REVIEW

Potential genetic polymorphisms predicting polycystic ovary syndrome

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Abstract

Polycystic ovary syndrome (PCOS) is a heterogenous endocrine disorder with typical symptoms of oligomenorrhea, hyperandrogenism, hirsutism, obesity, insulin resistance and increased risk of type 2 diabetes mellitus. Extensive evidence indicates that PCOS is a genetic disease and numerous biochemical pathways have been linked with its pathogenesis. A number of genes from these pathways have been investigated, which include those involved with steroid hormone biosynthesis and metabolism, action of gonadotropin and gonadal hormones, folliculogenesis, obesity and energy regulation, insulin secretion and action and many others. In this review, we summarize the historical and recent findings in genetic polymorphisms of PCOS from the relevant publications and outline some genetic polymorphisms that are potentially associated with the risk of PCOS. This information could uncover candidate genes associating with PCOS, which will be valuable for the development of novel diagnostic and treatment platforms for PCOS patients.

Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous and complex disorder of reproductive aged women, which usually causes reproduction and metabolism failure (1, 2). It often presents as hyperandrogenism, hyperinsulinemia, insulin resistance, ovulatory dysfunction and polycystic ovaries. The prevalence of PCOS may be as high as 15–20% of women of reproductive age (3). Although it was first reported in 1935 by Stein et al., its etiology is still unclear. PCOS has a complicated and ambiguous pathogenesis. Many risk factors have been identified, such as obesity, genetics and early childhood growth patterns (4, 5).

Data from many studies suggest that genetics is very important in the development of PCOS. A Dutch twin study supported the genetic contribution, with PCOS heritability predicted to be as high as 0.79 (6). Family studies also clarified the effects of genetics on PCOS (7, 8, 9) and its concomitant representations such as hyperandrogenemia (10) and insulin resistance (11). Current studies of the genetics of PCOS mainly concentrate on multiple candidate genes, benefiting from the advances in technology including the completed HapMap project and genome-wide scans. Candidate genes are usually chosen according to the available information for the potential pathophysiology of the symptoms. These genes are tested by analysis of the affected individuals (12). Several candidate genes in PCOS development have been clarified, including genes associated with steroid biosynthesis and action, gonadotropic secretion and action, folliculogenesis, weight and energy regulation and insulin action (13).

In this review, we aimed to provide an overview of the main genetic polymorphisms that were found or investigated in PCOS patients until now. Relevant literatures of case-control researches and meta-analysis studies were searched from PubMed database or by citation search and reference lists of relevant articles. Relationships of the candidate genes with PCOS that were found or discussed in these publications were summarized.
The genetic polymorphisms are classified as steroidogenic acute regulatory (STAR) gene polymorphisms, gonadotropin-releasing hormone receptor (GnRHR) gene polymorphisms, follicle-stimulating hormone receptor (FSHR) gene polymorphisms, fat mass and obesity-associated (FTO) gene polymorphisms, insulin receptor (IR) and IR substrate (IRS) polymorphisms, vitamin D receptor (VDR) polymorphisms, methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism, peroxisome proliferator-activated receptor gamma (PPAR-γ) polymorphism and interleukin-1beta/IL-1 receptor antagonist (IL-1β/IL-1Ra) gene polymorphisms.

**StAR polymorphisms**

Hyperandrogenism accounts for most of the etiology of PCOS, and it can disturb the steroidogenesis process. The StAR protein regulates the transport of cholesterol through the mitochondrial membrane in the first step of androgen biosynthesis (14, 15). Evidence suggests that patients with PCOS may have an abnormality in androgen biosynthesis, with StAR as one possible target of abnormality (16). Kashar-Miller et al. (16) hypothesized that increased production or concentration of StAR may be responsible for the increased ovarian and adrenal androgen found in PCOS of some patients. The authors provided evidence that StAR might participate in the earliest steps of androgen biosynthesis in PCOS. Data from this and subsequent investigations have identified the StAR gene as a candidate gene for PCOS (17). However, the association between StAR genetic polymorphisms with the pathology of PCOS remains unclear. In a case-control study, seven StAR gene polymorphisms have been detected using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method in 45 PCOS women and 80 controls. No relationships between most single nucleotide polymorphisms (SNPs) of the StAR gene with PCOS were evident (18). The authors suggested that further evaluation of changes in amino acid active sites and their effect on steroid biosynthesis will be helpful to uncover the association of StAR with PCOS. Use of larger study populations would also help definitively identify the exact roles of StAR genetic polymorphisms in PCOS.

