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The Genetic Aspects of Polycystic Ovary Syndrome: A General Review

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ABSTRACT

Polycystic ovarian syndrome is a complicated endocrine disorder with major reproductive, metabolic, and psychological complications that affects reproductive-aged women generally. Polycystic ovarian syndrome is caused by a combination of genetic, epigenetic, and environmental factors. This review explores the genetic factors associated with PCOS, summarizing results from candidate gene analyses and genome-wide association studies. Important genetic variations in genes involved in ovarian function, gonadotropin regulation, insulin resistance, and androgen production have been consistently implicated. The interaction between multiple genetic variations suggests a polygenic inheritance pattern, which contributes to the variety of clinical symptoms. Understanding these genetic alterations is critical to identifying the molecular basis of this syndrome and may pave the way for precision medicine strategies that target specific genetic profiles in the future.

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1. INTRODUCTION

Polycystic ovary syndrome, or PCOS, is a prevalent endocrine condition which primarily affects women who are of reproductive age. It is distinguished by life-threatening co-morbidities, endocrine imbalances, and metabolic abnormalities. The global incidence of PCOS is assessed to be 5-10% [1]-[3]. PCOS symptoms include infertility, hirsutism, obesity, acne, insulin resistance, hyperandrogenism, oligomenorrhea or amenorrhea, and polycystic ovaries identified by ultrasonography [4,5]. According to some estimates, 40% of female infertility is caused by PCOS and it is a major contributor to endometrial cancer [6]. A number of metabolic conditions, including, glucose intolerance, dyslipidemia, hepatic steatosis, diabetes mellitus type II (T2DM), and hypertension, are closely linked to PCOS in addition to reproductive problems [7]. Generally, females with PCOS are more likely to experience significant complications; one out of every five to six women suffers from serious difficulties related to infertility and irregular menstrual periods. The most common causes of PCOS are stress, obesity, and hormonal imbalance [8].

It is well-established that a variety of hormonal changes can contribute to the clinical manifestation of PCOS. Hormonal balance is essential for the proper functioning of the ovaries and the regulation of the menstrual cycle, both of which are crucial for maintaining fertility. When there is a persistent disruption in hormonal levels, it can negatively affect ovarian function. This disruption may lead to the formation of cysts within the ovarian follicles. For example, an abnormal increase in the levels of androgens leads to symptoms like irregular periods, acne, and excessive hair growth in females with PCOS [9]. While the exact reason for PCOS is unidentified, a mixture of genetic and environmental causes is believed to have a crucial role. PCOS pathophysiology primarily involves hormone fluctuations, chronic low-grade inflammation, resistance to insulin, and hyperandrogenism, which inhibit folliculogenesis and raise the danger of associated complications [10].

The genetic progress of PCOS is dependent on separate genes, gene to gene interactions, and environmental factors that affect genes. To assess the genetic makeup of PCOS, it is crucial to determine the variation in essential genes that alter their expression and sequence and influences protein activity [11].

2. CLINICAL DESCRIPTION OF PCOS

The clinical manifestations of PCOS differ widely amongst females; symptoms may include ovarian dysfunction, menstrual abnormalities, obesity, and there is evidence of androgen excess like acne, hirsutism, alopecia, and polycystic ovaries. PCOS is also a dominant reason for infertility and predisposes females to type 2 diabetes and endometrial cancer [12]. Subcellular abnormalities in theca cells are a result of increased concentrations of androgen in the PCOS patients. In theca cells of PCOS cases, a large amount of androgen is released due to the intrinsic stimulation of theca cell steroidogenesis in spite of the lack of trophic stimuli [13]. Additionally, this intrinsic stimulation influences the granulosa cells, which causes PCOS patients to have higher levels of anti-mullerian hormone in comparison with healthy women [14]-[16]. Numerous studies have demonstrated that PCOS is linked with higher pre-antral and small-antral counts of follicles [17]. In women with this syndrome, a disruption in the programmed cell death mechanism of mature follicles leads to an increase in their number. Insulin signaling pathway defects that happen separately of obesity are also caused by intrinsic abnormalities in PCOS [18]- [19]. Similarly, changes in the insulin gene expression pathway have been related to PCOS [20]. An additional glycol-oxidative stress mechanism had been observed as an underlying pathogenesis in PCOS. Oxidative stress can also cause insulin resistance, resulting in hypergonadism [21]. As the name indicates, PCOS is a multifaceted disease with a syndromic pathogenesis. The condition is complicated and causes a wide range of symptoms.

