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ASSOCIATIONS BETWEEN FAT MASS AND OBESITY ASSOCIATED (FTO) GENE rs9939609 A/T POLYMORPHISM AND POLYCYSTIC OVARY SYNDROME (PCOS) IN SOUTH INDIAN POPULATION

Shyni Mahadevan[1], Mani Mariappa[2], Suganthi Ramasamy[3]*, Aarthi Chinnaswamy Ravi[4], Sumathy Raj[5], Aishwarya Vetrivel[6]

[1]Department of Biotechnology, Dr NGP Arts and Science College, Coimbatore - 641 048, Tamil Nadu, India. E-mail: shynimaha@gmail.com
[2]Founder & Chief, Mani Microbiological laboratory, R S Puram, Coimbatore - 641 002, Tamil Nadu, India.
E-mail: director@microlabindia.com
[3]Department of Biotechnology, Dr NGP Arts and Science College, Coimbatore - 641 048, Tamil Nadu, India.
E-mail: suganthir@drngpasc.ac.in
[4]Department of Biotechnology, Dr NGP Arts and Science College, Coimbatore - 641 048, Tamil Nadu, India. E-mail: aarthi.cr@drngpasc.ac.in
[5]Department of Biotechnology, Dr G R Damodaran College of Science, Coimbatore - 641 014, Tamil Nadu, India.
E-mail: sumathy.r@grd.edu.in
[6]Department of Biotechnology, Dr G R Damodaran College of Science, Coimbatore - 641 014, Tamil Nadu, India.
E-mail: aishwarya.v@grd.edu.in

ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder affecting women of reproductive age, characterized by hyperandrogenism, ovulatory dysfunction, and metabolic complications such as obesity and insulin resistance. The **fat mass and obesity-associated (FTO)** gene is recognized as a major obesity susceptibility gene and has been implicated in the pathogenesis of PCOS through its role in energy metabolism and body weight regulation.

Objective: This study was undertaken to evaluate the association between polymorphisms in the FTO gene and the risk of PCOS among a population of South Indian women.

Methods: A case-control study was conducted involving 160 participants (80 women clinically diagnosed with PCOS and 80 healthy controls). Clinical evaluations included Body Mass Index (BMI)**,** and biochemical assays measured levels of luteinizing hormone (LH)**,** follicle-stimulating hormone (FSH)**,** fasting glucose, and cholesterol. Genomic DNA was isolated from blood samples using a split-second isolation protocol. Genotyping of the FTO SNP rs9939609 was performed using Tetra-primer Amplification Refractory Mutation System-Polymerase Chain Reaction (T-ARMS PCR)**.** Statistical significance was determined using student t-tests and chi-square analysis.

Results: PCOS subjects exhibited significantly higher mean BMI (21.77 ± 2.42 kg/m² for control vs. 25.67 ± 3.41 kg/m² PCOS), fasting glucose (112.28 ± 25.19 for control mg/dL vs. 188.1 ± 71.42 mg/dL for PCOS), cholesterol levels (164.91 ± 39.89 mg/dL for control vs 240.31 ± 42.44) compared to controls. FSH levels were significantly lower in the PCOS group (6.89 ± 2.44 mIU/ml for control vs 4.01 ± 1.38 mIU/ml for PCOS). For the FTO rs9939609 polymorphism, the frequency of the risk A allele was 76% in PCOS patients and 84% in controls, while the T allele frequency was 65% in PCOS patients and 95% in controls. However, statistical analysis revealed no significant difference in the distribution of FTO genotypes or alleles between the groups ($p > 0.05$).

Conclusion: Although clinical and biochemical markers such as increased BMI, glucose, and cholesterol were significantly associated with the syndrome, the FTO rs9939609 polymorphism did not show a statistically significant association with PCOS risk in the South Indian women studied. These findings suggest that FTO variants may act differently across different ethnicities, and further research with larger cohorts is needed to elucidate the genetic architecture of PCOS.

KEYWORDS: Polycystic ovary syndrome**;** FTO gene**;** Single nucleotide polymorphism**;** Obesity and PCOS

INTRODUCTION

The polycystic ovary syndrome (PCOS) is a heterogeneous collection of signs and symptoms that, gathered together, form a spectrum of a disorder which leads to disturbances in the reproductive, endocrinal and metabolic functions of women [1,2]. PCOS is a condition of uncertain etiology, with an indistinct pathophysiology and multiple endocrinal, reproductive and metabolic anomalies and is the single most common female disorder encountered in women of reproductive age [1,2].

The majority of PCOS patients have ovarian dysfunction, with 70% to 80% of women with PCOS presenting with oligomenorrhea or amenorrhoea. Among those with oligomenorrhea, 80% to 90% will be diagnosed with PCOS [3,4]. Because of hyperandrogenism and insulin resistance, the obesity of PCOS is of the android (central) type, which results in an increased waist-to-hip ratio and which is highly associated with diabetes mellitus and increased

cardiovascular risk [5]. These consequences of PCOS are worsened by obesity but appear to be present in all PCOS patients, including those who are not obese [5].

The pathogenesis of PCOS is not fully understood. Heritable tendencies have long been recognized, but complex interactions exist between genetic and environmental factors [6]. The manifestations of PCOS typically begin in early adolescence, and many investigators have hypothesized that peripubertal obesity promotes the development of adolescent PCOS [7].

