REVIEW ARTICLE

Review on Molecular and Biochemical Basis of Polycystic Ovary Syndrome: Interplay of Genetic Polymorphisms, Steroidogenesis, and Insulin Signaling Pathways

S. Preethi[1], Gurupavan Kumar Ganta[1], Periasamy Anbu[3], P. Parthiban[2], S. Vimal[1]

[1]Department of Biochemistry, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences, Chennai, Tamil Nadu, India, [2]Department of Pathology, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences (Deemed to be University), Chennai, Tamil Nadu, India, [3]Department of Microbiology, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences (Deemed to be University), Chennai, Tamil Nadu, India

Abstract

Polycystic ovary syndrome (PCOS) is a complex disorder that is highly prevalent in many females worldwide. This disorder has a strong genetic component with many candidate genes, including androgen receptor (AR), follicle-stimulating hormone receptor, m6A demethylase, Calpain protease and several members of the cytochrome P450 family. These genes are mainly related to AR signaling and steroidogenesis enzymes. The exact cause of PCOS is still partly unknown. It is important to understand genetic predispositions to understand risk factors and possible therapeutic targets. Metabolic and hormonal pathways are disrupted as a result of genetic polymorphisms, leading to ovarian dysfunction and the development of PCOS symptoms. In particular, variations in the genes encoding steroidogenesis and hormone receptors can disrupt the hormonal balance, leading to conditions such as hyperandrogenism and ovarian cyst formation. Insulin resistance is the most prominent feature of PCOS pathology that interacts with genetic factors and aggravates the condition. Management strategies are aimed at symptom relief with lifestyle modifications and pharmacological interventions to improve the quality of life and fertility outcomes in women with the condition. The ongoing investigations of the association of genetic polymorphisms with PCOS emphasize the complexity of this disease but also highlight the discrepancies in results with respect to genetic factors involved in the syndrome. One promising direction for this field is the trend toward subtyping PCOS. This may move the classification of PCOS from a largely subjective diagnosis to one based on discrete biological differences. Weight loss, a balanced diet, and regular use of prescribed medicines can help in managing the severity of PCOS effectively through preventive measures.

Key words: Hyperandrogenism, hyperinsulinemia, insulin resistance, ovulatory dysfunction, polycystic ovarian syndrome

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrine disorder of 5–15% of women of reproductive age group (18–44 years) worldwide.[1,2] It is marked by serious complications such as infertility and menstrual irregularities and is known by various alternate names such as schlerocystic ovaries and Stein–Leventhal syndrome, in recognition of the American gynecologists Irving F. Stein and Michael L. Leventhal.[3,4] Biochemically, insulin works synergistically with luteinizing hormone to increase theca cell androgen production, and also

Address for correspondence:
S. Vimal, Department of Biochemistry, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences, Chennai, Tamil Nadu, India.
E-mail: vimalbiotechs@gmail.com

Received: 11-05-2026
Revised: 16-06-2026
Accepted: 27-06-2026

decreases liver production of sex hormone-binding globulin (SHBG), increasing available free androgens. The endocrine disturbance inhibits normal follicle development and results in anovulation and cyst formation (12 cysts/ovary). Moreover, the expression of the syndrome changes in different stages of life, from a reproductive to a metabolic disorder.[5] The effects of infertility are of great concern in women with PCOS. Infertility occurs in 70–80% of women with PCOS due to ovulatory dysfunction, and in early pregnancy, complications such as ovarian hyperstimulation and miscarriage may occur. The disease has a genetic component, but females in the first degree of kinship of patients with PCOS may also present the disease. However, the specific mechanisms of infertility in PCOS are still largely obscure, impaired endometrial implantation being one of the possible factors.[6]

Despite extensive studies, the exact molecular mechanism of PCOS is not fully understood due to its heterogeneity and variation in different populations. Thus, a detailed understanding of the biochemical and genetic basis of PCOS is required to improve the accuracy of diagnosis and to design specific therapeutic strategies.

MOLECULAR BASIS AND MODE OF INHERITANCE OF PCOS

Cooper *et al*. first described the genetic contribution to PCOS in 1968, and subsequent studies have suggested familial patterns and autosomal dominant inheritance with a significant prevalence among first-degree relatives at 55–60%. This supported the hypothesis of autosomal dominant inheritance. Later, monogenic causes of hirsutism and oligo-menorrhea in women with PCOS and male-pattern baldness were identified.[7,8] However, twin studies of monozygotic and dizygotic pairs of twins suggested that PCOS may not be a simple autosomal-dominant or single-gene disorder but rather an X-linked disorder with polygenic inheritance. These studies estimated that 72% of the risk variance for PCOS has a genetic basis, emphasizing the significant genetic contribution to its pathogenesis [Table 1].[9-11]

ETIOLOGY AND BIOCHEMICAL PATHWAYS IN PCOS

The etiology of PCOS is influenced by genetic and environmental factors. Unhealthy lifestyle, poor diet, and infectious agents increase the risk of developing PCOS.[12] At the core of the condition is insulin resistance, which leads to ovarian dysfunction and increased androgen levels resulting in anovulation. Affected individuals also manifest hormonal imbalances in gonadotropin-releasing hormone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and prolactin. Genetic factors are significant, with at least 241 gene variations associated with PCOS, including polymorphism in genes involved in androgen and hormonal receptors.[13]

