

REVIEW

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# Hyperandrogenism in polycystic ovarian syndrome and role of *CYP* gene variants: a review

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## Abstract

**Background:** Polycystic ovary syndrome (PCOS) is a multifactorial endocrine disorder characterized by anovulation, hyperandrogenism, and polycystic ovarian morphology. The pathophysiology of PCOS is not clear; however, disturbance in hypothalamic-pituitary-ovarian axis and abnormal steroidogenesis along with genetic and environmental factors act as main contributors to this disorder.

**Main text:** Hyperandrogenism, the hallmark feature of PCOS, is clinically manifested as hirsutism, acne, and alopecia. Excessive androgen production by ovaries as well as from adrenals contributes to hyperandrogenism. Abnormalities in the neuroendocrine system like increased pulse frequency of gonadotropin-releasing hormone, stimulating the pituitary for excessive production of luteinizing hormone than that of follicle-stimulating hormone is seen in PCOS women. Excess LH stimulates ovarian androgen production, whereas a relative deficit in FSH impairs follicular development. The imbalance in LH: FSH causes proliferation of ovarian theca cells leading to increased steroidogenesis, and ultimately leading to hyperandrogenism in PCOS women. Various genetic factors have been shown to be associated with abnormal steroidogenesis. *CYP* genes involved in steroidogenesis play an important role in androgen production and are considered as key players in hyperandrogenism in PCOS.

**Conclusion:** Polymorphisms in *CYP* genes can aggravate the hyperandrogenic phenotype in women with PCOS by either upregulating or downregulating their expression, thus increasing androgens further. However, this hypothesis needs to be validated by further studies.

**Keywords:** PCOS, Steroids, Hirsutism, Androgens, Hyperandrogenism

## Background

Polycystic ovary syndrome (PCOS) is a multifactorial disorder affecting nearly 6–20% of women in their reproductive age [1, 2]. This disorder is characterized by hyperandrogenism, ovulatory dysfunction, and enlarged ovaries with multiple follicles. Moreover, women with PCOS have a high risk of developing insulin resistance, type 2 diabetes mellitus (T2DM), infertility, psychological disorders, cardiovascular diseases, and various gynecological cancers like endometrial and ovarian cancer at an advanced stage of this disorder [3, 4]. The basic etiology of PCOS is still unclear and the molecular basis of its progression is still a puzzle. The androgen excess is regarded as the major driving force

in the development of signs and symptoms of this disorder. Excessive androgen production by ovaries as well as from adrenals contributes to hyperandrogenism. Clinically, hyperandrogenism in women presents as hirsutism, acne, androgenic alopecia, and/or increased amounts of testosterone. Genetic and clinical heterogeneity associated with hyperandrogenic condition indicates the possible involvement of abnormalities in the steroid synthesis pathway [5]. Recent studies indicate that hyperandrogenic phenotype in PCOS is familial, suggesting maternal inheritance and hence the involvement of genetic factors particularly genes governing steroid hormone biosynthesis [6]. Furthermore, the altered expression of genes involved in the synthesis of androgens in PCOS mothers is known to alter the extent of androgen exposure in utero [7]. It has been hypothesized that exposure of the fetus to androgen excess in utero results in hypersecretion of luteinizing hormone, alteration in

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the differentiation process of theca cells, and male-type fat distribution in female offspring [8]. In addition, maternal nutrition and epigenetic changes have also been found to influence fetal programming [7, 9]. Contrary to this, other studies have shown that normal aromatization in the placenta, if maintained, does not induce PCOS in the female fetus when subjected to increased levels of androgens from mother [9]. Legro et al. [10] suggested a genetic basis of hyperandrogenism in PCOS. Genes involved in steroid synthesis especially cytochrome P450 are considered as candidate genes in the pathophysiology of PCOS. These candidate genes have been studied in detail in order to delineate their association with PCOS.

The present review will try to highlight the pathophysiological mechanisms by which hyperandrogenism may influence the development of PCOS. In addition, we will summarize the effect of dysregulated expression of *CYP* genes involved in steroidogenesis on hyperandrogenism in PCOS women and its clinical implications.

