THE GENETICS OF *CYP* GENE VARIANTS IN ASSOCIATION WITH POLYCYSTIC OVARY SYNDROME: A NARRATIVE REVIEW

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ABSTRACT

A multifactorial endocrinal condition, polycystic ovarian syndrome (PCOS) is typified by lack of ovulation, hyperandrogenism, and polycystic ovary shape. Although the exact dysfunctional physiology of PCOS is unknown, genetic and environmental factors, and disruption of the hypothalamic-pituitary-ovarian axis are the main causes of this condition. Hyperandrogenism, which manifests clinically as hirsutism, acne, and alopecia, is the hallmark of PCOS. The overproduction of androgen by the ovaries and adrenal glands results in hyperandrogenism. Women with PCOS have neuroendocrine system anomalies, including increased gonadotropin-releasing hormone pulse frequency and pituitary stimulation that produces more luteinizing hormone than follicle-stimulating hormone. When there is a relative deficiency in FSH, follicular growth is hampered, whereas excess LH increases ovarian androgen production. The LH imbalance: FSH promotes the growth of ovarian theca cells, which in turn increases steroidogenesis and ultimately results in hyperandrogenism in women with PCOS. Aberrant steroidogenesis has been linked to a number of genetic variables. The steroidogenic P450s gene variants that are involved in steroidogenesis are thought to be crucial in the generation of androgens in PCOS. By modulating their expression either up or down, CYP gene polymorphisms can exacerbate the hyperandrogenic phenotype in PCOS-affected women, hence raising androgen levels even higher. Further research is necessary to support this concept.

KEYWORDS: PCOS, Hyperandrogenism, CYP, CYP11, CYP17, CYP19.

INTRODUCTION

One of the most well-known hormonal problems is Polycystic Ovary Syndrome (PCOS). Affects 4% to 12% of women globally who are of conception age (1). Between 4% and 20% of people worldwide are thought to have PCOS (2). For women who are of generative stage, it is one of the most widely recognized endocrine dysfunctions (3). Significantly more Indian women than any other have PCOS. The combined commonness of PCOS was practically 10% when using the Rotterdam and Androgen Excess Society (AES) criteria; though, it was only 5.8% when utilising the National Institutes of Health (NIH) standards. (4). PCOS is a highly common conceptive endocrine condition that includes oligomenorrhea, polycystic ovaries, anovulatory infertility, hyperandrogenism, insulin blockage or hyperinsulinemia, and an increased risk of several metabolic illnesses (5). The overproduction of androgens in the ovaries that causes PCOS can result in major health problems such insulin resistance, obesity, endometrial cancer (6). The development and consequences of PCOS are significantly influenced by hyperandrogenism. Excess androgen may produce follicular dysplasia, the primary cause of anovulation, according to recent research (7). The disorder known as hyperandrogenism is characterised by a higher-than-normal level of androgens, or male hormones, in females. One of the primary side effects of PCOS is ovarian and extraovarian hyperandrogenism (8). Testosterone levels in PCOS patients will be significantly greater than average. The values of Sex steroid-binding protein (SSBP), androstenedione, dehydroepiandrosterone (DHEA), androgen, and SHBG are typically used to diagnose hyperandrogenism (9). High ovarian androgen levels are thought to be a classic sign of hyperandrogenism in PCOS, which impairs follicular maturation. This is because high androgen levels can negatively affect follicular growth, resulting in atresia. Although the ovaries are normally remembered to be the essential wellspring of androgen overabundance in PCOS,

research has shown that 20-30% of PCOS people additionally have raised adrenal androgen levels (10).

Because genetic factors predispose individuals to unusually high androgen production in ovarian tissue, they are also supposed to have a significant part in the progress of this condition. Here, we go over recent and past gene-associated discoveries in relation to the progress of knowledge about it. We are therefore providing an indication of the clinical consequences, role of cytochrome P450 (*CYP)* and its genetic part that intricate in the synthesis of biologically active steroid on hyperandrogenism, in PCOS patients.

