Original Article

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Exploring the Contribution of Single Nucleotide Polymorphisms in FSHR, LHR, PPAR-γ, and INSR Genes to the Pathogenesis of Polycystic Ovary Syndrome: A Case-control Study

Physiology Section

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ABSTRACT

Introduction: Polycystic Ovary Syndrome (PCOS) is a complex endocrine disorder influenced by genetic factors. Single Nucleotide Polymorphisms (SNPs) in genes such as Follicle-Stimulating Hormone Receptor (FSHR), Luteinising Hormone Receptor (LHR), Peroxisome Proliferator-Activated Receptor Gamma (PPAR-γ), and Insulin Receptor; Genetic polymorphism have been implicated in PCOS pathogenesis.

Aim: To investigate the contribution of SNPs in FSHR, LHR, PPAR-γ, and INSR genes to the pathogenesis of PCOS.

Materials and Methods: This case-control study conducted in Malla Reddy Institute of Medical Sciences (MRIMS), Telangana, India. This research included 600 female patients aged 15-45 years seeking care at the Gynaecology Outpatient Department (OPD) from the duration of September 2022 to September 2023.

A total of 300 cases (PCOS patients) and 300 controls (non PCOS individuals) were recruited, and Deoxyribonucleic Acid (DNA) samples were collected for genotyping of selected SNPs. Statistical analysis was performed to assess associations between SNPs and PCOS risk.

Results: The study identifies potential associations between SNPs in the SHFR (follicle development), LHR (ovulation regulation), PPAR-γ (insulin sensitivity and adipogenesis), and INSR (insulin signaling) genes and PCOS susceptibility. These findings suggest that genetic variations in these pathways may contribute to the hormonal and metabolic dysregulation characteristic of PCOS, highlighting a potential genetic basis for the disorder. However, further studies are required to elucidate the precise functional mechanisms.

Conclusion: This case-control study provides insights into the role of SNPs in FSHR, LHR, PPAR-γ, and INSR genes in PCOS pathogenesis, contributing to the understanding of the genetic basis of the disorder. Future studies should also examine the interactions between genetic factors, environmental influences, and hormonal imbalances to fully understand PCOS pathophysiology.

Keywords: Endocrine disorders, Follicle-stimulating hormone receptor, Insulin receptor-genetic polymorphism, Luteinising hormone receptor, Peroxisome proliferator-activated receptor gamma

INTRODUCTION

The PCOS is a prevalent endocrine disorder affecting approximately 16.6% of women in their reproductive years. Its manifestations in adolescents include irregular menstruation, absence of menstruation, and clinical signs of elevated androgens, posing long-term health risks such as infertility, metabolic syndrome, type 2 diabetes and cardiovascular disease. Genetic factors are known to significantly contribute to PCOS development and its associated symptoms [1]. Despite its prevalence, PCOS often remains undiagnosed during adolescence due to overlapping symptoms with normal puberty, such as acne and irregular menstrual cycles. Implementing lifestyle changes early is crucial to addressing underlying mechanisms and improving long-term prognosis, underscoring the importance of timely genetic testing for diagnosis [2]. Recent studies highlight the substantial heritability of PCOS, with estimates reaching up to 0.79 [3]. Candidate genes implicated in PCOS pathophysiology, including those involved in steroid biosynthesis, gonadotropic function, follicle development, weight regulation, and insulin action, have been identified [4]. This study aims to provide a comprehensive overview of major genetic polymorphisms identified or studied in PCOS patients to date, focussing on candidate genes such as FSHR, LHRH, PPAR-γ, and INSR [5]. The exploration of these relationships based on prior research will contribute to understanding the genetic basis of PCOS and its pathophysiological mechanisms. The case-control study addresses the critical need to elucidate the genetic basis of PCOS and its associated symptoms, aiming to improve early diagnosis and management. By investigating genetic polymorphisms in key candidate genes, the study seeks to enhance our understanding of PCOS etiology and identify potential therapeutic targets. Moreover, the scarcity of literature on gene polymorphisms in the Indian population highlights the importance of exploring these relationships in diverse ethnic populations to facilitate personalised approaches to PCOS management.