3. PREVALENCE OF PCOS

Differences in diagnostic criteria, geographical locations, and the inclusion of diverse symptoms within the syndrome all contribute to the reported variety in prevalence rates of PCOS [22,23]. PCOS is among the most common endocrinological disorders that females face during their period of reproduction [24]. Until the late 1990s, the studies regarding the incidence of PCOS were rare. Today, one out of ten women is diagnosed with PCOS through the world [25]. According to WHO estimates, 8–13% of women in their reproductive years have PCOS, and over 50% of the cases are undiagnosed [26].

4. ETIOLOGY OF PCOS

It can be challenging to determine the main causes of this multifactorial disorder because of its complicated, interrelated pathophysiology. Environmental contaminants, nutrition, lifestyle choices, genetic factors and obesity all have the potential to influence the onset, incidence, and modulation of the PCOS phenotype. These factors can contribute to the emergence of insulin resistance, partial folliculogenesis arrest, increased release of androgen from the ovaries, and chronic production of inflammatory substances from leukocytes, all of which contribute to the emergence of metabolic syndrome. There is increasing evidence that environmental contaminants play an essential role in the development of PCOS [27,28]. Sedentary lifestyles and high calorie diets may be risk factors for PCOS. A high-sugar diet may increase insulin resistance, change gut flora, cause chronic inflammation, and increase androgen production, all of which can lead to the development of this syndrome. Weight gain and obesity worsen the defining symptoms of PCOS syndrome [29]-[30]. Several epigenetic alterations, including the methylation of certain genes and/or the existence of miRNAs, appear to affect the PCOS phenotype [31]. It is most likely that multiple genes provide little contribution to the etiology of PCOS, and new genome-wide association studies have identified potential genes [32]-[33]. Several genes, including those linked with ovarian and adrenal steroidogenesis, gonadotropin and insulin activity, and inflammatory response, have been proposed as being implicated in the etiology of this condition. Nonetheless, strong evidence establishing the prevalence of a single gene in PCOS is still absent [34]. Several genetic investigations have found more than 100 susceptibility genes associated with PCOS. Linkage and association studies are used to investigate the relationship between specific genes and disease risk variations within a population or families [35]. Various genetic studies have found that different possible genes with SNPs or alterations are linked to a range of PCOS signs by impacting ovarian function, either directly or through indirect mechanisms [36].

5. GENES INVOLVED IN PCOS

Understanding the genetic basis of PCOS is critical not only for determining its complicated pathophysiology but also for developing targeted diagnostic methods and personalized therapeutic strategies. This review focuses on the main genes involved in PCOS and explains their roles in the molecular pathways underlying the syndrome. Important genes associated with PCOS include:

5.1 Genes involved in ovarian and adrenal steroidogenesis

5.1.1. *CYP11A1* gene

The *CYP11A1* gene is a member of the cytochrome P450 superfamily of enzymes, situated on chromosome 15q24. 1. The expression of these monooxygenases occurs within the inner mitochondrial membrane subsequently plays a crucial role in steroid biosynthesis. One of their main functions is the conversion of cholesterol to pregnenolone, which represents the initial and regulating step in the synthesis of steroid hormones [37].

It has been determined that alterations in *CYP11A1* play an important role in the etiology of PCOS. In a demographic survey conducted in South India, nearly 15 allele variants in *CYP11A1* were discovered, with the most common having 8 repetitions, mostly ranging from 2 to16 repeats. This study also examined the incidence of > 8 repeat alleles in women with PCOS, which suggests a threefold higher risk of PCOS susceptibility in comparison to healthy group [38]. According to a case-control study carried out in China, *CYP11A1* alteration is believed to be the main reason of PCOS. SNP (rs4077582) in *CYP11A1* gene is closely associated with PCOS and elevates androgen level by modulating luteinizing hormones in various genotypes [39].