Hyperandrogenism with PCOS

Ovulatory malfunctional, polycystic ovary morphology, and experimental or biological hyperandrogenism are two irregularities required for the finding of PCOS (11). Excessive androgen production in PCOS is caused by dysregulation of steroidogenesis in the theca cells as a result of both intra- and extraovarian causes (12). Adrenal hyperandrogenism is also caused by abnormal folliculogenesis, deregulation of a potential steroidogenesis gene, and increased peripheral cortisol metabolism (13). Hyperandrogenisms can also result from luteinizing hormone (LH) -stimulated theca cells, as shown in Figure 1; which are aromatized to oestrogen by follicular stimulating hormone (FSH) stimulated granulosa cells. This environmental change may result in anovulation and the polycystic ovarian stage (14).

Clinical features of hyperandrogenism

PCOS is characterised by hyperandrogenaemia, a biological trait. Acne, androgenic alopecia, as well as hirsutism, is the term for the masculine pattern of terminal hair on the body. This is among the primary features of it. Between 60 to 80% of PCOS-afflicted women have hirsutism (15). PCOS and hirsutism is linked to higher amounts of free testosterone in the blood and dihydrotestosterone, which is a more active form of testosterone. The furthermost dependable and constant sign for assessing experimental raised androgen levels is hirsutism. (16). The furthermost characteristic symptom of hyperandrogenism is acne vulgaris. It is more common in some ethnic groups than others; Indo-Asian women have been found to have the greatest frequency, while Pacific Islanders have the lowest. Pilosebaceous gland irritation is the cause of acne. Higher testosterone stimulates the generation of more powerful dihydrotestosterone, which promotes aberrant desquamation in follicular epithelial cells. Acne typically appears on face but can also appear on the back, chest, and shoulders (17). One more sign of the raised level of androgens that affects PCOS is alopecia, sometimes known as male pattern baldness. It is typified by miniaturisation, in which the terminal hair on the scalp region gradually changes into fewer, finer vellus hair by elevated testosterone levels, which cause male pattern of baldness (19).

Biochemical aspect of hyperandrogenism

The elevated levels of testosterone as well as other determined markers of hyperandrogenism, like luteinizing hormone (LH), free testosterone (FT), and FAI. There are two types of testosterones free and attached to proteins like albumin and SHBG. Normally, because there is less follicular stimulating hormone in the blood, only 1% of testosterone is released as free testosterone. The remaining 80% of androgen is bound to sex steroid binding protein, and 19% is bound to albumin (20).

Cytochrome P450

The production of a gene super-family, which presently has several members in species that produce CYPs, a family of haemoproteins that includes bacteria, vegetation, and wildlife. Approximately 40 distinct CYPs are found in humans, also they are essential because they catalyse processes in the biogenesis of steroid hormones, the oxidation of unsaturated fatty acids to intracellular messengers, the metabolism of drugs, fat-soluble vitamins, environmental pollutants, and other xenobiotics. Numerous different steroids are biosynthesised by cytochrome P450 systems, which also acting a part in the biogenesis of steroid hormones (21). The steroidogenic acute regulatory protein (StAR) facilitates the rate-limiting transport of cholesterol into the mitochondria, which is the first step in steroidogenesis. Pregnenolone, the initial precursor in the steroidogenic cascade, is produced there (22). As demonstrated in Figure 1 CYP11A1 (cholesterol side chain cleavage cytochrome P450), CYP17 (17a-hydroxylase), and CYP11B1 (113-hydroxylase cytochrome P450 or P450113) are among the up to six P450s involved in the multi-step pathways that produce steroid hormones. The sole distinction between CYP19 (aromatase cytochrome P450 or P450arom) and CYP11B2 (aldosterone synthase cytochrome P450) is that the genes are printed in italic. While glucocorticoids, mineralocorticoids, and androgens are predominantly produced by the adrenal gland, the gonads are the primary source of production for sex hormones, including oestrogens and testosterone. Two very thoroughly associated enzymes, CYP11B1 and CYP11B2, carry out the last steps in the production of cortisol, the primary glucocorticoid in humans, and aldosterone, the primary mineralocorticoid in humans. (23).