This case-control study provides genetic polymorphisms in PCOS, focusing on candidate genes associated with key biological pathways implicated in the disorder's pathogenesis. Additionally, it highlights the underexplored pharmacogenomics of PCOS and the need for further research in diverse populations to elucidate inter-relationships between gene variants and their impact on PCOS risk. The study aims to investigate the contribution of SNPs in the FSHR, LHR, PPAR-γ and INSR genes to the pathogenesis of PCOS, provide insights into the genetic factors involved in its development and progression, and explore the interplay between genetic, environmental and hormonal factors in PCOS pathophysiology, laying the groundwork for future research to further elucidate the role of these SNPs in the development and progression of PCOS.

MATERIALS AND METHODS

This case-control study included 300 female patients aged 15-45 years seeking care at the Gynaecology Outpatient Department from the duration of September 2022 to September 2023 in Malla Reddy Institute of Medical Sciences (MRIMS), Telangana, India.

diagnosed with PCOS. In this study, 300 females case subjects who were diagnosed with PCOS and 300 females (control) who were not diagnosed with PCOS, having regular menstrual cycle and showing no signs of clinical or biochemical hyperandrogenism were included. Prior to participation, all participants provided written informed consent. The diagnosis of PCOS in recruited patients adhered to the Rotterdam 2003 criteria [6]. Ethical clearance for the study protocol was obtained from the Institutional Ethics Committee of Malla Reddy Institute of Medical Sciences (MRIMS) and IRB: Malla Reddy Institute of Medical Sciences, No: MRIMS/DHR-IEC-20/2022. To maintain homogeneity in the study group, individuals using medications known to impact hormonal, lipid, carbohydrate metabolisms were excluded from participation in this study.

Inclusion criteria:

- A total of 300 patients were diagnosed with PCOS with a history of missed or irregular menstruation and/or infertility, which attended the OBGY OPD of the study hospital, were included as cases.
- The study included 300 age-matched non-hirsute normo-ovulatory female subjects selected from the female healthcare workers of the institute who were willing to participate in the study, as control subjects.
- All the PCOS patients (case group) were included following Rotterdam 2003 criteria [6]. (presence of two of the following: oligo/anovulation, clinical and biochemical signs of hyperandrogenism, and polycystic ovaries on ultrasonography).

Exclusion criteria

- Females who were taking oral contraceptive pills, oral steroids, had a habit of drinking alcohol or smoking, underwent hormone replacement therapy, or any medications that affected endocrine parameters or lipid profile were excluded.
- Pregnant females and those suffering from hypertension, diabetes mellitus, dyslipidemia, thyroid diseases, hyperprolactinemia, ovarian tumour (blood tests and USG were conducted for all cases and control subjects), critically ill patients, and those with BMI >25 kg/m^2 were also excluded.

Study Procedure

Fasting blood samples were collected from patients (venous). Blood (5 mL) was withdrawn and distributed into an anticoagulant-free plain tube (2 mL) and an Ethylene Diamine Tetra-acetic Acid (EDTA) tube (3 mL). The blood sample in the plain tube was centrifuged after 30 minutes of sampling, and serum was isolated and stored at -20°C and sent to the laboratory for biochemical analysis. The sample in the plain tube was used for hormonal assay. The EDTA blood was stored properly at -20°C for DNA extraction. The DNA from study subjects was isolated from peripheral blood (EDTA sample) using the standard phenol-chloroform method [7]. The integrity of genomic DNA was tested by resolving DNA extracts on a 0.8% agarose gel by electrophoresis (Low Electroendosmosis (EEO), Sisco Research Laboratories (SRL)). PCR/RFLP: Reference sequence and details of SNPs, PCR primers' design, and restriction enzymes were obtained by searching the University of California Santa Cruz (UCSC) Genome Bioinformatics Site, Primer3 program, and New England Biolabs (NEB) cutter program, respectively.