5.1.2. CYP21A2

The *CYP21A2* gene encodes the enzyme 21-hydroxylase, which is essential for the synthesis of steroids. A polymorphism in the *CYP21A2* gene results in insufficient anabolism of steroidogenesis, which is associated with PCOS [40]. Robeva *et al*. (2024) found that intron 2 variations of *CYP21A2* were linked with raised DHEAS levels and earlier menarche, proposing a modulatory influence on the production of androgen and metabolic features in PCOS patients [41]. On the other hand, Settas *et al*. (2013) reported no significant difference in the rate of heterozygous *CYP21A2* variations between PCOS cases and the healthy group, demonstrating that these variations are unlikely to have an important causative role in PCOS [42].

5.1.3. *CYP19*

The *CYP19* gene is located on chromosome 15 (15q21.1). It consists of 10 exons that cover a 123 kb region and encodes a major steroidogenic enzyme that is called aromatase (P450arom), which belongs to the cytochrome P450 family [43]-[44]. This enzyme triggers the last stage of estrogen synthesis, converting testosterone and androstenedione into estradiol and estrone, respectively [45]. Thus, it might be a significant factor in the emergence of hyperandrogenism. According to reports, females affected by PCOS show diminished levels of aromatase in their granulosa cells derived from medium-sized follicles [46]. Likewise, Jakimiuk *et al*. (1998) demonstrated that all PCOS follicles had decreased amounts of P450arom mRNA, estradiol, and lower aromatase stimulation activity in comparison to the control follicles [47].

5.1.4. *DENNDIA* gene

This gene encodes the protein DENND1A, which is involved in endocytosis processes and receptor turnover, and has been reported as related to PCOS in several genome-wide association studies. Numerous investigations have further confirmed these findings, with specific SNPs found to be correlated with increased PCOS susceptibility, indicating it as one of the most recognized genes associated with PCOS. Variations of DENND1A have also been connected with hyperandrogenism and ovarian dysfunction [48]-[51]. Ovarian thecal cells from PCOS-affected women release more androgen compared to those from non-affected women, according to laboratory studies, possibly associated with increased of enzymatic activity within steroidogenic pathways [52]. A DENND1A isoform, known as DENND1A.V2, has been involved in the enhanced expression of genes *CYP11A1* and *CYP17A1*, which both have crucial role in the synthesis of important enzymes essential in androgen steroidogenesis [53].

5.2. Genes involved in insulin secretion and action

5.2.1. Insulin (INS)

PCOS has been shown to induce defects in glucose tolerance because of irregular insulin production and function. Females with PCOS have pancreatic beta-cell malfunction and/or reduced insulin clearance by the liver [54]. Many PCOS patients have insulin resistance, which causes compensatory hyperinsulinemia. This hyperinsulinemia leads to hyperandrogenism by enhancing ovarian androgen production and inhibiting hepatic SHBG synthesis, thus raising the availability of testosterone. Additionally, insulin enhances ACTH-mediated adrenal androgen synthesis and increases ovarian steroidogenesis in response to LH stimulation [55]-[56].

5.2.2. Insulin receptor gene (INSR)

The observation of reduced insulin sensitivity in *vivo* and in *vitro* naturally led to the idea that genetic defects of the insulin receptor and/or post-receptor signaling were implicated in the development of family-linked PCOS [57]. Researchers have consistently examined the potential contribution of INSR alterations to insulin resistance observed in PCOS patients [58]. The insulin receptor gene encodes the insulin receptor, which has an essential role in the insulin signaling cascade, and variations within this gene are possible to have an effect on PCOS metabolic conditions like obesity and insulin resistance [59]. Siegel et al. (2002) investigated a variant in the tyrosine kinase domain of the INSR gene and discovered a relationship in lean women with PCOS. This variant may represent a risk-associated variation for PCOS or an outcome of linkage disequilibrium with different INSR variations [60].