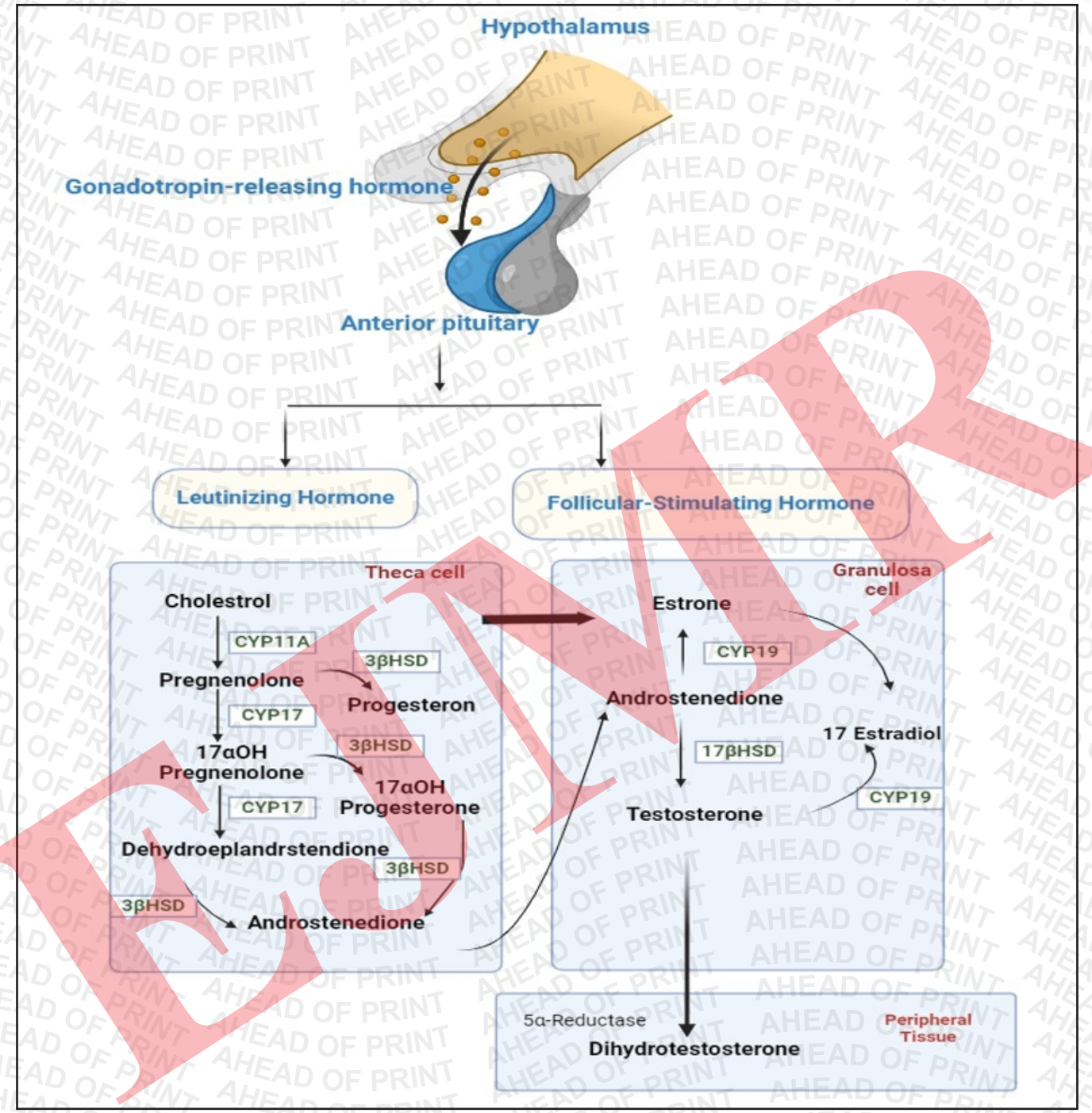

Fig. 1: Hypothalamic-pituitary-ovarian axis and Steroidogenesis (23)

Ovarian and Adrenal Steroidogenesis in PCOS

Excess androgens are thought to originate from the ovary as a result of dysregulated steroidogenesis, as describe in Figure 2. The key component of PCOS is hyperandrogenism. The hypothalamic-pituitary-gonadal axis, that affects steroidogenesis, is dysfunctional in patients. Steroidogenic dysregulation of theca cells in the ovaries increases the levels of circulating androgens. Furthermore, a hormonal imbalance results in an early disruption of follicular growth, which leads to infertility, polycystic ovaries, chronic anovulation, and amenorrhoea. Elevated levels of adrenal androgens, such as DHEA and androstenedione, have been seen in females with PCOS, as the ovaries are the core basis of androgen excess in the condition [24].