**GnRHR polymorphisms**

PCOS patients often have increased levels of plasma luteinizing hormone (LH) and lower levels of follicle-stimulating hormone (FSH) compared to the normal range. These changes might be due to the dysfunction of the GnRH pulse generator that displays decreased sensitivity to the inhibition of ovarian steroids (19). GnRHR is a G-protein-coupled receptor (GPCR) that is mainly expressed in the gonadotrope membrane of the anterior pituitary (20, 21). GnRH and its receptor are expressed in many extrapituitary tissues, including ovary, placenta, breast and cancer tissues (22). However, the effects of GnRHR on these extrapituitary tissues, especially the ovary, remain unclear. A study by Chen et al. involved 314 PCOS patients and 320 control individuals, in which GnRHR gene polymorphisms were detected using the PCR-RFLP assay. The results revealed that haplotypes with TCC, CCC and CCT increased the risk of PCOS, while haplotypes with TTT, TCT and TTC lowered the risk (23). A recent genome-wide analysis by whole-exome sequencing and Sanger sequencing confirmation studied three sisters of a consanguineous family diagnosed with PCOS. The results suggested that genetic variations in the hypothalamo–pituitary axis might contribute to the pathogenesis of PCOS (24).

**FSHR polymorphisms**

FSH participates in the processes of steroidogenesis, oocyte maturation and follicle development via the FSHR located on the surface of granulosa cells in ovary tissue (25). The FSHR is a G-protein-coupled receptor comprising transmembrane, intracellular and extracellular domains. The FSHR gene, which is located on chromosome 2p21, has 10 exons and 9 introns (25). Only two FSHR polymorphisms are known (p.Thr307Ala and p.Asn680Ser); both are located in exon 10 (17, 26, 27). The p.Asn680Ser variant allele is associated with a higher basal FSH level, longer menstrual cycles and higher ovarian threshold to ovulation induction, reflecting the difference of receptor sensitivity (28, 29, 30, 31, 32). Based on the knowledge that PCOS is characterized by follicular growth failure, several studies broadly investigated the association between p.Thr307Ala and p.Asn680Ser for FSHR genetic variations with PCOS. The findings were often inconsistent and controversial. Jin et al. (25) performed genotyping in 377 women with PCOS and 388 women without PCOS by TaqMan allelic discrimination assay and found that both p.Thr307Ala and p.Asn680Ser had a significant association with PCOS. The variant homozygote genotypes could increase the risk of PCOS. However, another two studies that used the same genotyping method did not confirm these associations (33, 34). Further studies are needed to better understand the effect of FSHR gene polymorphisms in PCOS.
**FTO polymorphisms**

The human *FTO* gene is located on chromosome 16q12.2. The gene product is a 2-oxoglutarate-dependent nucleic acid demethylase that is expressed in almost all tissues (35, 36), where it participates in energy metabolism (37). A genome-wide association study in 2007 associated the *FTO* gene with body mass index (BMI) and obesity (38). Obesity is a common characteristic of PCOS; more than 50% of PCOS patients are overweight (39). Thus, it is reasonable to suppose that the *FTO* gene might take part in the pathogenesis of PCOS through BMI and/or obesity. This supposition needs to be investigated. Recent studies identified a common SNP (rs9939609) in the first intron of the *FTO* gene with a T-to-A change in PCOS cases. However, whether *FTO* gene polymorphisms participate in PCOS is still controversial (40, 41, 42, 43, 44, 45, 46). A recent meta-analysis indicated that the FTO rs9939609 polymorphism is related to the risk of PCOS in East Asians rather than the overall population (47). Another meta-analysis that included five studies comprising 5010 PCOS cases and 5300 controls indicated the relevance of the rs9939609 A/T polymorphism of the *FTO* gene with PCOS risk and that an allele might be a risk factor for pathology of PCOS (48). Further studies involving more people or the consideration of distinct ethnic and geographical groups will help uncover the effects of *FTO* gene polymorphism on PCOS development.

