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Association of *Cyp11a* Gene with Polycystic Ovarian Syndrome Patients in Lahore, Pakistan

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ABSTRACT

Polycystic ovary syndrome is caused by gene polymorphisms that manufacture steroid hormones, androgens and cortisol. The overexpression or downregulation of *Cyp11a1* gene mutations of steroidogenesis worsens the hyper-androgenic phenomenon. However, there is a gap in the relationship between polycystic ovary syndrome, hyperandrogenism, and *Cyp11a* gene polymorphisms. **Objectives:** To investigate the association between *Cyp11a* gene in polycystic ovary syndrome, and to analyze the levels of di-hydro-testosterone in cases and controls. **Methods:** The descriptive cross-sectional study was conducted within six months at The University of Lahore. A sample of 75 participants (25 PCOS, 25 a-PCOS, and 25 controls was collected to test di-hydro-testosterone levels. Then 25 polycystic ovary syndrome patients and 25 control patient samples were used for PCR amplification for the *Cyp11a1* gene. **Results:** The mean age of polycystic ovary syndrome, a-PCOS (anovulatory), and Controls were 22.68, 22.5 and 22.13, respectively. The *Cyp11a1* (10:74348306 G>C) had an odds ratio of 1.199, indicating the presence of an allele in polycystic ovary syndrome and controls. Meanwhile, the odds ratio 1.179, indicated that the allele was 1.2 times more common in polycystic ovary syndrome than the controls. The polycystic ovary syndrome levels of di-hydro-testosterone were higher than the control and a-PCOS groups, with mean values of 278.18, 260.97, and 190.83, respectively. **Conclusions:** *Cyp11a* SNP rs6495096 was present in both polycystic ovary syndrome and controls, and a weak relationship exists between the *Cyp11a1* gene variation and polycystic ovary syndrome. The di-hydro-testosterone levels were high in both the polycystic ovary syndrome and a-PCOS groups compared to the control group.

INTRODUCTION

Polycystic ovarian syndrome is distinguished by anovulation, ovarian cysts, and endocrine variance [1]. In women between the ages of 17-45, Polycystic ovary syndrome (PCOS) prevalence is estimated to be between 5.5% and 12.6% worldwide [2]. The prevalence of PCOS is as high as 15.7-37% in Pakistan [3]. The most frequent androgen abnormality linked to PCOS is elevated free testosterone levels. Progesterone levels are moderate in an-ovulatory PCOS, and estradiol levels are moderate in the mid-follicular phase [4]. Research suggested that PCOS may emerge as a result of altered epigenetics brought on by the hormonal imbalance of the uterine environment, even if the genetic loci only account for 10% of its estimated 70% heritability [5]. The following biochemical pathways contain genes associated with PCOS: complement and coagulation cascade (VWF), steroidogenesis *(CYP11A1, CYP19A1, CYP17A1)*, insulin secretion *(INSR, INS, IRS-1)*, the signalling *(AMH, LHCGR, INS, ADIPOQ)*, chronic inflammation *(TNF-α, IL-6)*, and cancer *(MMP, INS, AR1)* pathways [6]. *CYP11* gene from the Cytochrome P450 family is among the critical genes involved in androgen secretion.The two primary components of this gene are *CYP11a1* and *CYP11b1*. These genes have 10 and 9 exons, respectively, and code for a member of the cytochrome P450 family [7]. Steroidogenesis gene abnormalities are the cause of androgen excess in PCOS. A crucial marker in the steroid synthesis pathway, *CYP11a1's* altered expression has been shown to interfere with steroid synthesis, increasing the likelihood of PCOS development [8]. Previous studies have not established a well-established relationship between

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PCOS, hyperandrogenism, and *Cyp11a* gene polymorphisms. Therefore, this study examined the relationship between Cyp11a gene polymorphism, levels of di-hydro-testosterone (DHT), and PCOS in a particular population.