### PCOS and hyperandrogenism

Hyperandrogenism is the defining feature of women with PCOS. It is caused by the disruption of normal ovarian or adrenal function resulting in the production of excess androgens. The first impact of androgen excess in PCOS is impaired folliculogenesis. Increased androgens in the early gonadotropin-independent stage stimulate the formation of primordial follicles and increase the number of small antral follicles [11]. Normally, the gonadotropin-releasing hormone is secreted in a pulsatile manner by the hypothalamus that stimulates the pituitary gland to release gonadotrophins, i.e., LH and FSH. Luteinizing hormone acts primarily on the ovarian theca cells carrying LH receptors and induces the production of androgens. Concomitantly, FSH acts on the ovarian granulosa cells and converts the androgens formed in theca cells into estrogens, principally estradiol, which is responsible for the development of follicles. However, in women with PCOS, it has been hypothesized that dysregulation in the neuroendocrine system leads to an imbalance in the hypothalamic–pituitary–ovarian axis, leading to the overproduction of gonadotrophins. An increased hypothalamic GnRH favors the production of the  $\beta$ -subunit of LH over the  $\beta$ -subunit of FSH that in turn favors the production of LH over FSH [12, 13], hence resulting in the classical hormonal hallmark of elevated LH/FSH ratio in PCOS. Owing to the increased LH stimulation, numerous follicles in the theca cells of ovaries get arrested mostly in the preantral and antral stages, causing hyperplasia of theca cells and subsequent accumulation of follicular fluid forming cyst-like structures along the periphery of the ovary giving it a string of pearls-like appearance [14]. Increased number of follicles and increased expression of key enzymes involved in the androgen synthesis thus produce an excessive amount of

androgens, as shown in Fig. 1. Furthermore, the hyperandrogenic state in PCOS also seems to be linked with the action of insulin. The increased insulin secretion possibly mimics the tropic action of luteinizing hormone on ovarian theca cells [15], which further causes an increase in androgens. This is further validated by the fact that the improvement of insulin resistance in PCOS women decreases the level of hyperandrogenism [16].

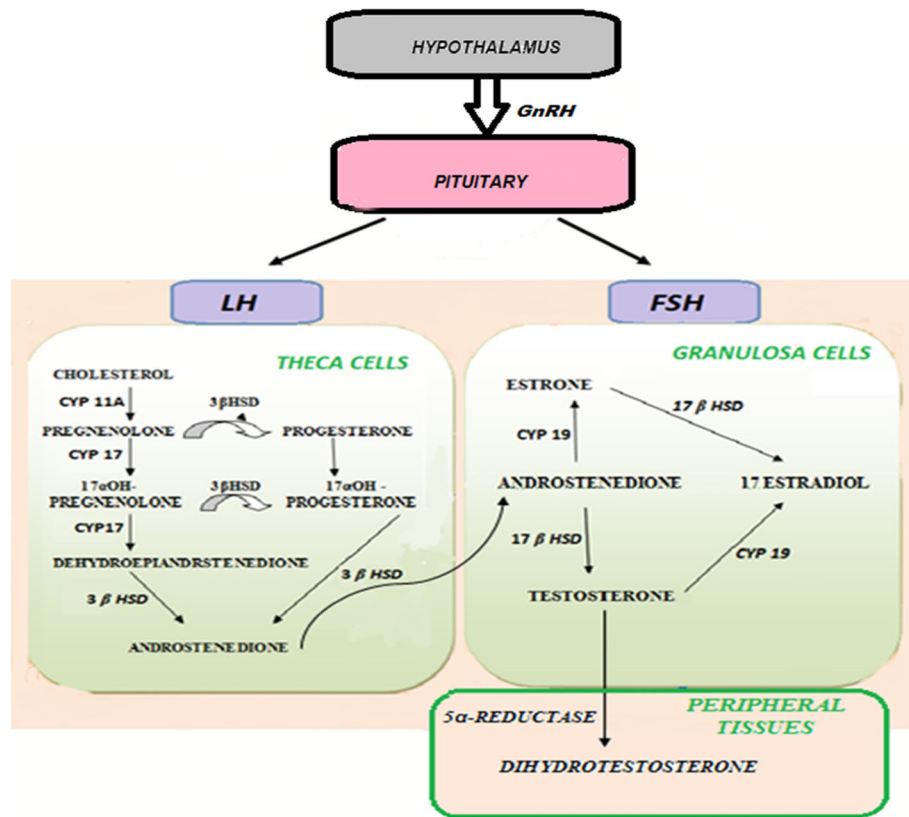
Biochemically, hyperandrogenism is defined as the high concentration of testosterone and other calculated parameters of androgen excess like free testosterone (FT) and free androgen index (FAI). Testosterone is present either in free form or bound with proteins like SHBG and albumin. Normally, 80% of testosterone is bound to sex hormone-binding globulin, 19% of it is bound to albumin, and only 1% circulates as a free testosterone [17, 18]. Furthermore, the measurement of testosterone, as well as SHBG concentration, helps in calculating free androgen index which is more useful than measuring T alone [19, 20]. According to the Rotterdam consensus, in order to detect hyperandrogenism in women with PCOS, circulating free testosterone (cFT) or FAI measurements should be employed instead of serum total T [21]. Therefore, the increased concentration of total T or FT levels is a key diagnostic feature of biochemical hyperandrogenism. Other androgens like dehydroepiandrosterone and androstenedione may also be helpful in diagnosing biochemical hyperandrogenism. Androstenedione, DHEA, and dehydroepiandrosterone sulfate are all bound to albumin with low affinity [22]. DHEAS is found abundantly in circulation, and due to the presence of its sulfate group, it is easily detected by commercial assays. Elevated levels of DHEA are seen in approximately 25% of PCOS patients [23]. High androstenedione levels are found in 18% of PCOS women [24].