**IR and IRS polymorphisms**

Insulin resistance is an important factor for etiology of PCOS, with a decreased response of glucose to insulin present in over 40% of PCOS cases (49). Genes related to insulin resistance have been widely investigated as risk factors of PCOS. IR and insulin receptor substrate (IRS) proteins are important role in insulin signal transduction. Many studies have explored the effects of *IR* and *IRS* gene polymorphisms on the etiology of PCOS, with a focus on His 1058 C/T for *IR* polymorphism, Gly972Arg for *IRS-1* polymorphism and Gly1057Asp for *IRS-2* polymorphism (50). The results have largely been inconsistent, and no single polymorphism has been directly associated with PCOS. Shi et al. (50) recently conducted a meta-analysis to evaluate the relevance between *IR* and *IRS* gene polymorphisms with the pathology of PCOS. The analysis of 28 articles comprising 2975 PCOS cases and 3011 controls suggested an association between the Gly972Arg polymorphism of IRS-1 and PCOS in Caucasians and between the Gly1057Asp polymorphism of IRS-2 and PCOS in Asians. However, no association of the His 1058 C/T polymorphism for *IR* and PCOS was evident.

**VDR polymorphisms**

VDR is a DNA-binding transcription factor that is widely distributed in almost all tissues (51). When vitamin D binds to the retinoid X receptor, it enhances the interplay between VDR and this receptor, resulting in the transcription of several vitamin D-regulated genes (52). Vitamin D has a great effect in the metabolic pathways influenced by PCOS (53), and the level of vitamin D is associated with the severity of PCOS. Moreover, VDR polymorphisms are related with some characteristics of PCOS. Several studies have investigated the possible relationships of these polymorphisms with the PCOS phenotype mostly using PCR-RFLP method. Mahmoudi et al. (54) studied the frequency of FokI, BsmI, Apal and Taql VDR polymorphisms in healthy Iranian women and Iranian women with PCOS. The CC genotype of Apal was accompanied by a higher risk of PCOS. Vakili et al. (55) demonstrated the dominance of the GG genotype in mild PCOS. GA/AA and A have been linked with the progression of PCOS. El-Shal et al. (56) confirmed that the higher frequencies of the C and CC genotypes of Taql in PCOS cases. However, Ranjzad et al. (57) did not observe a statistical difference in Apal between the women with PCOS and controls. As analyzed by PCR and minisequencing, Jedrezuk et al. (58) found no significantly difference between PCOS and healthy patients concerning the distribution of those polymorphisms. The different data could be explained by the ethnic factor and numbers of classic PCOS women, which need further studies.