Polycystic ovary syndrome (PCOS) is one of the most prevalent endocrine disorders among women of reproductive age, with a particularly high prevalence of 15.7–37% reported in Pakistan, driving significant burdens of infertility, hyperandrogenism, menstrual irregularity, and metabolic complications that profoundly affect quality of life. The CYP11A1 gene, encoding the cholesterol side-chain cleavage enzyme and serving as a critical regulator of the steroidogenic pathway, has been proposed as a candidate gene for PCOS susceptibility through its influence on androgen biosynthesis and beta-cell dysfunction, yet the specific relationship between CYP11A1 polymorphisms, hyperandrogenism quantified through dihydrotestosterone levels, and PCOS risk in Pakistani women remains poorly characterized and underinvestigated. While international studies from Iran, India, and Iraq have explored associations between CYP11A1 single nucleotide polymorphisms including rs6495096 and PCOS, locally contextualized genetic data from Lahore's predominantly urban Pakistani population are absent, leaving a critical evidence gap for understanding the population-specific genetic architecture of PCOS in this high-prevalence region. This study therefore aimed to investigate the association between the CYP11A1 gene polymorphism rs6495096 and PCOS, and to comparatively analyze dihydrotestosterone levels across PCOS, anovulatory PCOS, and control groups in a Lahore-based sample.

METHODS

The descriptive cross-sectional study was conducted at the Institute of Molecular Biology (IMBB) and Biotechnology, The University of Lahore (UOL), Lahore from 1 March 2024 to 15 August 2024. The study period was six months after the approval of the synopsis. Ethical Approval (Ref-IMBB/BBBC/24/1341) was obtained from the Ethics Committee/ Institutional Review Committee of the IMBB at UOL. The sample size was 75 (25 PCOS, 25 atypical PCOS (a-PCOS), and 25 controls collected using Convenient sampling from the Department of Endocrinology and the Department of Gynaecology, Jinnah Hospital, Lahore. Informed consent was obtained from women aged 15-30 years before collecting data and blood samples. Questions related to Polycystic diseases were asked using the questionnaire from the PCOS, a-PCOS, and control groups. The polymerase chain reaction (PCR) for the genotype analysis of the *Cyp11a1* gene was performed on 25 PCOS Patients and 25 controls. The sample size was calculated through an online sample calculator. Blood samples were collected from veins punctured aseptically to collect each subject's blood sample 3CC in ETDA vials for PCR and ELISA. The blood sample was centrifuged at 3000 rpm for 10 minutes for serum isolation. The serum sample isolated was then frozen at 4°C for analysis, and all information, including the patient's name and reference number, was recorded on the form. The DNA was extracted using the DNA Extraction Kit "DONGSHENG BIOTECH Quick Tissue/Culture Cells Genomic DNA Extraction Kit N1141" following the manufacturer's instructions. Three primers were designed for *Cyp11a* using the "Oligo-Calc Website" (Table 1).

Table 1: Primers for *Cyp11a*

Primer Label	Sequence	TM	GC	Length
Hs_*CYP11a1*_FC	AGTTCCACAACTTGCTGACTG	59.5	48%	21
Hs_*CYP11a1*_RN	CAGCAACAGTGATCATAAATCTC	59.2	39%	23
Hs_*CYP11a1*_RM	CAGCAACAGTGATCATAAATCTG	59.2	39%	23

Quantification using PCR was conducted using The "SimpliAmp Thermal Cycler," which utilized the CYP11a1_TD PCR software. The Steps of PCR are described (Table 2).