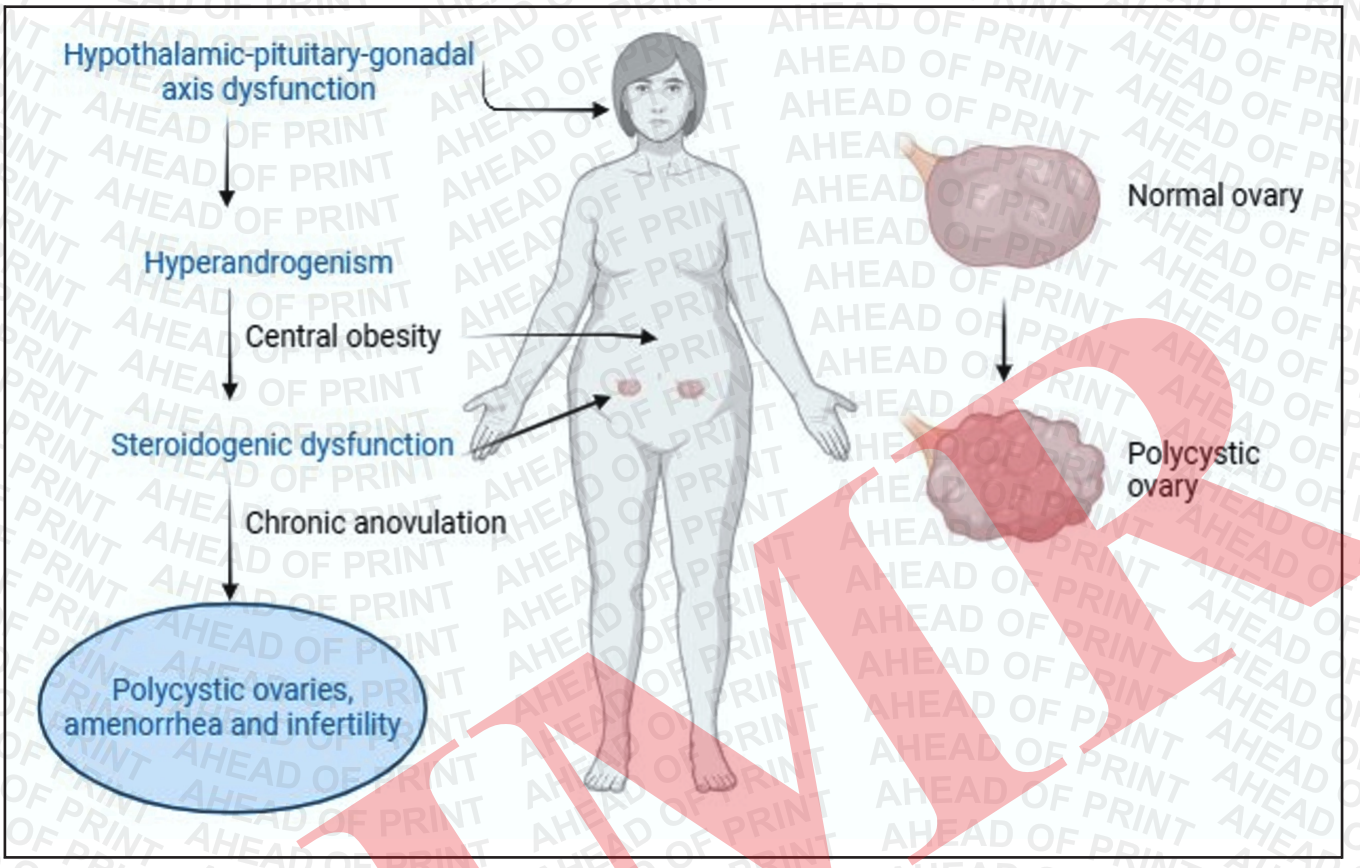

Fig. 2: Pathway that involved in the Pathophysiology of PCOS (24)