Gene expression analysis: Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) genotyping was utilised for the examination of FSHR, LHR, PPAR-γ, and INSR polymorphisms. Each PCR reaction was carried out in a total volume of 50 µL, consisting of 2.5 µL of extracted DNA, 50 pmol/µL of each primer, 100 µM dNTP, 1 U/µL unit of Taq DNA polymerase, and 2 mM $MgCl^2$. The PCR-RFLP assay employed specific primer sets, with their corresponding annealing temperatures and restriction enzymes detailed in [Table/Fig-1]. Following the PCR, electrophoresis on 2.0% agarose gels and 4.0% agarose gels for restriction enzyme products was conducted, followed by staining with ethidium bromide for visualisation. To ensure precision, three individuals re-evaluated all gels blindly, and 15% of the analyses were randomly repeated. The primary outcome of the study is to investigate the contribution of SNPs in the FSHR, LHR, PPAR-γ, and INSR genes to the pathogenesis of PCOS. The secondary outcome focusses on exploring the interplay between genetic factors, environmental influences and hormonal imbalances in the development and progression of PCOS.

STATISTICAL ANALYSIS

For Statistical analyses, Pearson's Chi-square test was employed to assess the relative association between patients and controls regarding genotype and allele frequencies. Odds Ratios (ORs) and corresponding 95% Confidence Intervals (CIs) were calculated using Statistical Package for Social Sciences (SPSS) version 13.0. Significance levels were categorised as follows: $p<0.01$ denoted a strong association, and from $p=0.01$ to 0.05, a weaker but still significant association was recognised.

RESULTS

The current study included 300 female control who were not diagnosed with PCOS, having regular menstrual cycle and showing no signs of clinical or biochemical hyperandrogenism and 300 female case subjects who were diagnosed with PCOS.

A number of SNPs, including AA, GA, and GG, were analysed to assess the expression of the LHR gene in PCOS and non PCOS women. These markers were evaluated and expressed as mean±Standard Error (SE). In the LHR gene, the AA genotype was observed in 19.6% of PCOS women and 28.0% of non PCOS women. The GA genotype was found in 59.3% of PCOS women and 43.6% of non PCOS women. While the GA genotype showed a higher frequency in PCOS women, this difference was not statistically significant when considered individually. However, when combined with the GG genotype (GA+GG group), the difference became statistically significant ($p=0.016$). The GG genotype was observed in 21.0% of PCOS women and 28.3% of non PCOS women, with a statistically significant difference ($p=0.040$). Overall, the findings indicate that variations in the LHR gene may play a role in PCOS susceptibility [Table/Fig-2].

In [Table/Fig-3], the genotype distribution of the FSHR gene was analysed among PCOS and non PCOS women. The observed frequencies were as follows: GG genotype was found in 26.0%

Gene	Polymorphism	Primer sequence	Annealing temp (°C)	Product size (bp)	Restriction enzyme	Allele size
FSHR	Ala307Thr (rs6165)	F: 5'-CCTGCACAAAGACAGTGATG-3' R: 5'-TGGCAAAGACAGTGAAAAAG-3'	55	577	AhdI	Ala: 403+174 Thr: 403+143+31
LHR	Asn291Ser (rs12470652)	F: 5'-CTGAAGTCCAAAAGCTCAAATGCT-3' R: 5'-TGTGCTTTCACATTGTTTGGAAAAGT-3'	65	395	ECO01091	Asn: 279 Ser: 129
PPAR-γ	Pro12Ala (rs1801282)	F: 5'-GCCAATTCAAGCCCAGTC-3' R: 5'-GATATGTTTGCAGACAGTGTATCAGTGAAGG-AATCGCTTTCCG-3'	60	237	BstU-I	Pro: 125 Ala: 112
INSR	Exon17C/T (rs1799817)	F 5'-CCAAGGATGCTGTGTAGATAAG-3' R 5'-CCAACAGAGGACTCTTGGTCT-3'	55	317	PmlI	T: 317 C: 274+43

[Table/Fig-1]: Primers, annealing temperatures, product sizes, restriction enzymes and allele sizes.