Table 2: Steps of PCR

PCR Steps	Temperature (°C) / Time (second)	Cycles
Initial Denaturing	94°C/ 5 min	1/1
Cyclic Denaturing	94°C/ 45 Sec	6x
Annealing	56°C/ 90 sec	--
Cyclic Extension	72°C/ 45 sec	--
Final Extension	72°C/ 30 sec	25x
Storage	4°C	--

The DHT levels were measured using the "Human DHT ELISA Kit" provided by Bio-laboratories, available at (www.arigobio.com) following the manufacturer's instructions. Using the "PLINK toolset" the genotyping frequencies were calculated and Chi-square analysis was performed to confirm the association between variant 6495096 *G>C* and *CYP11a1*. Moreover, the p-value and OR were calculated. SPSS version 26.0 was used, qualitative data were presented as frequency/percentage, and quantitative data as mean ± S.D. p-value≤0.05 was taken as significant.

RESULTS

In the study, the mean ± SD of PCOS was 22.68, the mean ± SD 4.801, a-PCOS was 22.5 ± 4.585, and the control group was 22.13 ± 4.719. The health-related questions data of PCOS, a-PCOS, and Controls comprised aspects such as menstrual regularity, spotting, discomfort during menstruation, weight gain, infertility, acne issues, mood swings, and hair growth or facial hair. Participants were also asked if their ultrasound scans revealed any ovarian enlargement (Table 3).

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Table 3: Descriptive Analysis of Health-Related Questions to All Patients

Questions	n	Frequency (%)					
		No	Yes	No	Yes	No	Yes
Q1.	25	0 (0%)	25 (100%)	0 (0%)	25 (100%)	0 (0%)	25 (100%)
Q2.	25	16 (64%)	9 (36%)	10 (40%)	15 (60%)	10 (40%)	15 (60%)
Q3.	25	12 (48%)	13 (52%)	13 (52%)	12 (48%)	13 (52%)	12 (48%)
Q4.	25	3 (12%)	22 (88%)	12 (48%)	13 (52%)	12 (48%)	13 (52%)
Q5.	25	12 (48%)	13 (52%)	13 (52%)	12 (48%)	12 (48%)	13 (52%)
Q6.	25	13 (52%)	12 (48%)	12 (48%)	13 (52%)	13 (52%)	12 (48%)
Q7.	25	15 (60%)	10 (40%)	12 (48%)	13 (52%)	11 (44%)	14 (56%)
Q8.	25	6 (24%)	19 (76%)	9 (36%)	16 (64%)	11 (44%)	14 (56%)
Q9.	25	12 (48%)	13 (52%)	13 (52%)	12 (48%)	10 (40%)	15 (60%)
Q10.	25	16 (64%)	9 (36%)	10 (40%)	15 (60%)	12 (48%)	13 (52%)
Q11.	25	13 (52%)	12 (48%)	14 (56%)	11 (44%)	13 (52%)	12 (48%)
Q12.	25	12 (48%)	13 (52%)	12 (48%)	13 (52%)	14 (56%)	11 (44)

Q1. Do you have a menstrual history? Q2. Do you have irregular menstruation? Q3. Do you have minute spotting in menstruation? Q1. Do you have a menstrual history? Q2. Do you have irregular menstruation? Q3. Do you have minute spotting in menstruation? Q4. Is your menstrual cycle regular? Q5. Do you have painful menstruation? Q6. Do you have pain between two successive menstrual cycles? Q7. Have you gained weight? Q8. Do you have difficulty in conceiving? Q9. Do you have an acne problem? Q10. Are you experiencing mood swings? Q11. Do you have hair growth or facial hair? Q12. Ovaries enlargement on ultrasound?

In PCR amplification of the *Cyp11a1* gene results, bands of heterozygous, homozygous wild, and homozygous mutant were detected on gel electrophoresis in both groups, with DNA ladder 100bp and product size 196 bp (Figure 1).

