage in PCOS and studies based on this have proved that PAI-Fx is a key reversible risk factor for miscarriage in women with PCOS [46]. Studies based on the relationship between the variation of the 4G/5G polymorphism of PAI-1 gene and PCOS have concluded that this polymorphism is associated with PCOS and in addition it increases the PAI-1 levels in PCOS patients [47], and it also concluded that 4G/6G polymorphism is associated with PCOS in Chinese women and particularly in non-obese PCOS patients and those with spontaneous miscarriage [48]. The variation of the 4G/5G polymorphism of PAI-1 gene has concluded that high PAI-1 levels seem to be linked with first-trimester miscarriage in PCOS women [49]; in addition, the 4G/5G variation increases the PAI-1 levels which are positively linked with the proinflammatory factors in PCOS patients [50].

Transcription factor-7-like 2 (TCF7L2)

TCF7L2 (T-cell specific, HMG-box) is a protein-coding gene. Studies based on the association between the variation in TCF7L2 locus (rs11196236 G) and PCOS have suggested that this polymorphism is linked with the peripheral insulin (INS) resistance in PCOS in European population [51]. It has been found that SNPs rs11196218 and rs290487 of the TCF7L2 gene are linked with a high threat for early impairment of glucose homeostasis in PCOS in Chinese women [52]. On a contradictory

note, it is being found that rs11196236 C/T in the TCF7L2 gene are not associated with PCOS in Southern Brazilian women [53].

Factor leiden V (F5)

F5 (coagulation factor V [proaccelerin, labile facto]) is a protein-coding gene, which encodes an important cofactor of the blood coagulation process. Factor V Leiden mutation is one of the causes for RPL and spontaneous abortion in PCOS patients. Studies have proved that the thrombophilic G1691A Factor V Leiden mutation is linked with RPL in women both with and without PCOS in the Caucasian population [54]. Administration of enoxaparin metformin leads to a reduction of pregnancy loss in patients with one or more prior spontaneous abortion along with thrombophilia and/or hypofibrinolysis [55].

INS

INS is a protein-coding gene. Investigations have showed that INS-variable number tandem repeat (VNTR) (the minisatellite in the regulatory region of the INS gene) is linked to PCOS [34]. Allelic variation of the INS VNTR gene is found to be associated with the pulsatility of INS secretion in PCOS [34]. INS gene VNTR polymorphism is linked with the etiology of PCOS in UK women [56]. Few studies reported that the INS VNTR gene polymorphism is not correlated with PCOS [57-60].

Insulin receptor (INSR)

INSR is a tyrosine kinase, which regulates the pleiotropic activities of insulin. Novel heterozygous mutation in exon 19 (His1130Arg) of INSR gene is found to have an association with the progression of PCOS [61]. A study on the polymorphism in exon 17 of the INSR gene and PCOS has revealed that this polymorphism is linked to an increased risk of insulin resistance in women with PCOS [62], and exon 17 C/T, 1058 site nucleotide polymorphism is linked with susceptibility to PCOS in lean subjects [63,64]. His 1058 C/T SNP found in exon 17 in the INSR gene is linked with the pathological process of PCOS in non-obese Japanese patients [65]. T/C SNP at codon Cys1008 (position 3128 of NM_000208) of INSR gene is linked with decreased insulin sensitivity in PCOS in Chinese women [66].

IRS

IRS 1 and 2 mediate the control of various cellular processes by insulin. Gly972Arg in the IRS-1 gene plays a functional role in the insulin-resistant component of PCOS [67] and found to be linked with the pathogenesis of the metabolic element of PCOS [68]. Studies based on the relationship between the variation of G972R in the IRS-1 gene and PCOS along with AA excess have concluded that this polymorphism is linked with the development of PCOS to a limited extent in non-Hispanic white women with PCOS [33]. On a contradictory note, several studies have concluded that the polymorphism Gly972Arg in the IRS-1 gene is not common and is not associated with PCOS [69] in Taiwanese [11], Croatian [60], and Spaniard [70] women.