Specific polymorphisms, including those affecting StAR, FSH receptors (FSHR), m6A demethylase (FTO), Vitamin D receptor (VDR), Insulin receptor (IR), IR substrates (IRS), and GnRHR, are associated with changes in gene transcription and, accordingly, the biochemical pathways regulating ovarian function.[14] Increased insulin and androgen levels can contribute to the severity and progression of PCOS. High insulin levels adversely affect ovarian theca cells, resulting in increased androgen production and decreased hepatic production of SHBG and IGFBP-1 [Figure 1]. High androgen levels stimulate visceral adipose tissue to produce free fatty acids, which lead to increased insulin resistance and demonstrate the complex relationship between genetic predisposition and hyperandrogenism in PCOS.[15] Current research has highlighted genes associated with PCOS, particularly genes encoding the *VDR* and adiponectin (*ADIPOQ*).

Table 1: Functional classification of genes associated with PCOS

Functional category	Genes	Chromosomal location	Biological role
Steroidogenesis	*CYP11A1, CYP17A1, CYP19A1, CYP21A2, CYP1A1*	15q24.1, 10q24.32, 15q21.2, 6p21.33	Androgen and estrogen biosynthesis
Hormone signaling	*AR, SHBG*	Xq11–q12, 17p13	Regulation of androgen action and hormone transport
Gonadotropin regulation	*FSHR, LH, AMH*	2p16.3, 19q13.32, 19p13.3	Follicular development and ovarian function
Insulin signaling	*CAPN10, INS, INSR, IRS-1, IRS-2*	2q37.3, 11p15.5	Glucose metabolism and insulin response
Metabolic regulation	*FTO, ADIPOQ, VDR*	16q12.2, 3q27, 12q13.11	Energy balance, adipogenesis, and insulin sensitivity

CYP11A1: Cholesterol side-chain cleavage enzyme, *CYP17A1*: 17α-hydroxylase, *CYP19A1*: Aromatase, *AR*: Androgen receptor, *SHBG*: Sex hormone-binding globulin, *FSHR*: Follicle-stimulating hormone receptor, *CAPN10*: Calpain protease, *FTO*: m6A demethylase, *ADIPOQ*: Adiponectin, *VDR*: Vitamin D receptor, *LH*: Luteinizing hormone, *AMH*: Anti-Müllerian hormone, *INSR*: Insulin receptor, *INS*: Insulin, *IRS*-1: Insulin receptor substrates 1, *IRS*-2: Insulin receptor substrates 2, PCOS: Polycystic ovary syndrome

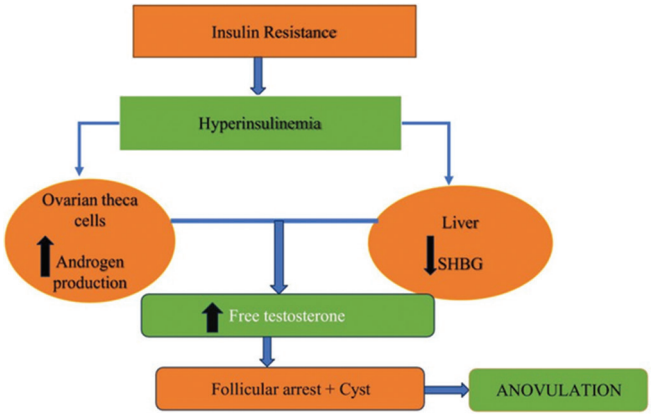

Figure 1: Flowchart illustrating insulin resistance as a cause of polycystic ovary syndrome

MOLECULAR GENETICS AND METABOLIC REGULATION

VDR and ADIPOQ in metabolic dysfunction

The gene encoding the VDR, located at the chromosomal locus 12q13.11, includes 14 exons and encodes 427 amino-acid residues. Notable single-nucleotide polymorphisms (SNPs) variants in this gene comprise TaqI (rs731236) in exon 9, BsmI (rs1544410) and ApaI (rs7975232) in intron 8, and FokI (rs10735810) in exon 2, with the TaqI and BsmI variants affecting mRNA stability and posttranscriptional processes due to their proximity to the 3' UTR region. The *ADIPOQ* gene, located on chromosome 3q27, is composed of three exons and two introns, showing high heritability and links to obesity and diabetes complications. Key SNPs for ADIPOQ include T45G (rs2241766) in exon 2 and G276T (rs1501299) in intron 2.[16-19]

In a meta-analysis by Abinaya *et al*., evidence for four polymorphisms from the *VDR* (rs731236, rs1544410) and *ADIPOQ* (rs2241766, rs1501299) genes associated with PCOS. The BsmI polymorphism (rs1544410 -located at 3'UTR region) has been shown to have low occurrence in PCOS women, and also highlighted variances across ethnicities. The *ADIPOQ* gene polymorphisms correlated with obesity and metabolic dysregulation, demonstrated no significant association in certain populations, yet findings from the meta-analysis indicated notable links with PCOS. The analysis emphasized the need for haplotype studies and exploration of gene interactions to better understand these associations.[20]