5.2.3. CAPN10

Calpain is a cysteine protease involved in pro-insulin processing, as well as insulin production and function [61]. PCOS patients are at risk of impaired glucose tolerance; hence, all genes related to type 2 diabetes mellitus may play an essential part in the etiology of PCOS [62].

5.3 Genes affect steroid hormones

5.3.1. Sex Hormone-Binding Globulin (SHBG)

The liver generates a sex hormone transporter called sex hormone-binding globulin (SHBG) that possesses strong binding capacity for circulating sex steroids and regulates their level in the blood, hence influencing their bioavailability. It's been demonstrated that a number of variations in the SHBG gene on chromosome 17 affect hepatic synthesis, plasma concentrations, and clearance efficiency of SHBG, thus modulating the systemic distribution and bioavailability of sex steroid hormones [63]. The relationship between SHBG gene variations and serum SHBG concentrations is of growing focus for ongoing studies however, SHBG variations are regarded as an essential indicator of hyperandrogenemia in PCOS patients [64].

5.3.2. Androgen receptor gene (AR)

PCOS is characterized by hyperandrogenism, thus, it is believed that variations in androgen activation genes contribute to the development of PCOS [65]. One of the most studied candidate genes is the androgen receptor (AR) gene, mainly a polymorphic CAG trinucleotide repeat located in exon 1, which encodes a polyglutamine (poly-Gln) tract within the N-terminal transactivation domain of the androgen receptor. The length of this CAG repeat, usually ranging from 8 to 35 repeats, is stably inherited and has been involved in modulating AR function [66]-[67]. The number of CAG repeats along the androgen receptor (AR) may be altered by pathogenic SNPs, affecting the gene's function and androgen hormone affinity. AR activity and CAG repeat number were discovered to be inversely correlated in earlier research, shorter CAG repeats raise AR activity and are linked with ovarian hyper-androgenism and hirsutism, whereas longer CAG repeats decrease AR activity, producing hypo-androgenicity and infertility in men [68]-[69].

5.4. The genes associated with gonadotrophin action

5.4.1. Follicle-Stimulating Hormone Receptor (FSHR)

PCOS is characterized by abnormal levels of gonadotropins like follicle stimulating hormone (FSH), luteinizing hormone (LH), and prolactin. Females with hyperandrogenic PCOS have elevated LH pulse frequency and decreased FSH levels due to consistently high-frequency GnRH activation [70]. Lower levels of FSH lead to arresting follicular growth, which results in ovulation problems in PCOS. These variations in FSH and LH secretion in women with PCOS might depend on genetic polymorphism of gonadotropic-related genes, like LH/choriogonadotropin receptor (LHCGR) and FSH receptor (FSHR), and have been confirmed by several research studies [71]. The FSHR gene is found on chromosome 2 at positions p21-p16 and contains ten exons and nine introns. In females, the FSHR gene is expressed in granulosa cells and regulates graffian follicle development, granulosa cell proliferation, and estrogen production [72]. The binding of FSH to its receptor triggers several intracellular signaling pathways [73]-[74]. Alterations in the FSHR gene, particularly in exon 10, can cause follicle development to stop at various stages of growth and have a variety of phenotypic implications, including variability in secondary sexual differentiation, primary amenorrhea, and hypoplastic ovary [75]-[76].

5.4.2. Luteinizing hormone/chorionic gonadotropin receptor (LHCGR)

LHCGR plays an essential role in coordinating the physiological processes required for appropriate sexual development and fertility maintenance [77]. LHCGR is a high-affinity receptor for LH that, when bound, promotes follicular growth, steroidogenesis, and corpus luteum formation [78].

The *LHCGR* gene is located on chromosome 2 (2p21) containing 11 exons that code for a 675 amino acid transmembrane glycoprotein [79]. Numerous *LHCGR* polymorphisms have been identified in PCOS patients; these polymorphisms may change the expression of the gene or the function of proteins, affecting their biological activity, causing typical PCOS symptoms in women of reproductive age [80]-[81].