### Clinical features of hyperandrogenism

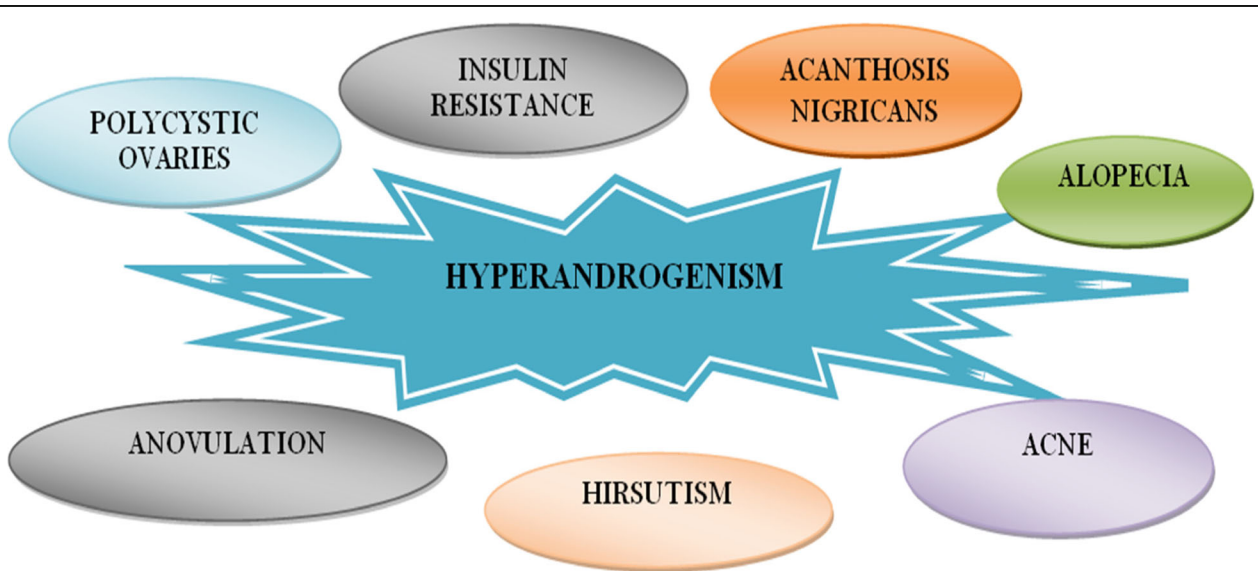
Hyperandrogenism in women with PCOS clinically presents as hirsutism, acne, and androgenic alopecia. Other manifestations like weight gain, menstrual irregularities, acanthosis nigricans, and insulin resistance are also manifested by increased androgen excess, depicted in Fig. 2.