LHR	PCOS women n (%)	Non PCOS women n (%)	Adjusted Odds Ratio (AOR) (95% CI)	χ^2 value	p-value
AA	59 (19.6%)	84 (28.0%)	1.00	-	-
GA	178 (59.3%)	131 (43.6%)	1.88 (1.36 to 2.60)	13.33	0.00061
GG	63 (21.0%)	85 (28.3%)	0.67 (0.46 to 0.98)	4.20	0.040
GA+GG	241 (80.3%)	216 (72.0%)	1.59 (1.09 to 2.32)	6.04	0.016

[Table/Fig-2]: Distribution of LHR between PCOS and Non-PCOS women. Statistical analysis was performed using Pearson's Chi-square test to assess genotype distribution differences between PCOS and non PCOS women. ORs and 95% CIs were calculated to estimate risk. The p<0.05 was considered statistically significant. LHR: Luteinising hormone receptor; PCOS: Polycystic ovary syndrome

of PCOS women and 23.6% of non PCOS women; GA genotype was observed in 49.3% of PCOS women and 49.6% of non PCOS women; and AA genotype was detected in 24.6% of PCOS women and 26.6% of non PCOS women. SNPs such as GG, GA, and AA were evaluated and expressed as mean±Standard Error (SE).

FSHR	PCOS women n (%)	Non PCOS women n (%)	Adjusted Odds Ratio (AOR) (95% CI)	χ^2 value	p-value
GG	78 (26%)	71 (23.6%)	1.00	-	-
GA	148 (49.3%)	149 (49.6%)	1.04 (0.72 to 1.50)	0.16	0.85
AA	74 (24.6%)	80 (26.6%)	0.89 (0.59 to 1.35)	0.40	0.60
GA+AA	222 (74%)	229 (76.3%)	0.96 (0.68 to 1.36)	0.32	0.82

[Table/Fig-3]: Distribution of FSHR between PCOS and Non-PCOS women. Statistical analysis was performed using Pearson's Chi-square test to evaluate genotype distribution differences between PCOS and non PCOS women. ORs and 95% CIs were calculated to estimate risk. p<0.05 was considered statistically significant. FSHR: Follicle-stimulating hormone receptor; PCOS: Polycystic ovary syndrome

The GG genotype showed a slightly higher frequency in PCOS women (26.0%) than in non PCOS women (23.6%), but this difference was not statistically significant (p=0.85). The GA genotype was nearly identical in both groups (p=0.85), indicating no significant difference. Similarly, the AA genotype was slightly more frequent in non PCOS women (26.6%) compared to PCOS women (24.6%), but the difference was not statistically significant (p=0.60). When GA and AA genotypes were combined (GA+AA group), there was no significant association with PCOS susceptibility (p=0.82). Thus, the analysis suggests that FSHR gene polymorphisms do not show a significant association with PCOS risk in this study population [Table/Fig-3].

In [Table/Fig-4], the genotype distribution of the INSR gene was analysed among PCOS and non PCOS women. The observed frequencies were as follows: CC genotype was found in 76.3% of PCOS women and 87.0% of non PCOS women; CT genotype was observed in 1.3% of PCOS women and 1.0% of non PCOS women; and TT genotype was detected in 22.3% of PCOS women and 12.0% of non PCOS women.

INSR gene	PCOS women n (%)	Non PCOS women n (%)	Adjusted Odds Ratio (AOR) (95% CI)	χ^2 value	p-value
CC	229 (76.3%)	261 (87.0%)	1.00	-	-
CT	4 (1.3%)	3 (1.0%)	1.52 (0.33 to 6.98)	0.03	0.58
TT	67 (22.3%)	36 (12.0%)	2.16 (1.34 to 3.47)	10.70	0.002
CT+TT	71 (23.6%)	39 (13.0%)	2.05 (1.30 to 3.22)	10.70	0.002

[Table/Fig-4]: Distribution of INSR gene PCOS and non PCOS women. Statistical analysis was performed using Pearson's Chi-square test to assess genotype distribution differences between PCOS and non PCOS women. ORs and 95% CIs were calculated to estimate risk. p<0.05 was considered statistically significant. INSR: Insulin receptor gene; PCOS: Polycystic ovary syndrome