**MTHFR C677T polymorphism**

MTHFR is important in the processing of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which is required for the transformation of homocysteine to methionine (59, 60, 61). An abnormal level of folates inhibits ovulation in immature superovulated rats (62). Folate-deficient monkeys have degraded Graffian follicles and an increased number of atretic and cystic follicles (63). In humans, clinical evidence indicates that PCOS patients usually have an abnormal homocysteine level, which can return to the normal range with folic acid supplementation (64, 65, 66). The collective data implicate *MTHFR* as an ideal candidate gene for PCOS.
Table 1  Association of gene polymorphisms with the risk of PCOS.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Description</th>
<th>Polymorphism</th>
<th>Population</th>
<th>Number of PCOS patients</th>
<th>Methods</th>
<th>Association</th>
<th>Ref.</th>
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<tbody>
<tr>
<td>StAR</td>
<td>Steroidogenic acute regulatory</td>
<td>rs104894086</td>
<td>Iranian</td>
<td>45</td>
<td>PCR-RFLP</td>
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<td>(18)</td>
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<td></td>
<td>rs104894089</td>
<td>Iranian</td>
<td>45</td>
<td>PCR-RFLP</td>
<td>N</td>
<td>(18)</td>
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<td></td>
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<td>45</td>
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<td>(18)</td>
</tr>
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<td></td>
<td></td>
<td>rs137852689</td>
<td>Iranian</td>
<td>45</td>
<td>PCR-RFLP</td>
<td>N</td>
<td>(18)</td>
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<td></td>
<td>rs10489487</td>
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<td>45</td>
<td>PCR-RFLP</td>
<td>N</td>
<td>(18)</td>
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<tr>
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<td></td>
<td>rs104894085</td>
<td>Iranian</td>
<td>45</td>
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<td>(18)</td>
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<td>GnRHR</td>
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<td>Chinese</td>
<td>314</td>
<td>PCR-RFLP</td>
<td>Y</td>
<td>(23)</td>
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<td>Chinese</td>
<td>314</td>
<td>PCR-RFLP</td>
<td>Y</td>
<td>(23)</td>
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<td></td>
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<td>Chinese</td>
<td>314</td>
<td>PCR-RFLP</td>
<td>Y</td>
<td>(23)</td>
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<td></td>
<td></td>
<td>rs104893836</td>
<td>French</td>
<td>3</td>
<td>Whole-exome sequencing</td>
<td>Y</td>
<td>(24)</td>
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<tr>
<td>FSHR</td>
<td>Follicle-stimulating hormone receptor</td>
<td>rs6165</td>
<td>Korean</td>
<td>377</td>
<td>TADA</td>
<td>Y</td>
<td>(25)</td>
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<td></td>
<td></td>
<td></td>
<td>Caucasian, Chinese</td>
<td>518 (33), 384 (34)</td>
<td>TADA, sequencing analysis</td>
<td>N</td>
<td>(33, 34)</td>
</tr>
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<td></td>
<td></td>
<td>rs6166</td>
<td>Korean</td>
<td>377</td>
<td>TADA</td>
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<td>(25)</td>
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<td></td>
<td></td>
<td></td>
<td>Caucasian, Chinese</td>
<td>518 (33), 384 (34)</td>
<td>TADA, sequencing analysis</td>
<td>N</td>
<td>(33, 34)</td>
</tr>
<tr>
<td>FTO</td>
<td>Fat mass and obesity associated gene</td>
<td>rs9939609</td>
<td>Chinese, European, Korean</td>
<td>215 (40), 463 (41), 3599 (42), 552 (44)</td>
<td>Sequencing analysis, TaqMan assay, GWAS</td>
<td>Y</td>
<td>(40, 41, 42, 44)</td>
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<td></td>
<td></td>
<td>Brazilian, American</td>
<td>199 (43), 395 (46)</td>
<td>TADA</td>
<td>N</td>
<td>(43, 46)</td>
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<td></td>
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<td>Brazilian, American</td>
<td>199 (43), 395 (46)</td>
<td>TADA</td>
<td>N</td>
<td>(43, 46)</td>
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<td></td>
<td>rs1421085</td>
<td>American</td>
<td>395</td>
<td>TADA, sequencing analysis</td>
<td>N</td>
<td>(46)</td>
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<tr>
<td></td>
<td></td>
<td>rs17817449</td>
<td>American</td>
<td>395</td>
<td>TADA, sequencing analysis</td>
<td>N</td>
<td>(46)</td>
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<td></td>
<td></td>
<td>rs9930506</td>
<td>American</td>
<td>395</td>
<td>TADA, sequencing analysis</td>
<td>N</td>
<td>(46)</td>
</tr>
<tr>
<td>IR</td>
<td>Insulin receptor</td>
<td>rs1799817</td>
<td>Chinese, Turk, UK, Korean, Japanese, Indian, Iranian, Iraqi, Croatian</td>
<td>2975</td>
<td>Meta-analysis</td>
<td>Y</td>
<td>(50)</td>
</tr>
<tr>
<td>IRS</td>
<td>Insulin receptor substrate</td>
<td>rs1801278</td>
<td>Greek</td>
<td>2975</td>
<td>Meta-analysis</td>
<td>Y</td>
<td>(50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>French, Chilean, German, Japanese, American, Spanish, Turkish, Chinese, Italian, Indian, Greek, Slovakian, Croatian</td>
<td>2975</td>
<td>Meta-analysis</td>
<td>N</td>
<td>(50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>rs1805097</td>
<td>French, Chinese, German, Spanish, Greek, Vietnamese, Japanese, American, African, Indian, Chinese, Korean, Japanese, Italian, Slovakian, Croatian</td>
<td>2975</td>
<td>Meta-analysis</td>
<td>Y</td>
<td>(50)</td>
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<tr>
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<td>French, Chilean, German, Japanese, American, Spanish, Turkish, Chinese, Italian, Indian, Greek, Slovakian, Croatian</td>
<td>2975</td>
<td>Meta-analysis</td>
<td>N</td>
<td>(50)</td>
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<tr>
<td>VDR</td>
<td>Vitamin D receptor</td>
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<td>Iranian</td>
<td>162</td>
<td>PCR-RFLP</td>
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<td>(54)</td>
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<td></td>
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<td></td>
<td>Egyptian, Polish</td>
<td>150 (56), 92 (58)</td>
<td>PCR-RFLP, minisequencing</td>
<td>N</td>
<td>(56, 58)</td>
</tr>
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<td></td>
<td></td>
<td>rs10735810</td>
<td>Iranian, Polish</td>
<td>162 (54), 92 (58)</td>
<td>PCR-RFLP, minisequencing</td>
<td>N</td>
<td>(54, 58)</td>
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<td></td>
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<td>rs1544410</td>
<td>Iranian, Polish</td>
<td>162 (54), 92 (58)</td>
<td>PCR-RFLP, minisequencing</td>
<td>N</td>
<td>(54, 58)</td>
</tr>
<tr>
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<td></td>
<td>rs731236</td>
<td>Egyptian, Polish</td>
<td>150</td>
<td>PCR-RFLP</td>
<td>Y</td>
<td>(56)</td>
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<tr>
<td></td>
<td></td>
<td>rs757343</td>
<td>Iranian</td>
<td>260 (55), 181 (57)</td>
<td>PCR-RFLP</td>
<td>N</td>
<td>(55, 57)</td>
</tr>
</tbody>
</table>