#### Hirsutism

Hirsutism is defined as the occurrence of terminal hair in a masculine pattern on the face and/or body. It is one of the main characteristics of hyperandrogenism in PCOS. The incidence of hirsutism in PCOS women ranges between 60 and 80% [25–28]. The extent of hirsutism also varies with the ethnicity of the population. The amount and distribution of hair growth is determined by the androgens, particularly testosterone. Hirsutism in PCOS women is attributed to increased circulatory levels of free testosterone and more active form of testosterone, i.e., dihydrotestosterone, formed by



**Fig. 1** Hypothalamic-pituitary-ovarian axis and steroidogenesis



**Fig. 2** Clinical implications of hyperandrogenism in PCOS

the activity of 5 $\alpha$  reductase on testosterone in the pilosebaceous gland. Hirsutism is the most consistent and reliable symptom used for evaluating clinical hyperandrogenism. Ferriman and Gallwey [29] described a visual scoring method to clinically assess the degree of hirsutism known as the Ferriman-Gallwey (FG) score. According to the FG score, hair is scored in nine parts of the body, which include the upper lip, chin, chest, upper and lower back, upper and lower abdomen, and upper and lower limbs. A score of 0–4 is given on these nine body parts to determine the extent of hirsutism, with a score of 0 representing a complete absence of terminal hair and a score of 4 represents extensive hair growth. The score of all nine areas is added up to get the final score used for diagnosis. Women with an FG score of 8 or higher are regarded as hirsute [30].

### Acne vulgaris

Acne is the second most common sign of hyperandrogenism. The prevalence of acne varies according to ethnicity; the highest reported incidence regards Indo-Asian women and lowest in Pacific Islanders. The prevalence of acne in PCOS women of Kashmir is 48% [28]. The prevalence of acne was reported to be 17.7% in Allahabad [31]. Some other studies have estimated the prevalence of acne in patients with PCOS at 9.8–34% [32, 33]. Acne results from the inflammation of pilosebaceous glands. Increased testosterone favors the production of more potent form dihydrotestosterone that increases sebum production in the sebaceous glands and causes abnormal desquamation in the follicular epithelial cells. This accumulation of sebum and epithelial cell debris gets colonized by the bacterium *Propionibacterium acnes* that results in acne. According to WHO criteria, acne is graded into mild, moderate, and severe forms. Mild acne includes comedones and papules, moderate ones include pustules, and severe consists of nodules, cysts, and scars [34]. Acne is frequently observed on the face, upper back, neck, and in pectoral regions, and its severity varies from one individual to another.

### Alopecia

Androgenic alopecia or male pattern baldness is another symptom of hyperandrogenic condition occurring in PCOS women. The incidence of alopecia in PCOS appears to be common, varying widely between 3.2–34.8% in various populations [24, 35, 36]. It is characterized by miniaturization, wherein the mature terminal hair on the scalp region shortens the anagen (growth) phase and gradually get transformed into fewer, finer vellus hair [37]. On one hand where the female with PCOS has trouble dealing with excess facial hair growth, conversely, they deal with the problem of thinning scalp hair. This is because PCOS women have high levels of

testosterone which is responsible for the hair loss as it does in males. However, the hair follicle remains alive in the PCOS women with androgenic alopecia which increases the chance that the hair lost will grow again by hair therapy in these females. The anterior hairline in PCOS women usually remains intact, and hair loss is seen in the anterior mid-vertex area with postero-lateral extension to the crown as a “triangular” patch. The loss of hair in the scalp region has a significant psychological impact in hyperandrogenic women. To wrap up, premenopausal women with alopecia should be investigated for endocrine evidence of androgen excess.