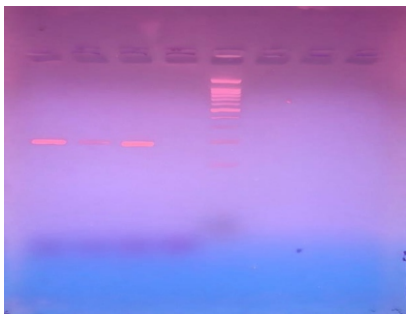


Figure 1a



Figure 1b



Figure 1c

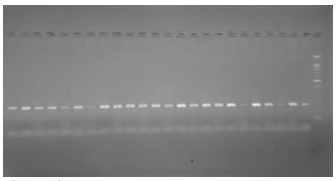


Figure 1d

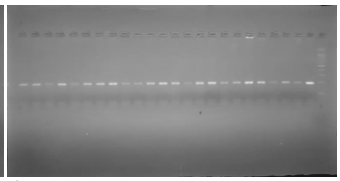


Figure 1e

Figure 1: PCR Amplification of the *Cyp11a1* Gene

There were 12 (48%) heterozygous, 5 (20%) homozygous wild, and 8 (32%) homozygous mutants present in Controls, while in PCOS, 16 (64%) heterozygous, 2 (8%) homozygous wild type, and 7 (28%) homozygous mutants were present. The data fits the Hardy-Weinberg Equilibrium (HWE) with a p-value of 0.3894. The Chi-square test, yielded a p-value of 0.6853, suggesting that allele frequencies between PCOS and Controls are not statistically significant. The odds ratio was 1.179, implying that the mutant allele is more frequent in PCOS than in the control group (Table 4).

Table 4: Chi-Square Analysis of Cyp11a1 gene SNP in PCOS

CHR	SNP	BP	A1	F_A	F_U	A2	CHISQ	p-value	OR
10	1	74348306	1	0.44	0.4	2	0.1642	0.6853	1.179

CHR: Chromosome; SNP: Single Nucleotide Polymorphism; BP: Base Pair. A1: alternative allele (mutant C); A2: reference allele; OR: Odds Ratio. F_A: Frequency of the alternative allele (mutant C) in affected individuals (PCOS). F_U: Frequency of the alternative allele in unaffected individuals (control group).

DHT levels were also measured in this study. DHT levels varied significantly between the groups (p=0.000). The PCOS group had considerably higher DHT levels than the Control group ($p<0.001$), and DHT levels were substantially greater in the a-PCOS group than in the Control group ($p<0.01$). The PCOS and a-PCOS groups did not differ significantly (p=0.45) (Table 5).

Table 5: DHT Analysis in PCOS, aPCOS and Control Group

DHT Analysis in Groups	n	Reference Range (pg/ml)	Minimum (pg/ml)	Maximum (pg/ml)	Mean ± SD (pg/ml)
PCOS	25	24 - 368	153.0	427.0	278.188 ± 84.1140
PCOS	25	24 - 368	96.00	393.00	260.9750 ± 89.98997
Control	25	24 - 368	29.00	359.00	190.8312 ± 95.74881

The link between *Cyp11a1* gene variations and DHT levels in the PCOS and control groups was assessed (Table 6).

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Table 6: Correlation between Gene variants and DHT in PCOS and Control Group

Cyp11a1 Gene Variants			DHT Values of PCOS			DHT Values of Controls		
PCR-Results	n	Reference Range	Mean ± SD	Min	Max	Mean ± SD	Min	Max
Heterozygous	12	24–368	176.52 ± 100.80	49.75	352.0	244.25 ± 79.16	154.0	378.0
Homo-Mutant	8	24–368	282.43 ± 35.24	250.0	354.0	334.81 ± 46.18	267.0	398.0
Homo-Wild	5	24–368	234.00 ± 62.23	190.0	278.0	296.60 ± 56.24	211.0	354.0