Major Genes Associated with Ovarian and Adrenal Steroidogenesis

The very usual endocrine disorder related with PCOS is an increased androgen level so, the hyperandrogenic state in PCOS is linked to heterogeneity in clinical features and genetic variants, suggesting the potential involvement of anomalies related to the steroidogenic pathway. PCOS candidates are thought to be genes that encode for enzymes implicated in the steroidogenesis. The most thoroughly researched genes among them are *CYP11, CYP17,* and *CYP19.*

CYP11

The most important phase in the synthesis of steroid hormones is catalysed by the cytochrome side-chain cleavage enzyme and it is encoded by the CYP11 gene, which is found at 15q24. This enzyme act as the rate-limiting in the alteration of cholesterol to progesterone [25]. With ten exons and nine introns, it is about 30 kb long. In the synthesis of steroid hormones, its code for the cytochrome P450 superfamily enzyme cholesterol side-chain cleavage (P450 scc), which catalyses the first rate-limiting step in the conversion of cholesterol to pregnenolone and is found in the inner membrane of the mitochondria [26]. This is mostly expressed in organs that are steroidogenic, such as the placenta, gonads, and adrenal cortex. Genetic variations in *CYP11A1* alter its expression, leading to certain hormone-related illnesses such as polycystic ovarian syndrome, endometrial cancer, breast cancer, and prostate cancer [27]. It is hypothesised that variations in this gene show a crucial part in controlling the expression of *CYP11A1* through transcriptional up- or down-regulation, which results in increased or decreased androgen production [28]. Numerous polymorphism investigations concerning the *CYP11* gene in relation to PCOS have been conducted. Numerous studies as shown in Table 1; have documented the correlation between a microsatellite polymorphism (TTTTA) in the *CYP11A1* promoter region and modified gene expression observed in PCOS. A strong correlation was found between PCOS risk and the *CYP11A1* penta nucleated repeat polymorphism in a study conducted by Reddy KR et al. (2014) [29]. Shan B. et al. (2016) demonstrated a substantial correlation with PCOS in their study, which is consistent with our findings. The risk of developing PCOS was 2.5 times higher for those with the heterozygous genotype [30]. Additional research

(Abdel-Mageed W S. et al.) [31] demonstrated the possible impact of *CYP11A1* gene single nucleotide polymorphisms (SNP) in various populations. On the other hand, (tttta)n polymorphism is not correlated with the presence of hirsutism in a study of Chinese women [32].

CYP17

The endoplasmic reticulum-resident enzyme cytochrome P450 17α-hydroxylase-17, 20-lyase is encoded by this gene, which is located on chromosome 10q24–q25. The hydroxylase and lyase activities of this bio-catalyst are important in the making of steroid hormones. Pregnenolone and progesterone are converted to 17-hydroxypregnenolone and 17-hydroxyprogesterone, respectively, by its 17αhydroxylase and 17αlyase activities. These steroids are then converted to dehydroepiandrosterone and 4-androstenedione [33]. The hydroxylase and lyase activities of this enzyme are important in the production of steroid hormones. Its 17αhydroxylase and 17αlyase activities change progesterone and pregnenolone into 17-hydroxyprogesterone and 17-hydroxypregnenolone, respectively, and then these steroids are converted to 4-androstenedione and dehydroepiandrosterone [34]. The ovarian hyperandrogenism linked with PCOS is believed to be caused in part by dysregulated P450 CYP17 enzyme [35]. Ovarian hyperandrogenism linked with PCOS is believed to be caused in part by dysregulated P450 CYP17 enzyme [36]. Single nucleotide polymorphism rs743572 of *CYP17* has been linked in the past to PCOS and related phenotypes [37]. Diamanti-Kandarakis et al. reported similar findings in Greek patients, demonstrating a markedly elevated occurrence of C alleles of the *CYP17* gene in PCOS [38]. Additionally, research by Pusalkar et al. conducted a study in which they come with a result that in PCOS the occurrence of the C alleles of the *CYP17* gene was higher [39]. Moreover, there are some studies also that were not thought to be a chief influence in the progress of PCOS [40].