### Steroid metabolism

Since PCOS is characterized by abnormalities in steroid synthesis, resulting in a hyperandrogenic state, it is important to define the steroid metabolism in the normal state. Steroids are low molecular weight, lipophilic compounds, derivatives of cholesterol that are known to regulate a number of cellular physiological processes including metabolism, development, and various signaling pathways. The steroidogenic pathway in humans consists of several proteins and enzymes that produce biologically active steroid hormones from cholesterol. Cholesterol is first translocated from the outer to the inner mitochondrial membrane by steroidogenic acute regulatory protein (StAR) [38]. Cholesterol is converted to pregnenolone by a rate-limiting step catalyzed by cytochrome P450 side-chain cleavage encoded by the *CYP11A* gene [39]. In the next step, pregnenolone can be hydroxylated by cytochrome P450 17 $\alpha$ -hydroxylase to produce 17 $\alpha$ -hydroxypregnenolone. P450c17 besides having hydroxylation activity also possesses lyase activity by which 17 $\alpha$ -hydroxypregnenolone is converted to dehydroepiandrosterone. P450c17 is expressed in ovarian theca cells [40] and its regulation serves as a branch-point in the steroid synthesis pathway that determines whether androgens or progestins are produced. Further, pregnenolone can also be converted by type II 3 $\beta$ -hydroxysteroid- $\Delta^5$ -steroid dehydrogenase to progesterone. Progesterone can be hydroxylated by P450c17 to form 17 $\alpha$ -hydroxyprogesterone that is further converted to androstenedione by C17, the 20-lyase activity of P450c17. Alternatively, DHEA is acted upon by 3 $\beta$ -HSDII converting it to androstenedione which is consequently converted to testosterone by the action of 17 $\beta$ -hydroxysteroid dehydrogenase. Testosterone and androstenedione formed in theca cells of ovaries are taken up by granulosa cells where the P450arom enzyme, under the control of FSH, converts them into estrogen [41]. Testosterone is converted to a more potent form known as 5 $\alpha$ -dihydrotestosterone by the action of 5 $\alpha$ -reductase in the peripheral tissue. This potent androgen is responsible for various symptoms of hyperandrogenism present in PCOS women.

### CYP genes in PCOS

Heterogeneity in clinical features, as well as genetic variations observed in PCOS, is associated with hyperandrogenic condition indicating the possible involvement of abnormalities associated with the steroidogenic pathway [5]. Genes that code for enzymes involved in the steroidogenic pathway are considered as candidates for PCOS. Among those, the most extensively studied genes are the *CYP11A* gene (cytochrome P450 side-chain cleavage enzyme gene), *CYP17* gene (cytochrome P450 17 $\alpha$ -hydroxylase/17, 20-desmolase gene), and *CYP19* gene (aromatase). Studies have shown that ovarian theca cells of PCOS women overexpress enzymes involved in androgen biosynthesis [42] resulting in an increased production of 17-hydroxyprogesterone, testosterone, and androstenedione compared with theca cells from non-hyperandrogenic women [43]. Moreover, there is decreased activity of aromatase enzyme, further increasing the androgens. Therefore, abnormalities in androgen production lead to hyperandrogenism in PCOS.

#### CYP11 gene

The first step in the steroid hormone biosynthesis is catalyzed by cytochrome side-chain cleavage enzyme. The enzyme is encoded by the *CYP11* gene located at 15q24. *CYP11* catalyzes the rate-limiting step of the conversion of cholesterol into progesterone [44]. Studies have reported that the deletion of the *CYP11* gene in rabbits eliminates steroid synthesis suggesting that steroidogenesis begins with the action of this enzyme [45]. It has been suggested that polymorphisms present in the *CYP11* gene either up- or downregulates the expression of *CYP11*, resulting in an increased or decreased production of androgen. A number of polymorphic studies have been carried out on the *CYP11* gene in association with PCOS. Many of them have reported the association of a microsatellite polymorphism (TTTTA) in the promoter region of *CYP11A1* with altered gene expression found in PCOS. In a study carried out by Gharani et al. [46], 5'-untranslated region (UTR) consisting of (tttta) $n$  pentanucleotide is associated with PCOS and serum testosterone levels in PCOS women. The absence of the more common four repeats allele in variable number of tandem repeats (VNTR) polymorphism was found to be associated with high serum testosterone levels in hirsute PCOS patients [46]. These results were further supported by two independent case-control studies from Greece [47] and China [48] where the absence of four repeat alleles was found to be associated with PCOS. Deshmund et al. [49] studied women from the USA and found that nine-repeat alleles were more common in PCOS patients and four- and six-repeat alleles were more frequent in controls. The association of *CYP11A1* (tttta) $n$  repeat polymorphism with PCOS was also confirmed in India by Reddy et al. [5]. Pusalkar et al. [50]