DISCUSSION

It has been demonstrated that *CYP11A1*'s altered expression interferes with steroid production, a critical marker in the steroid synthesis pathway, and increases the risk of PCOS development [6]. While our study objectives were to determine whether *Cyp11a* gene variants, PCOS, and hyperandrogenism are related in a particular community, the current investigation showed a weak connection between the *CYP11a1* gene variation (10:74348306 G>C) and the Pakistani population with PCOS. Current study groups found the following age-related mean ± S.D.s: PCOS 22.68 ± 4.801, a-PCOS 22.5 ± 4.585, and the control group 22.13 ± 4.719. 57.5% acknowledged aberrant menstrual cycles, while 47.5% reported spotting. Menstrual cycle consistency was reported by 52.5% as irregular, 50% with no pain, whereas another 50% said they experienced depression. 47.5% reported pain between two consecutive menstrual cycles, 40% reported weight growth, 75% experienced difficulties during conceiving, and 52.5% reported acne. Furthermore, 35% reported mood swings. 50% reported facial hair, and 52.5% reported enlarged ovaries on ultrasound. A similar study on irregular menstrual cycles in patients with PCOS concluded that menstrual cycle issues affected 72.2% of the population overall, 24% of women, and 15.1% of overweight women were obese. Additionally, 56.4% had acne, and 36% had androgenetic alopecia [9]. Another study showed that about one in five to six women experience severe issues related to irregular menstruation cycles and infertility. Globally, stress, obesity, and fluctuations in hormone levels are the leading causes [10]. In another study, 88% of women experienced irregular menstruation, and 55.9% of participants experienced heavy menstrual flow. PCOS was estimated to have 25.5% and 5.2% prevalence rates, respectively [11]. The current investigation showed a weak connection between the CYP11a1 gene variation (10:74348306 G>C) and the Pakistani population with PCOS. All 50 samples, including 25 cases and 25 controls, were genotyped. Results indicated that of the total genotyped, 48% were heterozygous, 20% were homozygous wild type, and 32% were homozygous mutants. The Chi-square value that was computed is 0.1642. A p-value of 0.6853 indicates no statistically significant difference in allele frequencies between PCOS and Controls. However, the odds ratio in our study is 1.179. This suggests that the mutant allele is more common in the affected group than in the unaffected group. The mutant allele is approximately 1.2 times more common in the PCOS group than in the control group. These results were consistent with a past study that showed that a crucial marker in the steroid synthesis pathway, *CYP11a1's* altered expression, has been shown to interfere with steroid synthesis, increasing the likelihood of PCOS development [8]. A past study found that SNPs in the *CYP11a1* gene (rs1484215 and rs6495096) are associated with PCOS [12]. The rs6495096 polymorphism's C with G alleles was strongly related to PCOS susceptibility (p-0.001). The GG genotype of rs6495096 was also significantly connected with the length of infertility [12]. Another study showed a strong correlation between the *CYP11a1* gene and PCOS. According to dichotomous genotypic analyses, the (tttta) genotype may raise the risk of PCOS in a recessive model, and the (tttta)6 genotype may lower the risk of PCOS in a dominant model [13]. Another variable of the current study was DHT levels, measured in PCOS, a-PCOS, and Control. DHT is a potent androgen generated from testosterone, and elevated levels have been related to disorders like PCOS. In women with PCOS, the hyperandrogenic phenomenon may be exacerbated by overexpressed or downregulated CYP genes implicated in steroidogenesis, which alter androgen levels [14]. A study by Sukanti and colleagues included the testosterone-to-de-hydro-testosterone ratio. The PCOS group had a considerably greater testosterone-to-de-hydro-testosterone ratio than the control group, with p<0.001 [15]. In another study, the findings revealed a significant difference between the PCOS and control groups' levels of DHT p-value 0.009 and testosterone p-value 0.018 [16]. Similar results were found in another study. The study group's mean DHT value was 584.27 pg/mL, whereas the control group's was 257.15 pg/mL, with a p-value of less than 0.00001 and an area under the ROC curve of 0.895. According to the study findings, the DHT is the best biomarker available and can be used to diagnose hyperandrogenemia in PCOS women [17]. Excessive levels of *Cyp11a1* or any protein mutation may boost steroidogenesis, leading to hyperandrogenism and a role in the pathophysiology of PCOS [18, 19]. In the current study,