FTO and energy homeostasis

The *FTO* gene, referred to as an alpha-ketoglutarate-dependent dioxygenase, is located cytogenetically at chromosomal region 16q12.2 and comprises 14 exons. Various research studies have established a correlation between *FTO* and obesity and body mass index (BMI), as well as type 2 diabetes mellitus. Notably, research conducted in Pakistan has identified polymorphisms within the *FTO* gene in patients with PCOS. In particular, the study highlighted the presence of the rs9939609 single-nucleotide polymorphism (SNP) within an intronic variant, highlighting that individuals affected by this condition present a statistically significant difference in terms of BMI when compared with healthy individuals. Furthermore, the link between *FTO* gene SNPs and PCOS has been substantiated within the Pakistani population, reinforcing the genetic influence of the *FTO* gene on metabolic conditions such as obesity and PCOS.[21,22]

HORMONE SIGNALING AND RECEPTOR DYSFUNCTION

Androgen receptor (AR) and SHBG

The *AR* gene is located on the X chromosome, located at the Xq12 chromosomal locus, consists of 11 exons and encodes a protein that exceeds 90 kb in length, featuring a total of three major functional domains.[23] The AR, which has been associated with PCOS, is influenced by X-chromosome inactivation (a single copy is significant), leading to disruptions in the androgen signaling pathway that can result in elevated activity. Moreover, conducting a genome-wide association study (GWAS) in PCOS could help detect novel mutations as well as other genetic variants contributing to the development of this condition.[24]

The *SHBG* gene, located on the 17p13–p12 chromosomal region, encodes a protein product containing 373 amino acids that plays a crucial role in regulating sex hormone levels by binding to androgens, primarily testosterone and estrogens.[25] Most *SHBG* is produced by liver hepatocytes, and its production is influenced by various metabolic factors, including androgens and insulin. In females with PCOS, *SHBG* levels are often lower due to the inhibitory influence of hyperinsulinemia on its production.[26] SNPs in the *SHBG* gene have a significant effect.[27]

GONADOTROPIN DYSREGULATION AND FOLLICULOGENESIS

FSHR

The *FSHR* gene is located on the 2p16.3 chromosomal region and consists of 14 exons. It produces a protein classified as a type of G protein-coupled receptor, which has an important function in gonadal development.[28] Alterations in hormone levels can significantly impact the endocrine reproductive system. Among various hormones, imbalanced levels of FSH are linked to the severity of PCOS. Abnormalities in the FSHR can lead to dysfunctions in follicular activity and ovarian function. Statistical analyses and restriction fragment

length polymorphism studies using the restriction enzyme Eam11051 revealed significant differences between healthy individuals and those affected by the condition in a research study conducted in northern Iraq.[29]

Anti-Müllerian hormone (AMH)

The AMH gene, located at cytogenetic position 13.3 on chromosome 19q, comprises five exons and produces a protein relevant to infertility.[30] Whole exome sequencing and GWAS have recognized variations in the AMH gene that are linked to PCOS, as well as being significant predictors for the condition.[31]

LH and its receptor gene

A high concentration of LH increases androgen production, while negative feedback results in decreased FSH, potentially indirectly exacerbating excess androgen in the ovaries due to reduced conversion of androgens into estrogens. Research into the genes encoding LH and its receptor in PCOS has revealed point mutations, including Trp8Arg and Ile15Thr, within the B subunit gene, which, although initially reported in PCOS patients, is also found in 15% of the normal population and is considered nonpathogenic. In addition, LH β-subunit gene polymorphisms have been associated with PCOS.[32-36]

INSULIN SIGNALING AND GENETIC VARIABILITY

Genes involved in insulin signaling, including Calpain protease (CAPN10), INS, INSR, IRS-1, and IRS-2, play an important role in the metabolic aspects of PCOS. Insulin binding to its receptor activates downstream signaling cascades, primarily the PI3K/Akt and MAPK pathways. The abnormal phosphorylation of IRS-1 and IRS-2 causes the defect of signal transduction and decreased glucose uptake, and increased insulin resistance in PCOS. CAPN10 is a calcium-dependent protease involved in glucose metabolism and insulin secretion, further supporting a role for genetic variation in metabolic dysfunction. Therefore, CAPN10 is one of the most promising candidate genes for the study of the genetic basis of PCOS.[37,38]

IGF2BP2 and *IGFBP3*

A 2024 study published in J Clin Lab Anal finds significant associations of gene variants IGF2BP2 (rs1470579) and IGFBP3 (rs2854744) with increased risk of PCOS in Indian women. These genes are linked to insulin resistance, a prevalent characteristic of PCOS. *IGF2BP2*, which interacts with IGF-II, plays a role in PCOS development. A study carried out in Southern India, particularly Hyderabad, emphasizes the connection between high rates of type 2 diabetes mellitus (T2DM) and genetic susceptibility to PCOS related to insulin resistance. In addition, the IGF2 Apa1 A820G (rs680) gene polymorphism has been implicated in PCOS, particularly in women with higher BMI as well as insulin resistance. The *IGFBP3* rs2854744 variant corroborates findings in other populations as a risk factor for developing PCOS.[39]