also showed the positive association of six repeats of (TTTTA) $n$  polymorphism with increased testosterone levels in PCOS women. However, a similar study was carried out on Han Chinese women where (tttta) $n$  polymorphism did not show any association with hirsutism [51]. Similarly, other studies conducted have also failed to find any significant association of this VNTR and PCOS [52, 53]. One more polymorphism, rs4077582 of the *CYP11* gene, was found to be significantly associated with PCOS [54, 55] and altered testosterone and LH levels [55] in Chinese women. Another polymorphism rs11632698 of *CYP11* gene carried out in China showed both positive [54] as well as negative [55] association with PCOS risk.

#### CYP17 gene

This gene located on chromosome 10q24-q25 codes for the enzyme cytochrome P450 17 $\alpha$ -hydroxylase-17, 20-lyase present in the endoplasmic reticulum. This enzyme plays a key role in the process of biosynthesis of steroid hormones by its hydroxylase as well as lyase activity. It converts pregnenolone and progesterone into 17-hydroxypregnenolone and 17-hydroxyprogesterone, respectively, by its 17 $\alpha$ -hydroxylase and 17, 20-lyase activity and subsequently converts these steroids to dehydroepiandrosterone and 4-androstenedione [6]. Dysregulated P450 *CYP17* enzyme is thought to be one of the causes of ovarian hyperandrogenism found in PCOS [56]. Other studies also suggested that increased expression of P450c17 enzyme resulted in increased production of androgens in PCOS [57, 58]. Later in 2004, Wickenheisser et al. [59] reported increased transactivation of the *CYP17* promoter in theca cells of ovaries derived from PCOS women. A year later, Wickenheisser et al. [60] reported in PCOS theca cells that the dysregulated expression of *CYP17* is at the level of mRNA. From all these studies, it can be concluded that the increased production of androgens in PCOS is the result of overexpression of the *CYP17* enzyme. A large number of polymorphic studies have been carried in various parts of the world to explore the association of the *CYP17* gene with the increased androgens levels in PCOS. Three different single nucleotide polymorphisms in the *CYP17* gene have been identified and described by Carey, Crocitto, and Miyoshi. Crocitto et al. [61] reported the single base-pair change (C  $\rightarrow$  A transition) in the intron 6 of the *CYP17* gene at nucleotide 5471. Miyoshi et al. [62] reported a SNP (G  $\rightarrow$  A) at nucleotide 1951 in the promoter of the *CYP17* gene. Another most widely investigated polymorphism was described by Carey et al. [63] in the 5'-untranslated region (5'-UTR), a single base-pair change (T-C) in the promoter region, 34 base pairs upstream from the translational initiation point. All these studies found an association of this single nucleotide polymorphism with PCOS. Similar results were confirmed by Diamanti-

**Table 1** Significance of polymorphisms of *CYP* genes in PCOS in different ethnic populations. Summarizes the studies on *CYP* genes in PCOS