SNPs such as CC, CT, and TT were evaluated and expressed as mean±SE. The CC genotype was more frequent in non PCOS women (87.0%) than in PCOS women (76.3%), indicating that the wild-type CC genotype was more common in controls. The CT genotype was observed in 1.3% of PCOS cases and 1.0% of controls, with no statistically significant difference (p=0.58). The TT genotype, however, was significantly more frequent in PCOS women (22.3%) compared to non PCOS women (12.0%), showing a statistically significant association with PCOS risk (p=0.002). When combining CT and TT genotypes, the CT+TT group was more frequent in PCOS women (23.6%) than in controls (13.0%), also showing statistical significance (p=0.002). Thus, the results suggest that the TT genotype of the INSR gene is significantly associated with PCOS susceptibility, whereas the CT genotype alone does not show a significant difference [Table/Fig-4].

In [Table/Fig-5], the PPAR-γ gene was analysed in PCOS and non PCOS women. The observed genotype frequencies were: CC in 80.3% of PCOS women and 100% of non PCOS women, CG in 19.6% of PCOS women but absent in controls and GG in 0% of both groups. SNPs such as CC, CG, and GG were evaluated and expressed as mean±SE. The CG genotype was found exclusively in PCOS cases (19.6%) but absent in controls, making statistical comparisons challenging. The GG genotype was not observed in either group, preventing meaningful analysis. Given that CG and GG genotypes were not present in the control group, statistical comparisons could not be performed for these variants. The observed differences suggest a potential association of the CG genotype with PCOS, but further validation in larger cohorts is needed [Table/Fig-5].

PPAR-γ	PCOS women n (%)	Non PCOS women n (%)	Adjusted Odds Ratio (AOR) (95% CI)	χ^2 value	p-value
CC	241 (80.3%)	300 (100%)	1.00	-	-
CG	59 (19.6%)	0	-	-	-
GG	0	0	-	-	-

[Table/Fig-5]: Distribution of PPAR-γ gene PCOS and Non-PCOS women. Statistical analysis was performed using Pearson's chi-square test to assess genotype distribution differences between PCOS and non PCOS women. ORs and 95% CIs were calculated to estimate risk. p<0.05 was considered statistically significant. PPAR-γ: Peroxisome proliferator-activated receptor gamma; PCOS: Polycystic ovary syndrome

DISCUSSION

The PCOS is a prevalent infertility condition that impacts a substantial number of women worldwide. It is the leading cause of anovulatory infertility in women and stands as the most common endocrine disorder among women of reproductive age, with a prevalence ranging from 8% to 13%, depending on criteria and studied populations [8]. PCOS is characterised by the presence of multiple follicular cysts in enlarged ovaries, and individuals with this condition face increased risks of infertility, obesity, and Insulin Resistance (IR) [9,10]. Given its multifactorial and intricate nature, diagnosing PCOS can be challenging due to the overlap of symptoms. The pathophysiology involves various pathways and proteins, making sole reliance on single genetic diagnostic tests difficult. Despite progress in PCOS management and diagnosis, there is still much to unravel regarding the molecular factors and signaling pathways involved in the syndrome [11]. PCOS is recognised as a polygenic and multifactorial disorder, with numerous genes influencing fertility either directly or indirectly [12,13]. However, despite extensive research and studies on PCOS patients from diverse families, the search for fully penetrant variant(s) has remained inconclusive [11,14]. Numerous studies have presented evidence of the genetic component of PCOS, highlighted by the elevated risk ratio among siblings of individuals with PCOS compared to the general population [12,15,16].

PCOS is a chronic and heterogeneous clinical disorder with an unknown etiology, emphasising the complexity of the condition. However, a strong familial component suggests that genetic factors play a significant role in the disease onset [17]. Common symptoms

of PCOS include irregular menstrual cycles, hyperandrogenism, weight gain, hirsutism, diabetes, hair loss, and infertility [17,18].