(Continued)
Participation of *MTHFR* polymorphisms in the regulation of the folate pathway or decreased activity of the homocysteine pathway has been revealed in a variety of pathologies, including Alzheimer’s disease, neural tube defects, acute leukemia, colon cancer and PCOS (67). Laboratory data indicate that variant C677T in the *MTHFR* gene decreases the activity of the folate pathway by 50% (59, 68, 69). However, the few clinical studies done to date have obtained similar results that indicate the association between *MTHFR* and PCOS (70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81). More recently, Wang et al. (82) conducted a meta-analysis to evaluate the effect of *MTHFR* C677T polymorphism on the risk of PCOS. The results from the analysis of 14 articles involving 1478 PCOS cases from 16 distinct populations showed that the *MTHFR* C667T variant had different roles in the risks of PCOS in different ethnicities. The T allele significantly increased the risk of PCOS in Asians, had a protective effect in Caucasians and had no significant associations in Middle Eastern individuals.

**PPAR-γ** polymorphism

PCOS is related to some extent with hormonal and metabolic disorders, with insulin resistance being one of the most common metabolic disturbances (83). The *PPAR-γ* (*PPARG*) gene participates in the management of insulin sensitivity and in lipid metabolism (84). The gene product (PPAR-γ) plays an important part in the management of energy storage and insulin sensitivity based on its roles in glucose regulating and lipid metabolism (85). Wang et al. (86) investigated the association of *PPARG* and *PPARG-1alpha* gene polymorphisms with PCOS among 201 Chinese Han PCOS women and 147 controls. The results suggested that these gene polymorphisms were not associated with the risk of PCOS. A meta-analysis conducted in 2010 evaluated the relationship of Pro12Ala polymorphism of *PPARG* with PCOS (87). The results from the analysis of 13 studies that included 1598 PCOS cases and 1881 controls revealed no significant association of the Pro12Ala polymorphism with PCOS. However, in a more recent investigation of the association of *PPARG* Pro12Ala polymorphism with PCOS, the frequency of the polymorphic allele was significantly higher in PCOS cases than in the controls, suggesting that the *PPARG* Pro12Ala polymorphism might contribute to the risk of PCOS (88).