Gene	Locus/variant	Ethnicity	Sample size	Association	Reference	
CYP11	(tttta) <sub>n</sub>	Greek white	80 PCOS/90 controls	Yes	[47]	
		Chinese	201 PCOS/147 control	Yes	[48]	
		British	51 PCOS/280 controls	Yes	[49]	
		Indian	267 PCOS/275 controls	Yes	[5]	
		Indian	100 PCOS/100 controls	Yes	[50]	
		Chinese	96 PCOS/78 controls	No	[53]	
	rs4077582	Chinese	290 PCOS/344 controls	Yes	[54]	
		Chinese	604 PCOS/658 control	Yes	[55]	
	rs11632698	Chinese	290 PCOS/344 controls	Yes	[54]	
		Chinese	604 PCOS/658 control	No	[55]	
CYP17	– 34 T/C SNP	Caucasian	NA	Yes	[63]	
		Greece	50 PCOS/50 controls	Yes	[64]	
		Korean	134 PCOS/100 controls	Yes	[65]	
		Indian	100 PCOS/100 controls	Yes	[50]	
		White Asian	49 PCOS/47 controls	No	[66]	
		British	259 PCOS/161controls	No	[67]	
		Chilean	159 PCOS/93 controls	No	[68]	
		Caucasian	287 PCOS/187 controls	No	[69]	
		Indian	60 PCOS/54 controls	No	[70]	
		Indian	75 PCOS/73 controls	No	[71]	
CYP19	rs2414096	Spanish	186 PCOS/71 controls	Yes	[80]	
		Egyptian	30 PCOS/30 controls	Yes	[82]	
		Chinese	785 PCOS/ 297	Yes	[91]	
		Indian	249 PCOS/257	Yes	[83]	
		Mexican–mestizo	25 PCOS and 50 controls	No	[87]	
	rs2470152	Indian	103 PCOS	No	[88]	
		Chinese	364 PCOS/297 controls	No	[79]	
		(ttta) <sub>n</sub>	Greek	180 PCOS/160 controls	Yes	[84]
			Greek	132 PCOS/200 controls	Yes	[85]
			Han Chinese	123 PCOS/113controls	Yes	[51]

Kandarakis et al. [64] in Greek patients and Park et al. in Korea [65]. Pusalkar et al. [50] from India also showed a significantly increased frequency of C alleles of the *CYP17* gene in PCOS women. Conversely, in other studies, this polymorphism was not considered as a significant factor for the development of PCOS [66–69]. Studies from India also concluded that the single nucleotide polymorphism at the – 34 region in the promoter site of the *CYP17* is not associated with hyperandrogenemia and central obesity [70] or insulin resistance in PCOS women [71]. This polymorphism (T to C transition) of *CYP17* has also been evaluated in males as a marker of various cancers. The A2 allele of the gene was positively associated with increased risk of

male breast cancer [72, 73] as well as increased risk of prostate cancer [74, 75].

#### **CYP19 gene**

The enzyme P450 aromatase is encoded by the *CYP19* gene located at 15p21. The enzyme complex consists of cytochrome P450 aromatase (P450arom) as well as nicotinamide adenine dinucleotide phosphate (NADPH) and cytochrome P450 reductase. It catalyzes the conversion of the androgens into estrogens. Diminished aromatase activity has been seen in a number of patients with hyperandrogenism. Erickson et al. [76] have demonstrated decreased aromatase expression in granulosa cells obtained from women with PCOS. Similarly,

Jakimiuk et al. [77] studied mRNA expression of aromatase in follicles of PCOS as well as control women and concluded that PCOS follicles have decreased aromatase activity and contained low levels of P450arom mRNA and hence low levels of estradiol. This decrease in aromatase activity is possibly the reason for androgen excess contributing to abnormal follicular development. Hyperandrogenemia in PCOS women is thought to be the result of reduced aromatase activity in granulosa cells of ovaries [78, 79]. Various association studies utilizing SNPs and haplotypes showed association of PCOS with different symptoms and testosterone levels [80, 81]. Chen and colleagues [8] found the estradiol to testosterone ratio (E2/T) was significantly lower in PCOS than non-PCOS controls and intronic variant rs2414096 was significantly associated with increased risk of development of PCOS, hence concluding that reduced aromatase activity is the main cause behind androgen excess in PCOS women. Another study in Egypt concluded that rs2414096 of the *CYP19* gene is associated with reduced aromatase activity in PCOS women with hyperandrogenism [82]. Similarly, another association carried in India by Reddy et al. [83] concluded that the three different gene variants of *CYP19*, i.e., rs700519, rs2414096, and rs60271534, are significantly associated with PCOS. Further, a study carried on different polymorphism, rs2470152 in the *CYP19* gene, suggested that heterozygous TC genotype was associated with increased testosterone levels and decreased E2/T ratio but did not affect PCOS risk, hence concluding that this polymorphism had a role in regulating the activity of aromatase [79]. Another common polymorphism, consisting of tetranucleotide repeats (TTTA) in intron 4 has been studied [8]. Other studies demonstrated the presence of short alleles consisting of seven repeats in Greek [79, 84] and Han Chinese [85] women with PCOS and their absence in the control group. These short repeat alleles were further found to have a positive association with hormonal parameters like increased testosterone levels and elevated LH: FSH ratios [51]. However, other studies investigating the genetic polymorphism of *CYP19* did not reveal any evidence of *CYP19* being involved in the etiology of PCOS [86–88].