The insulin gene

Insulin influences androgen synthesis in theca cells through the phosphoinositide 3-kinase/protein kinase B pathway, particularly active in PCOS. Elevated insulin levels enhance androgen synthesis similarly to LH. The *INS* gene is mapped to 11p15.5, flanked by tyrosine hydroxylase and *IGF*-II genes, with its transcription regulated by VNTR polymorphism in the 5′ untranslated region, which varies in repeat number between 26 and 200 and has been associated with PCOS. This gene encodes a turmeric-derived protein with two α and two β chains. Research on the connection between infertility in obese women and PCOS yielded no significant findings. Studies by Conway *et al*. and Talbot *et al*. on the *INSR* gene and its tyrosine kinase domain in women with PCOS also found no link. However, a notable association with PCOS was identified at the D19S884 locus on chromosome 19p13.2, which includes the *INSR* gene.

The insulin binding receptor gene

Insulin attaches to its receptor, triggering receptor auto-phosphorylation and activation of the receptor. This activation enables the receptor's tyrosine kinase to phosphorylate *IRS-1* and *IRS-2*, which subsequently participate in downstream signaling events. Some studies have examined the association between PCOS and variants of the *IRS-1* and *IRS-2* genes, but the results have been inconsistent. Petermann *et al*. reported a higher frequency of the IRS-1 Arg972 mutation in women with PCOS, while El Mkadem *et al*. found no significant difference compared with controls. Diselek *et al*. reported a higher prevalence of the IRS-1 Gly972Arg variant in Turkish women with PCOS. Such differences may be indicative of a possible role of environmental and ethnic factors.[40]

STEROIDOGENESIS AND CYP450 ENZYME DYSFUNCTION

Steroidogenesis enzymes such as aromatase belong to the Cytochrome P450 family and are essential for the conversion of androgens into estrogens. Aromatase deficiency prevents this conversion pathway and adversely affects ovarian function, resulting in increased levels of androgens due to the lack of transformation of C19 steroids to C18.

In the context of PCOS, specific aromatase genes were identified in relevant databases, including CYP11A1,

CYP11B2, CYP17A1, CYP19A1, CYP1A1, CYP21A2, and CYP3A7 [Table 2]. Changes in the cytochrome P450 enzyme family increase the chances of PCOS progression [Figure 2].[41]

CYPA1A

Gene *CYPA1A*, cytochrome P450 family 1 subfamily a. A member 1 at chromosome 15q24.1 is heavily implicated in the development of PCOS. It consists of 7 exons and encodes cytochrome P450 proteins that are localized to the endoplasmic reticulum and primarily activated by polycyclic aromatic hydrocarbons.[42-44] Studies have also shown that the prevalence of isoleucine/valine polymorphism is higher in PCOS patients than in healthy controls. The prevalence of the CYP1A1 isoleucine/valine genotype was found to be 7.8-fold compared to the 7.4-fold prevalence of CYP1A1 isoleucine/valine genotype. Changes in phase I and phase II enzyme activities may be involved in abnormal ovarian function and cyst formation. In particular, the *CYP1A1* gene T6235C polymorphism is significantly associated with susceptibility to PCOS. This genetic variation modifies the enzymatic pathways and increases the risk of developing and progressing PCOS.[45-47]

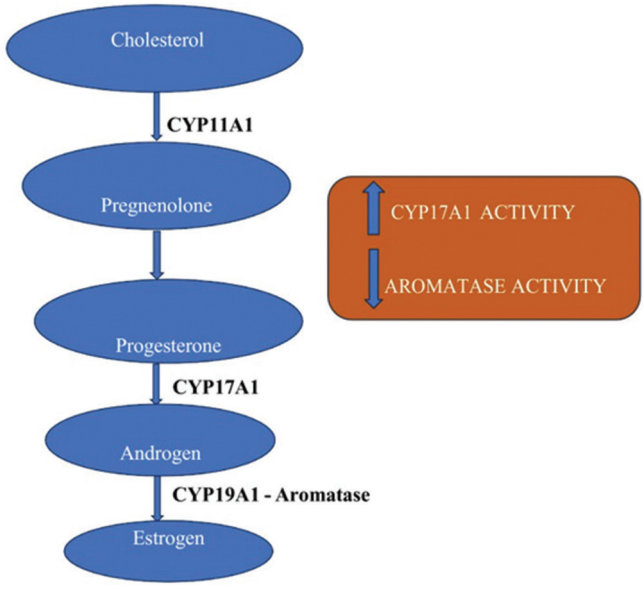

Figure 2: Steroidogenesis pathway

CYP11A1

Cytochrome P450, family 11, subfamily A (CYP11A1) A member 1, encodes for a protein existing in the inner mitochondrial membrane and plays an essential role in converting cholesterol to pregnenolone, playing a key role in steroidogenesis. The gene is located on chromosome 15q24.1 and is composed of 10 exons.[4] It is of note that polymorphisms in the TTTTA pentanucleotide repeat are associated with a genetic predisposition for PCOS with CYP11A1 polymorphism being a molecular marker for the syndrome. The risk is increased by the interplay between genetic and environmental factors. A South Indian cohort study identified 15 allelic variants, and the most common was the 8-repeat allele. The >8 repeat alleles increased the risk of PCOS 3 times as compared to controls. Furthermore, a Chinese case-control study reported that the SNP rs4077582 in CYP11A1 was significantly associated with PCOS and was associated with increased androgen levels affected by LH in different genotypes.[48-50]