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PCOS group, people with the Heterozygous *Cyp11a1* gene variant (n=12) had DHT levels of 244.25. Those with the Homo-mutant *Cyp11a1* gene variation (n=8) had a higher mean DHT value of 334.81, whereas those with the Homo-wild *Cyp11a1* gene variation (n=5) had 296.60. In contrast, in the control group, people with the Heterozygous *Cyp11a1* gene variant (n=16) had a lower mean DHT level of 176.52. The homo-mutant group in the control (n=7) had a substantially higher mean DHT value of 282.43, whereas those with the Homo-wild *Cyp11a1* gene variant (n=2) had an average level of 234.00. These findings point to a potential role for *Cyp11a1* gene variants in regulating DHT levels in both PCOS and control persons, implying differences in DHT regulation between the two groups. Our findings were consistent with a study, genotyping variations between the two groups and conducting a comparative study, the *CYP11A1* gene's promoter region was genotyped for penta-nucleotide (AAAAT) repeats. The mean levels of prolactin and testosterone differed considerably ($p<0.05$) between the PCOS and healthy groups. There were five unique *CYP11A1* (AAAAT) repetitions, which matched to repeat units 3, 6, 7, and 8. The study found a significant difference ($p<0.05$) in penta-nucleotides (AAAAT) between PCOS and healthy women, with five and three repetitions, respectively[20].

This study was critically constrained by its very small sample size of only 25 PCOS cases and 25 controls for genetic analysis and 75 participants total for DHT measurement, which severely limits statistical power to detect modest genetic associations and renders the non-significant chi-square result potentially attributable to type II error rather than true absence of association. The single-center convenient sampling design, restriction to a narrow age range of 15–30 years, and analysis of only one CYP11A1 SNP without investigation of other steroidogenesis-related variants such as CYP17A1 and CYP19A1 further constrain the comprehensiveness and generalizability of conclusions to the broader Pakistani PCOS population. The absence of full hormonal profiling including testosterone, LH, FSH, and insulin resistance markers limited the ability to contextualize DHT findings within the complete metabolic and endocrine phenotype of PCOS. Future research should employ larger, multicenter, population-based case-control designs with ethnically stratified sampling across Pakistan's diverse provinces, incorporating genome-wide association approaches and comprehensive hormonal and metabolic panels alongside CYP gene variant analysis. Longitudinal studies examining how CYP11A1 genotype interacts with environmental factors such as diet, obesity, and insulin resistance to modulate PCOS phenotype severity would provide the translational evidence needed to advance personalized diagnostic and therapeutic strategies for PCOS management in Pakistan.

CONCLUSIONS

It was concluded that this study further studies the complex relationship between the *CYP11a1* gene and PCOS in a specific Pakistani community. The study implies that while the gene *Cyp11a1* may have a role in the start of PCOS, it is not the key driver. The study findings revealed significantly higher DHT levels in both the PCOS and a-PCOS groups compared to the control group. This result supports the previously established role of hyperandrogenism in the origin of PCOS, emphasizing the importance of hormonal imbalances in the disorder's genesis. The findings of this study add to the growing body of knowledge about the complex interplay between genetic factors, hormonal imbalances, and clinical indicators of PCOS. Nonetheless, the findings are limited due to the small sample size, only including the *CYP11a1* gene variant, and the focus on a specific Pakistani population. Further studies with more extensive and diverse populations are required to confirm the link between the *CYP11a1* gene variant and PCOS and investigate the potential effect of other genetic and environmental variables.

Authors' Contribution

Conceptualization: AR
Methodology: AUJR, ZW, HKQ, RJ
Formal analysis: AR
Writing and Drafting: AR, AUJR, ZW, HKQ, RJ
Review and Editing: AR, AUJR, ZW, HKQ, RJ

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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