The polymorphism (TTTA repeat in intron 4) of aromatase *CYP19* has been studied in males also and has been associated with low bone mass. This polymorphism causes differences in estrogen levels in men, which predisposes them to increased age-related bone loss and fracture risk [89]. The same genotype was also seen to be associated with the risk for gynecomastia in males [90] (Table 1).

## Conclusion

In this review, we summed up the basic facet of PCOS and the role of *CYP* gene variants in clinical

manifestations of hyperandrogenism. The increase in androgen is contributed to the dysregulation of enzymes involved in steroid synthesis pathway and hyperplasia of theca cells of ovaries of the affected women. Increased androgens cause a lack of negative feedback on the hypothalamic-pituitary axis resulting in increased GnRH pulse frequency. Increased LH stimulates theca cells of ovaries to undergo rapid proliferation which further results in increased steroidogenic capacity and hence increased androgen production. Genes like *CYP11*, *CYP17*, and *CYP19* that code for the enzymes involved in steroid metabolism are extensively studied and are regarded as candidate genes involved in PCOS pathophysiology. These genes are overexpressed in the ovarian theca cells resulting in increased production of 17-hydroxyprogesterone, testosterone, and androstenedione and decreased the activity of aromatase, further upregulating the androgen production. Several association studies have been carried between PCOS and different genetic variants of these genes involved in the steroidogenesis. Polymorphisms in *CYP* genes can aggravate the hyperandrogenic phenotype in women with PCOS by either upregulation or downregulation of the expression, thus increasing androgens further. Though a number of studies have found significant association between the genetic variants of these genes and PCOS, results are still inconclusive. This can be due to the lack of uniformity in diagnostic criteria, limited sample size, ethnic variation, and environmental factors.

## Abbreviations

17 $\beta$ -HSD: 17 $\beta$ -Hydroxysteroid dehydrogenase; 3 $\beta$ -HSDII: 3 $\beta$ -Hydroxysteroid- $\Delta^5$ -steroid dehydrogenase; 5'-UTR: 5'-Untranslated region; cFT: Circulating free testosterone; *CYP*: Cytochrome P450; DHEA: Dehydroepiandrosterone; DHEAS: Dehydroepiandrosterone sulfate; E2/T: Estradiol to testosterone ratio; FAI: Free androgen index; FG: Ferriman-Gallwey; FSH: Follicle-stimulating hormone; FT: Free testosterone; GnRH: Gonadotropin-releasing hormone; LH: Luteinizing hormone; mRNA: Messenger ribonucleic acid; NADPH: Nicotinamide adenine dinucleotide phosphate; PCOS: Polycystic ovary syndrome; SHBG: Sex hormone-binding globulin; SNP: Single nucleotide polymorphism; T2DM: Type 2 diabetes mellitus; VNTR: Variable number tandem repeat; WHO: World Health Organization

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## Authors' contributions

SA contributed to the manuscript writing and data collection. MN contributed to the manuscript editing and literature review. SR contributed to the manuscript editing, manuscript design, and analysis. FR contributed to the critical revision of the manuscript. SA contributed to the conception and design, management, and funding. All the authors have read and approved the final manuscript.

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## Availability of data and materials

The data and material will be provided by authors on reasonable request.

**Ethics approval and consent to participate**

The study was approved by the Institutional Ethics Committee, Sher-i-Kashmir Institute of Medical Science, Srinagar (IEC-SKIMS Protocol-RP-73/2016)

**Consent for publication**

NA

**Competing interests**

The authors declare that they have no competing interests.

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