CYP19A1

The *CYP19* gene is involved in cholesterol, steroid, and lipid biosynthesis. It encodes cytochrome P450 family 19

Table 2: Key genes and their biochemical mechanisms in PCOS

Gene	Encoded Protein	Pathway involved	Functional impact in PCOS	References
CYP11A1	Cholesterol side-chain cleavage enzyme	Steroidogenesis	Initiates steroid hormone synthesis	[46-48]
CYP17A1	17α-hydroxylase	Androgen biosynthesis	Increases androgen production	[54-56]
CYP19A1	Aromatase	Estrogen synthesis	Reduced activity→androgen accumulation	[49-51]
AR	Androgen receptor	Hormone signaling	Increased androgen sensitivity	[23-24]
SHBG	Sex hormone-binding globulin	Hormone transport	Decreased levels → ↑ free testosterone	[25-27]
FSHR	FSH receptor	Folliculogenesis	Impaired follicular maturation	[29]
CAPN10	Calpain protease	Insulin signaling	Insulin resistance	[37]
FTO	m6A demethylase	Energy metabolism	Obesity and metabolic dysfunction	[21-22]
ADIPOQ	Adiponectin	AMPK pathway	Reduced insulin sensitivity	[16-19]
VDR	Vitamin D receptor	Transcription regulation	Impaired metabolic regulation	[20]

CYP11A1: Cholesterol side-chain cleavage enzyme, *CYP17A1*: 17α-hydroxylase, *CYP19A1*: Aromatase, *AR*: Androgen receptor, *SHBG*: Sex hormone-binding globulin, *FSHR*: Follicle-stimulating hormone receptor, *CAPN10*: Calpain protease, *FTO*: m6A demethylase, *ADIPOQ*: Adiponectin, *VDR*: Vitamin D receptor

subfamily A polypeptide 1, which is important in estrogen biosynthesis. This gene is found on the chromosomal location 15q21.2 and has 18 exons and 17 introns. Important SNPs are rs700519 (C/T) in an exon and rs710059 (C/T) in an intron. The total gene spans over 123 kb, comprising a 93 kb regulatory area and a 30 kb coding region.[50] Variations in *CYP19*is are linked not only to PCOS but also to increased risks of endometrial, breast, and prostate cancers.[51] SNP rs2414096, located in the *CYP19* gene, shows significant genotype differences (AG, AA, GG) between PCOS patients and control groups, indicating its association with PCOS susceptibility.[49] SNPs at the exonic region (rs700519variant) and two intron-based regions (rs2414096 and rs60271534variants) were additionally identified in the South Indian population.[5]

CYP21A1

Cytochrome P450, family 21 subfamily A member 2 (*CYP21*), located at chromosomal position 6p21.33 and comprising 10 exons, is identified as a gene associated with the risk of the development and progression of PCOS. Research indicates that a heterozygous mutation in this gene may contribute to the pathogenesis of PCOS, with approximately 14 different molecular anomalies reported in relation to *CYP21*'s role in the condition. The mutation frequencies in control individuals and PCOS patients are 5.9% and 7.6%, respectively, indicating the importance of the gene but not a conclusive explanation for its role in PCOS cases.[52,53]

CYP17A1

The cytochrome P450, family 17, subfamily A, member 1 (CYP17) is a steroidogenesis enzyme that is located on the 10q24.32 chromosomal region and contains 8 exons. CYP17 has been implicated in the pathogenesis of PCOS, especially in a study conducted in a Chilean population, where a C>T polymorphic variant in CYP17 was reported to contribute to the progression of PCOS. Hormonal and clinical evidence show that this polymorphism is associated with increased body weight, insulin resistance, and lipid profile. In addition, the Chinese population studied had the T/C variant in the *CYP17A1* gene, with genotypes of TC, TT, and CC accounting for 43.71%, 49.69% and 6.6%, respectively. Women with the CC genotype had higher levels of testosterone than women with TT or TC genotypes. However, the association of T/C polymorphism with PCOS may be indirect and due to increased testosterone and insulin resistance.[54-56]

FUTURE PERSPECTIVE

Future PCOS research should take a more integrated multi-omic approach to study the interaction between genetic variation, steroid production, and insulin signaling pathways. Genomic analysis and next-generation sequencing of large populations is important for the identification of new variants and the understanding of gene-gene interactions associated with different expressions of PCOS. Functional genomics and systems biology approaches can provide additional insight into how these genetic differences impact biological pathways, especially those involved in insulin resistance and androgen production. Moreover, there is increasing evidence that epigenetic modifications and environmental factors are involved in the gene expression of the development of susceptibility to PCOS, which emphasizes the importance of long-term studies for identifying early markers and therapeutic targets. Animal and laboratory models are important in the development of knowledge of the molecular mechanisms of the disease. The advances in precision medicine and pharmacogenetics pave the way for personalized therapies. Overall multidisciplinary efforts are needed for overall progress in the understanding and management of PCOS to integrate clinical, genetic, and biological data for early diagnosis, risk assessment, and targeted treatment.