In [Table/Fig-2], the distribution of LHR gene variants in cases and controls is as follows: Cases- AA=19.6%, GA=59.3%, GG=21.0%; Controls- AA=28.0%, GA=43.6%, GG=28.3%. However, it is noteworthy that a study by Kim H et al., involving 108 Korean women with endometriosis or PCOS did not find any LHβ G1052A homozygous gene variants among them [19]. Similarly, Tan ALM et al., [20] also, reported no variants in Malays or Indians with PCOS. These findings suggest that genetic variability in PCOS patients may be influenced by ethnicity and environmental factors. Notably, LHR is observed to be overexpressed in theca cells and granulosa cells from PCOS patients [21]. This study indicates that the LHCGR polymorphism (rs2293275) is improbable to be linked with the development of PCOS. Conversely, the findings from most studies [22] suggest a strong association between the rs2293275 polymorphism in exon 10 of the LHCGR gene variant and PCOS, although a limited number of reports [23] indicate otherwise.

In [Table/Fig-3], the distribution of FSHR gene variants in cases and controls is as follows: Cases- GG=26%, GT=49.3%, AA=24.6%; Controls- GG=23.6%, GA=49.6%, AA=26.6%. Nevertheless, this study investigation did not detect any notable association between the polymorphisms of FSHR rs6165 and rs6166 with PCOS. It is crucial to emphasise that prior research on the correlation between FSHR gene polymorphisms (rs6165 and rs6166) and PCOS has produced inconsistent outcomes, with some studies indicating an association, while others have not found any significant link. In contrast, Valkenburg et al., concluded that FSHR gene variants exhibited a strong association with the severity of PCOS and its clinical features, although not with the overall risk of the disease [24]. A recent GWAS study linked the FSHR gene with PCOS in Han Chinese and European-derived populations [25]. Variants rs6165 (Thr307Ala) and rs6166 (Asn680Ser) in exon 10 of the FSHR gene have been investigated in relation to PCOS [26]. However, meta-analysis results only associated SNP rs6166 (Asn680Ser) with PCOS, while rs6165 (Thr307Ala) did not [27]. Another polymorphism, rs2268361, was associated with PCOS in the Chinese but not Dutch population [28,29]. The relationship between FSHR genotype and PCOS development remains unclear, suggesting FSHR gene variants may be a risk factor for PCOS regardless of racial differences.

In [Table/Fig-4], the distribution of INSR gene variants is as follows: Cases- CC=76.3%, CT=1.3%, TT=22.3%; Controls- CC=87.0%, CT=1.0%, TT=12.0%. The INSR gene encodes the insulin receptor, playing a crucial role in insulin signaling. Dysregulation of INSR function is implicated in IR, a hallmark of PCOS. Genetic variations in INSR may contribute to IR and hyperinsulinemia, key features of PCOS pathogenesis, highlighting its clinical significance in disease development and management. Furthermore, we observed that the TT and CT genotype frequencies were significantly lower in both cases and controls compared to the wild-type genotype (CC).

Dunaif A and Thomas A suggested that IR associated with PCOS may have a distinct genetic basis compared to IR linked to obesity or insulin-independent diabetes [30]. Ezeh U et al., reported that IR in PCOS patients was associated with a reduction in the GLUT-4 transporter in adipocytes [31]. The mechanisms underlying IR in PCOS may involve defects in insulin binding to its receptor or alterations in insulin signal transmission. In [Table/Fig-5], the distribution of PPAR-γ gene variants is as follows: Cases- CC=80.3%, CG=19.6%, GG=0%; Controls- CC=100%, CG=0%, GG=0%. The GA+GG grouping represents the dominant genetic model, a common approach in genetic association studies. This model helps assess whether the G allele (GA/GG) is associated with PCOS risk compared to the AA genotype alone, providing greater statistical power and biological relevance. A recent study conducted in South India observed a marginally significant difference in allelic frequency (p=0.05) for a particular polymorphism in PCOS women (N=243) compared to controls (N=281), while no significant difference was noted in genotypic frequency (p=0.23). The PPAR-γ gene encodes a nuclear receptor involved in adipocyte differentiation and insulin sensitivity. Variations in this gene are associated with altered lipid metabolism and IR in PCOS. Understanding PPAR-γ gene variants can offer insights into the pathogenesis of metabolic disturbances in PCOS and guide targeted therapeutic interventions. This study investigation affirms that the Pro12Ala polymorphism within the PPAR-γ gene offers robust protection against PCOS risk, whereas the His447H variant does not make a significant contribution. Both SNPs exert an influence on insulin-related traits and enhance glucose metabolism in Indian women with PCOS. The Ala variant, associated with reduced transcriptional activity of PPAR-γ, may impact IR. It amplifies insulin action by suppressing lipolysis, resulting in decreased production of Free Fatty Acids (FFAs) and their storage in adipocytes. The diminished PPAR-γ activity might also modify the expression of genes like GLUT-4 and adiponectin, possessing putative PPAR response elements. This alteration leads to enhanced glucose utilisation in skeletal muscles, inhibition of hepatic glucose production, and increased storage of FFAs in adipose tissues. In conclusion, this study investigated the genetic variants in LHR, FSHR, INSR, and PPAR-γ genes in PCOS patients and controls. The distribution of LHR gene variants showed a significant difference between cases and controls, with variations in allele frequencies observed in different ethnic populations. Notably, the overexpression of LHR in theca and granulosa cells from PCOS patients further supports its involvement in the pathogenesis of the syndrome. On the contrary, this study did not reveal a significant association between the FSHR gene polymorphisms (rs6165 and rs6166) and PCOS. However, previous investigations into this association have presented diverse findings, with some studies indicating a connection and others failing to identify a significant link.