**IL-1β/IL-1Ra** gene polymorphisms

PCOS is recognized as pro-inflammatory condition (89). Elevation of circulating inflammatory mediators have been observed in PCOS (90), including pro-inflammatory cytokines, white blood cells, chemokines and multiple endothelial inflammation markers (91). Cytokines are important in inflammatory processes and are also thought to be associated with the etiology of PCOS (92). IL-1β is a member of the IL-1 family; it is a valid pro-inflammatory cytokine that has a great impact on the physiology of reproduction. IL-1β has also been reported as a crucial moderating element in ovulation, fertilization, embryo implantation and tissue restructuring (93, 94). Another important member of the IL-1 family is IL-1RA; it may

<table>
<thead>
<tr>
<th>Gene</th>
<th>Description</th>
<th>Polymorphism</th>
<th>Population</th>
<th>Number of PCOS patients</th>
<th>Methods</th>
<th>Association</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>MTHFR</em></td>
<td>Methylene tetrahydrofolate reductase</td>
<td>C677T</td>
<td>Italian, Korean, Turkish, Iranian, Indian, Polish</td>
<td>70 (73), 227 (75), 86 (76), 38 (77), 92 (78), 98 (79), 76 (80), 261 (81)</td>
<td>PCR-RFLP, real-time PCR</td>
<td>N</td>
<td>(73, 75, 76, 77, 78, 79, 80, 81)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A1298C</td>
<td>Iranian</td>
<td>38</td>
<td>PCR-RFLP</td>
<td>Y</td>
<td>(77)</td>
</tr>
<tr>
<td><em>PPAR-γ</em></td>
<td>Peroxisome proliferator-activated receptor gamma</td>
<td>Pro12Ala</td>
<td>European, Egyptian</td>
<td>1598</td>
<td>None</td>
<td>N</td>
<td>(80)</td>
</tr>
</tbody>
</table>

GWAS, genome-wide association study; N, gene polymorphisms show none significant association with PCOS; PCR-RFLP, polymerase chain reaction-restriction fragment-length polymorphism assay; TADA, TaqMan allelic discrimination assay; Y, gene polymorphisms show significant association with PCOS.
be able to minimize the inflammatory response. Various IL-1Ra gene polymorphisms have been identified and six distinct alleles have been recognized to date. A recent study by Rashid et al. (95) involving 95 women with PCOS and 45 healthy women as controls analyzed the connection between IL-1β and IL-1Ra gene polymorphisms with the risk of PCOS. The findings indicated that polymorphisms in these cytokines genes may contribute to the risk of PCOS.

Conclusions

PCOS is a common endocrine disorder among women of reproductive aged. Many risk factors affect the occurrence and development of PCOS, including ovary abnormalities, obesity and environmental factors. Multiple studies have suggested that genetic factors are essential in the etiology of PCOS. As we have described, a number of polymorphic variants of candidate genes associated with PCOS have been identified in case–control association studies (Table 1). However, the genetic significance and the exact pathophysiological relevance of most of these genes with PCOS, which include STAR, FSHR and FTO, are still unclear and need to be confirmed. For the putative candidate genes identified so far, more studies are needed for a better understanding of their molecular and physiological roles in PCOS. These data will clarify the risk factors of PCOS and contribute to the prediction of the disorder, which could improve diagnosis and treatment of PCOS patients. Polymorphic variants of genes have been garnered mainly by genome-wide analysis and epigenetic regulation such as DNA methylation and noncoding RNAs have been more recently linked with PCOS. The advances in epigenetic studies on PCOS have been reviewed elsewhere (96).

The etiology of PCOS remains difficult to clarify because of heterogeneities in its features and origins. With the systematic acquisition of more data, identification of better phenotypes and studies involving larger populations, the pathological mechanisms of PCOS will become better understood, which will further improve the diagnosis and knowledge of the clinical manifestations of PCOS. These data will also help us determine whether one genetic polymorphism has a compelling association with PCOS. Several candidate genes have been associated with the PCOS susceptibility. However, controversial findings still exist, which may ascribe to the diverse populations and genotyping methods. There is a long way to go before we entirely understand the genetic effects on this complex and heterogeneous disorder. Further studies should consider address genetic and environment factors, including obesity and nutrition, which will provide a better understanding of the etiology of PCOS.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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Author contribution statement
Yao Chen was the primary author of this manuscript. She reviewed and edited the manuscript and approved the final version. Shu-ying Fang contributed to the writing and formatting of this work.

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