CYP19

The enzyme P450 aromatase is encoded by the CYP19 gene, which is located at 15p21. The enzyme compound is composed of cytochrome P450 reductase, cytochrome P450 aromatase, and nicotinamide adenine dinucleotide phosphate. It is the catalyst that turns androgens into oestrogen. Numerous patients with hyperandrogenism have been observed to have diminished aromatase activity [41]. This enzyme may be crucial in the emergence of hyperandrogenism since it catalyses the last stage of oestrogen biosynthesis, which converts testosterone and androstenedione into estradiol and estrone, respectively. Research has shown that women with PCOS have low amounts of aromatase in the granulosa cells that are derived from medium-sized follicles [42]. This enzyme may be crucial in the emergence of hyperandrogenism since it catalyses the last stage of oestrogen biosynthesis, which converts testosterone and androstenedione into estradiol and estrone, respectively. Low levels of aromatase have been observed in granulosa cells derived from medium-sized follicles in PCOS [43].

GENE	SNPs	ORIGIN	SAMPLE NUMBER	KINSHIP	REFERENCE
CYP11	(tttta)n	South India	267 cases 275 controls	Yes	[29]
	rs4887139 *rs48866595*	China	285 cases 299 controls	Yes	[30]
	rs4077582	Egypt	53 cases 53 controls	Yes	[31]
	rs11632698 *rs4077582* *rs4887139*	North India	270 cases 270 controls	Yes	[32]
CYP17	*rs743572*	Pakistan	204 cases 100 controls	Yes	[33]
	34 T/C SNP	Greece	50 cases 50 controls	Yes	[34]

Table 1: The contribution of different CYP gene SNPs in PCOS with different ethnicity

		Indian	100 cases 100 controls	Yes	[35]
		Indian	60 cases 54 controls	No	[36]
		Caucasian	287 cases 187 controls	No	[37]
CYP19	*rs2414096*	Chinese	785 cases 297 controls	Yes	[20]
		Indian	249 cases 257 controls	Yes	[29]
		Egyptian	30 cases 30 controls	Yes	[44]
		Pakistan	204 cases 100 controls	Yes	[45]
		Kashmir	396 cases 306 controls	Yes	[46]

Cont. Table 1: The contribution of different CYP gene SNPs in PCOS with different ethnicity

A different study conducted in Egypt came to the conclusion that in PCOS women with hyperandrogenism, *rs2414096* of the *CYP19* gene is linked to decreased aromatase action [44]. Accordingly, a same study has been done on the same SNP that concluded with strongly association [45]. Additionally, several researches on a different polymorphism, *rs2470152* in the *CYP19* gene, revealed that heterozygous TC genotype was linked to higher testosterone levels and a lower E2/T ratio but had no effect on PCOS risk. This finding suggested that the polymorphism had a function in controlling aromatase activity [46].

CONCLUSION

The prevalence of PCOS has considerably grown in recent decades. We give an outline of the capability of *CYP* gene varieties in hyperandrogenism in this review. The deregulation of bio-catalyst participated in the steroidogenic production pathway and the enlargement of theca cells in the ovaries, are factors contributing to the rise in androgen. GnRH rhythm rate rises leads a result of increasing androgens because they block the hypothalamic-pituitary axis' negative feedback loop. A rise in LH causes the ovaries' theca cells to proliferate quickly, which in turn increases their ability to produce steroids and, ultimately, androgens. The bio-catalyst participated in steroid metabolism are encoded by genes including *CYP11, CYP17* and *CYP19*, which have been well investigated and are supposed to potential contenders for roles in the causing PCOS. These genes are overexpressed in the ovary, which leads to elevated testosterone, androstenedione, and 17-hydroxyprogesterone production. Additionally, the action of aromatase is lowered, which additional upregulates the production of androgens. Numerous research has examined the correlation between various genetic variations of these steroidogenesis-related genes and PCOS. By also upregulating or downregulating the expression, *CYP* gene polymorphisms can exacerbate the hyperandrogenic phenotype in PCOS-affected women, hence raising androgen levels even higher.

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