CONCLUSION

The common and heterogeneous endocrine disorder, PCOS, is characterized by amenorrhea, excess androgen levels, hirsutism, obesity, and insulin resistance with a significantly higher likelihood for T2DM. The estimated prevalence of PCOS in reproductive-aged women is 4–12%. There is a known familial and ethnic variation in the prevalence and presentation of PCOS. The disorder's pathogenesis is due to multiple biochemical pathways involving genes associated with steroid hormone metabolism, gonadotropin action, obesity regulation, and insulin signaling. Women with PCOS frequently have insulin resistance, and certain genetic factors, including the INS VNTR (specifically the Class III alleles), may predispose to anovulatory PCOS and diabetes risk. Evidence of abnormal serine phosphorylation in relation to insulin receptor function and of possible shared etiologies of insulin resistance and hyperandrogenism. Insulin-receptor substrate genes (*IRS*-1 and *IRS*-2) variants may be involved in insulin resistance in PCOS. On the other hand, evidence available does not support an involvement of follistatin gene polymorphisms in this respect. Moreover, some genetic variations in the *CYP11A* gene may result in increased androgen production. Polymorphisms of the AR gene correlate with the androgen effects, especially in hirsutism cases with normal testosterone levels. Polycystic ovaries have shown increased 5-alpha-reductase activity and abnormal estrogen receptor expression, suggesting a role for androgens in PCOS pathogenesis. The precise cause of PCOS is still unknown, but it is thought to be multifactorial in nature and not due to a single cause. Many interrelated factors affect the presentation of PCOS.

ETHICS

This study did not involve human participants or experimental animals directly; therefore, ethical approval was not required.

ACKNOWLEDGMENT

None.

DATA ACCESS

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

1. Azziz R. Polycystic ovary syndrome. Obstet Gynecol 2018;132:321-36.
2. Lauritsen MP, Bentzen JG, Pinborg A, Loft A, Forman JL, Thuesen LL, *et al*. The prevalence of polycystic ovary syndrome in a normal population according to the Rotterdam criteria versus revised criteria including anti-Mullerian hormone. Hum Reprod 2014;29:791-801.
3. Meier RK. Polycystic ovary syndrome. Nurs Clin North Am 2018;53:407-20.
4. Legro RS. Stein-Leventhal Syndrome. United States: Encyclopedia Britannica; 2009.
5. Ranjith Reddy K, Deepika ML, Prasanna Latha K, Sagurthi SR, Lakshmanarao SS, Fazul Rahman P, *et al*. Polycystic ovary syndrome: Role of aromatase gene variants in south Indian women. Int J Pharma Bio Sci 2015;6:1283-96.
6. Jain D, Sood A, Jain AK. Time to stop complicating a complex disease: Adopt simple treatment for polycystic ovarian syndrome. Gynecol Minim Invasive Ther 2020;9:110-1.
7. Cooper HE, Spellacy WN, Prem KA, Cohen WD. Hereditary factors in the stein-leventhal syndrome. Am J Obstet Gynecol 1968;100:371-87.
8. Carey AH, Chan KL, Short F, White D, Williamson R, Franks S. Evidence for a single gene effect causing polycystic ovaries and male pattern baldness. Clin Endocrinol (Oxf) 1993;38:653-8.
9. Jahanfar S, Eden JA, Warren P, Seppala M, Nguyen TV. A twin study of polycystic ovary syndrome. Fertil Steril 1995;63:478-86.
10. Jahanfar S, Eden JA, Nguyen T, Wang XL, Wilcken DE. A twin study of polycystic ovary syndrome and lipids. Gynecol Endocrinol 1997;11:111-7.
11. Vink JM, Sadrzadeh S, Lambalk CB, Boomsma DI. Heritability of polycystic ovary syndrome in a Dutch twin-family study. J Clin Endocrinol Metab 2006;91:2100-4.
12. Muthukumaran D, Anitha V, Baskar G, Shanmugam R. Polycystic ovarian syndrome - Exploring the therapeutic and biomedical insights into the role of silver nanoparticles. J Steroid Biochem Mol Biol 2026;259:106968.
13. Joseph S, Barai RS, Bhujbalrao R, Idicula-Thomas S. PCOSKB: A Knowledge base on genes, diseases, ontology terms and biochemical pathways associated with polycystic ovary syndrome. Nucl Acids Res 2016;44:D1032-5.
14. Chen Y, Fang SY. Potential genetic polymorphisms predicting polycystic ovary syndrome. Endocr Connect 2018;7:R187-95.
15. Shaikh N, Dadachanji R, Mukherjee S. Genetic markers of polycystic ovary syndrome: Emphasis on insulin resistance. Int J Med Genet 2014;2014:478972.
16. Ganie MA, Vasudevan V, Wani IA, Baba MS, Arif T, Rashid A. Epidemiology, pathogenesis, genetics and management of polycysticovary syndrome in India. Indian J Med Res 2019;150:333-44.
17. Shahmoradi A, Aghaei A, Ghaderi K, Jafar Rezaei M, Azarnezhad A. A meta-analysis of the association of ApaI, BsmI, FokI, and TaqI polymorphisms in the Vitamin D receptor gene with the risk of polycystic ovary syndrome in the Eastern mediterranean regional office population. Int J Reprod Biomed 2022;20:433-46.
18. Shi XY, Huang AP, Xie DW, Yu XL. Association of Vitamin D receptor gene variants with polycystic ovary syndrome: A meta-analysis. BMC Med Genet 2019;20:32.
19. Siddamalla S, Reddy TV, Govatati S, Erram N, Deenadayal M, Shivaji S, *et al*. Vitamin D receptor gene polymorphisms and risk of polycystic ovary syndrome in South Indian women. Gynecol Endocrinol 2018;34:161-5.
20. Abinaya GP, Iyshwarya BK, Veerabathiran R. Association of gene polymorphisms with polycystic ovary syndrome: A meta-analysis. Gynecol Minim Invasive Ther 2024;13:232-40.
21. Liu Y, Yuan Q, Xie L. The AlkB Family of Fe (II)/Alpha-Ketoglutarate-Dependent Dioxyg enases Modulates Embryogenesis through Epigenetic Regulation.Curr Stem Cell Res Ther 2018;13(2):136-43.
22. Rizwan S, Ghazanvi S, Rasheed N, Ullah MI. Association of FTO common RS9939609 polymorphism with obesity and polycystic ovarian syndrome in Pakistani Women. J Med Res Biol Stud 2018;1:101.
23. AR Androgen Receptor [*Homo Sapiens* (Human)]; 2018. Available from: https://www.ncbi.nlm.nih.gov/gene/367
24. Urbanek M. The genetics of the polycystic ovary syndrome. Endocrinol Metab 2014;3:103-11.
25. Bérubé D, Séralini GE, Gagné R, Hammond GL. Localization of the human sex hormone-binding globulin gene (*SHBG*) to the short arm of chromosome 17(17p12---p13). Cytogenet Genome Res 1990;54:65-7.
26. Nestler JE, Powers LP, Matt DW, Steingold KA, Plymate SR, Rittmaster RS, *et al*. A direct effect of