Research based on the relationship between the variation of Gly1057Asp IRS-2 gene and PCOS has concluded that this polymorphism manipulates the blood sugar levels in non-diabetic white or African American women with PCOS; in addition, people with IRS-2 Gly/Gly genotype may develop Type 2 diabetes in the later stages [71], and the polymorphism Gly1057Asp of IRS-2 gene might play a functional role on the insulin-resistant component of PCOS [67].

Luteinizing hormone beta-subunit (LHB)

LHB polypeptide is a protein-coding gene. It promotes ovulation by stimulating the ovaries to synthesize steroids. A study was conducted to determine the relationship between LH-beta subunit mutations (Trp8 to Arg8 and Ile15 to Thr15 in the LH beta subunit gene) and PCOS in women. The results revealed that these mutations were considerably associated with PCOS [72]; the presence of these mutations may help to diagnose the threat for PCOS particularly in obese women [73]. Further study on the point mutations (nucleotide mutations within codons 8 and 15 in the LH beta-subunit gene) in British population revealed that the incidence was not higher in women with PCOS, though it

was increased in obese women with PCOS [74]. Studies based on the association between the rs1056917 variant of the luteinizing hormone β -subunit gene and PCOS have suggested that this polymorphism is not of much significance with PCOS in south Indian women [75].

LH/choriogonadotropin receptor (LHCGR)

LHCGR is a protein-coding gene. An investigation on S312N polymorphism of the LHCGR gene revealed that this variant is strongly linked with PCOS in the Sardinian population [76]. The association of rs13405728 variant in the LHCGR gene and PCOS was found in Caucasian patients of Danish origin [77] and have suggested that the gene products of the LHCGR gene is linked with the diagnosis of PCOS, despite ethnicity [78,79].

Peroxisome proliferator-activated receptor (PPAR)-gamma2 (PPARG)

PPARG is a protein-coding gene. This gene encodes a member of the PPAR subfamily of nuclear receptors. Studies based on the relationship between the variation of the Pro(12)Ala polymorphism in PPARG gene and PCOS have concluded that this polymorphism is linked with the alterations in insulin resistance in Caucasian women with PCOS [80] and has concluded that this polymorphism is linked with the pathological process of PCOS [81], high insulin sensitivity in PCOS [82], and might act as a modifier of insulin resistance in patients with PCOS [83], and manipulate the insulin resistance in Indian women with PCOS [84]. The C→T substitution in exon 6 of the PPARG gene is linked with the pathological process (obesity) of PCOS [85].

Follicle-stimulating hormone receptor (FSHR)

FSHR is a protein-coding gene. It is the receptor for Follicle-stimulating hormone and functions in gonad development. The single nucleotide polymorphism (rs1922476) in FSH receptor gene is linked to the cause or reason for PCOS in Chinese and European population, and the variation is possibly important in PCOS irrespective of the ethnicities [78]. Several studies related to the association of FSHR and PCOS have revealed negative correlation. A study was conducted to search for any mutations in the FSHR gene with two known polymorphisms, namely Thr307Ala and Ser680Asn, and its association with PCOS. However, not a single mutation could be identified in the entire coding region of the FSHR gene. Hence, it appears that this gene is not the cause for PCOS in Chinese Singapore women [86]. Investigations based on the relationship between FSHR p. Asn680Ser polymorphism and PCOS have revealed that there is no association between FSHR p. Asn680Ser polymorphism and PCOS in women [87]. Studies based on the relationship between FSHR Ala307Thr and Ser680Asn polymorphisms and PCOS have revealed that both these variants are not a cause for PCOS in Northern Chinese Han women [88].

CONCLUSION AND FUTURE PERSPECTIVES

In summary, although the etiology of PCOS is still unclear, the pathology of PCOS can be associated with the macro and micro environmental factors. The genetic variations play an important role in the pathogenesis of PCOS across different ethnicities, as it is associated with various other endocrine disorders including diabetes, insulin resistance, cardiovascular diseases, hyperandrogenism, reproductive disorders, etc. The underlying mechanism and the network help in identifying the candidate genes or biomarkers in the disease conditions. The next step of this research is to publish the results to the scientific community in the form of searchable relational database.

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