Valkenburg O et al., noted that FSHR gene variants exhibited a strong association with the severity of PCOS and its clinical features, but not with the overall risk of the disease [24]. The present study also identified a distinct distribution of INSR gene variants in cases and controls, with the TT and CT genotypes showing lower frequencies compared to the wild-type genotype. IR associated with PCOS may have a different genetic basis compared to IR related to obesity or insulin-independent diabetes, as suggested by Dunaif A and Thomas A [30]. Moreover, Ezeh U et al., linked IR in PCOS patients to a reduction in the GLUT-4 transporter in adipocytes [31]. Furthermore, the current study analysis of the PPAR-γ gene variants uncovered a noteworthy distinction in allelic frequency. The Pro12Ala polymorphism exhibited robust protection against PCOS risk, whereas the His447His variant did not contribute significantly. Both variants of the PPAR-γ gene impacted insulin-related traits and enhanced glucose metabolism among Indian women with PCOS. The diminished transcriptional activity of PPAR-γ associated with the Ala variant may contribute to the modulation of IR, thereby improving glucose utilisation and storage in adipose tissues. Overall, the findings of the study contribute to the understanding of the genetic basis of PCOS and its implications for IR and glucose metabolism in affected individuals. The clinical importance of this study lies in its potential to elucidate the genetic basis of PCOS. By investigating SNPs in key genes associated with PCOS pathogenesis, such as FSHR, LHR, PPAR-γ, and INSR, this research aims to uncover novel insights into the molecular mechanisms underlying the disorder. Understanding the genetic factors contributing to PCOS can inform personalised diagnostic and therapeutic approaches, ultimately improving patient care and outcomes. Additionally, identifying genetic biomarkers associated with PCOS susceptibility may facilitate early detection and intervention strategies, leading to more effective management of this prevalent endocrine disorder.

Limitation(s)

The study's case-control design introduces potential selection bias and limits causal inference. The sample size may be inadequate to detect small genetic effects or account for population heterogeneity. Moreover, findings may lack generalisability to diverse populations due to potential ethnic or geographic differences. Additionally, the study's scope may not encompass all relevant genetic variants or environmental factors contributing to PCOS pathogenesis. Future research with larger, more diverse cohorts and longitudinal designs could address these limitations and provide a more comprehensive understanding of the genetic underpinnings of PCOS.

CONCLUSION(S)

In conclusion, this case-control study delves into the potential contribution of single SNPs in FSHR, LHR, PPAR-γ, and INSR genes to the pathogenesis of PCOS. While our findings provide valuable insights into the genetic landscape of PCOS, further research is warranted to elucidate the precise role of these SNPs in the development and progression of the syndrome. Additionally, considering the multifactorial nature of PCOS, future studies should explore the interplay between genetic factors, environmental influences, and hormonal imbalances to comprehensively understand PCOS pathophysiology.

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