5.4.3. Anti-Müllerian hormone (AMH)

Polycystic ovaries contain numerous pre-antral and antral follicles, which are the main source of anti-mullerian hormone (AMH). AMH is a part of the transforming growth factors- beta family. The *AMH* gene is situated on the short arm of chromosome 19, specifically at locus 19p13.3 [82]-[83]. According to published research, the *AMH* gene and its type 2 receptor (AMHR2) play a major role in the etiology of PCOS. Women with PCOS have more follicles, and elevated expression of AMH and AMHR2 per follicle. Conversely, normal ovulatory women did not express the *AMH* gene after follicle maturation. AMH contributes to anovulation by inhibiting follicular growth and recruitment. Additionally, it probably enhances insulin resistance and hyperandrogenism in PCOS [84]–[88].

5.5. Other genes

5.5.1. Fat Mass and Obesity-Associated Gene (FTO)

The fat mass and obesity-associated gene **(***FTO*), which is located on chromosome 16q12.2, is expressed in almost all tissues in humans [89, 90]. The *FTO* gene encodes a 2-oxoglutarate-dependent nucleic acid demethylase protein that is important in energy metabolism [91]. A genome wide association study conducted in 2007 discovered that FTO has an association with body mass index (BMI) and obesity [89]. Obesity is frequently observed among patients with PCOS, with over 50 percent of PCOS cases are overweight or obese [92]. Studies in China, Finland, the UK, and South Brazil revealed a significant association between the FTO gene and PCOS [93–96]. Others researches showed that *FTO* and BMI were related in PCOS patients; despite they don't seem to play an important role in the reproductive characteristics of PCOS [97]– [99]. Cai *et al.* (2014) discovered that the *FTO* (rs9939609) SNP was associated with a higher risk of PCOS in East Asians, unlike the Caucasian population [100]. The *FTO* rs9939609 showed considerably higher in PCOS females than in healthy, and it appeared to be mainly linked with obesity and T2DM [101].

5.5.2. *SRD5A1*and *SRD5A2*

The metabolism of androgens depends on an important enzyme termed 5α-reductase, it triggers the irreversible enzymatic conversion of testosterone into 5α-DHT in the skin and cortisol into dihydrocortisol in the liver [102]. Types 1 and 2 of the 5α-reductase isoenzymes are both associated with PCOS hyperandrogenism. Type 1 isoenzyme expression in the skin and liver and type 2 isoenzyme expression in fertility-related tissues. 5α-reductase type 1 is encoded by the *SRD5A1* gene, and type 2 is encoded by the *SRD5A2* gene. It has been established that variations in *SRD5A1* and *SRD5A2* genes are linked to the occurrence of PCOS in women with low body weight [103]. Additionally, girls with early hormonal risk factors for PCOS have elevated 5α-reductase activity [104]. Thus, alterations in 5α-reductase activity may contribute to the pathophysiology of PCOS, causing aberrant levels of androgen that represent a crucial component of the disorder [103].

5.5.3. Vitamin D receptor (VDR)

The *VDR* gene is placed on chromosome 12q13.11, spans more than 75 kb of genomic DNA and contains 11 exons [105]. This gene exhibits a high degree of polymorphism, and the rate of its polymorphic markers varies between ethnic groups [106]. Polymorphisms in the vitamin D receptor gene are expected to contribute to the development of PCOS via the insulin signaling pathway. These variations may also have an impact on PCOS symptoms through the parathyroid hormone (PTH)-vitamin D axis. Moreover, VDR is implicated in estrogen metabolism, affecting ovarian function [107]-[109].

6. CONCLUSION

PCOS is a condition with diverse genetic and phenotypic characteristics. Recent developments in genetic studies have identified many important loci, mostly in metabolic and hormonal pathways, that contribute to its pathogenesis. Nevertheless, transferring these results into clinical practice needs more validation, functional research, and comprehensive approaches that consider interactions between genes and environmental conditions. Determining the genetic basis of PCOS is important not only for establishing its complex pathophysiology but also for creating specialized diagnostic approaches and personalized therapeutic strategies.

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Conflict of Interest
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Ethical Clearance
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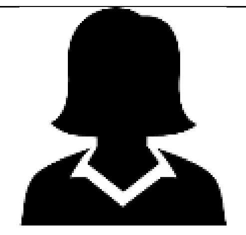

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