hyperinsulinemia on serum sex hormone-binding globulin levels in obese women with the polycystic ovary syndrome. J Clin Endocrinol Metab 1991;72:83-9.
27. Chen C, Smothers J, Lange A, Nestler JE, Strauss Iii JF, Wickham Iii EP. Sex hormone-binding globulin genetic variation: Associations with type 2 diabetes mellitus and polycystic ovary syndrome. Minerva Endocrinol 2010;35:271-80.
28. FSHR Follicle Stimulating Hormone Receptor [*Homo Sapiens* (Human)]; 2018. Available from: https://www.ncbi.nlm.nih.gov/gene/2492
29. Baban AS, Korsheed SH, Hayawi AY. The FSHR polymorphisms association with polycystic ovary syndrome in women of Erbil, Kurdistan in North of Iraq. Ibn Al-Haitham J Pure Appl Sci 2018:262.
30. Cate RL, Mattaliano RJ, Hession C, Tizard R, Farber NM, Cheung A, *et al*. Isolation of the bovine and human genes for müllerian inhibiting substance and expression of the human gene in animal cells. Cell 1986;45:685-98.
31. Gorsic LK, Kosova G, Werstein B, Sisk R, Legro RS, Hayes MG, *et al*. Pathogenic anti-Müllerian hormone variants in polycystic ovary syndrome. J Clin Endocrinol Metab 2017;102:2862-72.
32. Karthikeyan M, Sabarathinam S, Mohan H, Usha B. An integrated network pharmacological approach unveils the therapeutic mechanism of bonducellin, a homoisoflavonoid from *Caesalpinia bonducella*, against polycystic ovary syndrome. Tradit Med Res 2025;10:65.
33. Furui K, Suganuma N, Tsukahara S, Asada Y, Kikkawa F, Tanaka M, *et al*. Identification of two point mutations in the gene coding luteinizing hormone (LH) beta-subunit, associated with immunologically anomalous LH variants. J Clin Endocrinol Metab 1994;78:107-13.
34. Nilsson C, Matzuk MM, Pettersson K, Millar RP, Coerver KA, Huhtaniemi IT. Worldwide frequency of a common genetic variant of luteinizing hormone: An international collaborative research. International collaborative research group. Fertil Steril 1997;67:998-1004.
35. Roy AC, Liao WX, Chen Y, Arulkumaran S, Ratnam SS. Identification of seven novel mutations in LH beta-subunit gene by SSCP. Mol Cell Biochem 1996;165:151-3.
36. Kritheka CP, Dhanraj G, Murthukumar K, Revathi D. Genetic association of PPARG (peroxisome proliferator activated receptor gamma-rs1801282) polymorphism with OSCC. AIP Conf Proc 2025;3306:040019.
37. CAPN10 Calpain 10 [*Homo sapiens* (Human)]; 2018. Available from: https://www.ncbi.nlm.nih.gov/gene/11132
38. Urbanek M. The genetics of the polycystic ovary syndrome. Nat Clin Pract Endocrinol Metab 2006;3:103-11.
39. Govahi Kakhki F, Sargazi S, Montazerifar F, Majidpour M, Karajibani A, Karajibani M, *et al*. IGF2BP2 and IGFBP3 genotypes, haplotypes, and genetic models studies in polycystic ovary syndrome. J Clin Lab Anal 2024;38:e25021.
40. Khan MJ, Ullah A, Basit S. Genetic basis of polycystic ovary syndrome (PCOS): Current perspectives. Appl Clin Genet 2019;12:249-60.
41. Mukherjee AG, Wanjari UR, Kannampuzha S, Murali R, Namachivayam A, Ganesan R, *et al*. The implication of mechanistic approaches and the role of the microbiome in polycystic ovary syndrome (PCOS): A review. Metabolites 2023;13:129.
42. CYP1A1 Cytochrome P450 Family 1 Subfamily A Member 1 [*Homo sapiens* (Human)]; 2018. Available from: https://www.ncbi.nlm.nih.gov/gene/1543
43. Esinler I, Aktas D, Otegen U, Alikasifoglu M, Yarali H, Tuncbilek E. *CYP1A1* gene polymorphism and polycystic ovary syndrome. Reprod BioMed Online 2008;16:356-60.
44. Arvind Babu K, Rao KL, Kanakavalli MK, Suryanarayana VV, Deenadayal M, Singh L. *CYP1A1, GSTM1 and GSTT1* genetic polymorphism is associated with susceptibility to polycystic ovaries in South Indian women. Reprod BioMed Online 2004;9:194-200.
45. CYP11A1 Cytochrome P450 Family 11 Subfamily A Member 1 [*Homo sapiens* (Human)]; 2018. Available from: https://www.ncbi.nlm.nih.gov/gene/1583.
46. Reddy KR, Deepika ML, Supriya K, Latha KP, Rao SS, Rani VU, *et al*. *CYP11A1* microsatellite (tttta) n polymorphism in PCOS women from South India. J Assist Reprod Genet 2014;31:857-63.
47. Saravanan M, Ameya KP, Sekar D, Ashikha Shirin Usman PP. Identification & expression of microRNA-34a-3p and its target Rapamycin-insensitive companion of mTOR (RICTOR) in polycystic ovarian syndrome in South Indian population. Acta Marisiensis Seria Med 2024;70:163-8.
48. CYP19A1 Cytochrome P450 Family 19 Subfamily a Member 1 [*Homo sapiens* (Human)]; 2018. Available from: https://www.ncbi.nlm.nih.gov/gene/1588
49. Tsuchiya N, Wang L, Suzuki H, Segawa T, Fukuda H, Narita S, *et al*. Impact of *IGF-I* and *CYP19* gene polymorphisms on the survival of patients with metastatic prostate cancer. J Clin Oncol 2006;24:1982-9.
50. Jin JL, Sun J, Ge HJ, Cao YX, Wu XK, Liang FJ, *et al*. Association between *CYP19* gene SNP rs2414096 polymorphism and polycystic ovary syndrome in Chinese women. BMC Med Genet 2009;10:139.
51. National Center for Biotechnology Information. CYP21A2 Cytochrome P450 Family 21 Subfamily a Member 2 [*Homo sapiens* (Human)]. Bethesda: National Center for Biotechnology Information; 2018.
52. Settas N, Dracopoulou-Vabouli M, Dastamani A, Katsikis I, Chrousos G, Panidis D, *et al*. CYP21A2 mutations in women with polycystic ovary syndrome (PCOS). Horm Metab Res 2013;45:383-6.
53. CYP17A1 Cytochrome P450 Family 17 Subfamily a Member 1 *[Homo sapiens* (Human)]; 2018. Available

from: https://www.ncbi.nlm.nih.gov/gene/1586
54. Echiburu B, Pérez-Bravo F, Maliqueo M, Sánchez F, Crisosto N, Sir-Petermann T. Polymorphism T → C (34 base pairs) of gene *CYP17* promoter in women with polycystic ovary syndrome is associated with increased body weight and insulin resistance: A preliminary study. Metabolism 2008;57:1765-71.
55. Li L, Gu ZP, Bo QM, Wang D, Yang XS, Cai GH. Association of CYP17A1 gene-34T/C polymorphism with polycystic ovary syndrome in Han Chinese population. Gynecol Endocrinol 2015;31:40-3.
56. Renukadevi J, Sneha P, Mridula DS, Nimithasree K, Sanjay V. Bioengineered isoflavone-probiotic functional foods for sustainable modulation of metabolic and reproductive health in PCOS. Food Bioeng 2026;5:45-72.

Source of Support: Nil. **Conflicts of Interest:** None declared.