In recent years, a total of more than 100 candidate genes have been set out to explore the associations between single nucleotide polymorphism (SNP) and PCOS [8], such as fat mass and obesity associated (FTO) gene. The human FTO gene is located on the chromosome 16q12.2 with a wide expression range of almost all tissues [9, 10]. The protein coded by FTO gene belongs to 2-oxoglutarate-dependent nucleic acid demethylase, involving energy metabolism [11]. In 2007, a genome-wide association study reported that FTO is associated with body mass index (BMI) and obesity [8]. Obesity is a common characteristic in PCOS patients [12]. It is reported that more than 50% PCOS cases are overweight/obese [12]. So it is reasonable to assume that FTO gene might play a role in the pathogenesis of PCOS via BMI and/or obesity.

Recently, a common single nucleotide polymorphism (SNP) (rs9939609) in the first intron of FTO gene with T to A change is widely investigated in PCOS [13]. However, the results from different studies are controversial. Some studies observed the positive association of FTO with PCOS [13-16], while others studies found the opposite relationship [17-19]. A recent meta-analysis by Cai et al. showed that FTO rs9939609 polymorphism was associated with PCOS risk in East Asians but not in overall population [20]. Imperfectly, this meta-analysis considered only one genetic model and not all included studies were involved in FTO rs9939609 polymorphism. Therefore, we carried out current systemic review and meta-analysis to clarify the associations between the SNP rs9939609 and susceptibility to PCOS.

MATERIALS AND METHODS

Collection of Samples: In this genetic study carried out at Dr. N G P arts and Science College, Coimbatore from July to December, 2025, all the 160 subjects were native to India and were females. The study population considered of two groups of women 1) clinically diagnosed with PCOS (n=80) and 2) normal healthy controls (n=80). The blood samples were collected with oral consent from Mani Microbiological Laboratory, Coimbatore, Tamil nadu, India. Blood samples (5ml) were drawn after an overnight fast of 12-16 hours, using standardized laboratory techniques.

Clinical and Biochemical data: Clinical and Biochemical data, such as Body mass index (BMI), age, serum concentrations of Luteinising hormone (LH) and Follicle Stimulating Hormone (FSH), Glucose level, Cholesterol content, were collected from the study individuals. The comparison was done between the two groups of patients diagnosed with PCOS and normal healthy controls.

SNPs and polymorphism genotyping analysis: Selected polymorphisms were chosen from the NCBI site (http://genome.ucsc.edu/cgi-bin/hgPcr?command=start).

The specificity of all the primers was verified using *In silico* PCR. Both the primers were made to run on BLAST tool and thus the primers were selected based on the results. DNA was isolated using Split Second DNA isolation method. The reaction volume containing genomic DNA to be amplified and restricted contains 4µl nuclease free water, 1µl inner forward primer (IF 5'TAGGTTCCTTGCGACTGCTGTGAATATA-3'), 1 µl of inner reverse primer (IR 5'GAGTAACAGAGACTATCCAAGTGCATCTCA-3'), 1µl of outer forward primer (OF 5'TGGCTCTTGAATGAAATAGGATTCAGAA-3'), 1µl outer reverse primer OR (5'AGCCTCTCTACCATCTTATGTCCAAACA-3'), 5µl template DNA, and 12 µl of amplicon. Tetra-primer amplification refractory mutation system polymer chain reaction (T-ARMS PCR) was performed using the thermal cycler as follows: an initial denaturation at 95ºC for 5 min, followed by 40 cycles of denaturation at 95 ºC for 30 seconds, annealing at 55 ºC for 30 seconds, extension at 72 ºC for 30 seconds and the final extension at 72 ºC for 5 min. All PCR products were visualized under UV light using by 2% agarose gel electrophoresis stained with ethidium bromide. T-ARMS PCR Analysis of FTO gene is AT-321 bp, 210 bp, 178bp; TT-321bp, 178 bp; AA-321 bp, 201bp.

Statistical Analysis: To determine the significance of clinical and biochemical characters in the prognosis of polycystic ovary syndrome and to determine their impact on the development of the diseases statistical analysis were done using SPSS (Statistical package for social science) for windows version 16(IBM, USA) to determine the p-value. Comparisons between groups on continuous measures were made using the student t-test and a p-value of (<0.05) was considered significant at 95% levels of significance.

RESULTS

A total of 160 women, comprising 80 clinically diagnosed PCOS patients and 80 healthy controls, were included in the study. The clinical, hormonal and biochemical characteristics of the study participants are presented in Table 1. The mean age did not differ significantly between the control and PCOS groups (28.74 ± 4.99 versus 27.79 ± 4.45 years; p = 0.18), indicating comparability of the groups with respect to age.

Table 1: Clinical, Biochemical and metabolic parameters of the study groups

Parameters	**Control (n = 80)** [mean ± SD]	**PCOS (n = 80)** [mean ± SD]	**p-Value**
Age (Years)	28.74 ± 4.99	27.79 ± 4.45	0.18
BMI (kg/m²)	21.77 ± 2.42	25.67 ± 3.41	0.00***

LH (mIU/ml)	4.20 ± 1.56	9.07 ± 3.11	0.00***
FSH (mIU/mL)	6.89 ± 2.44	4.01 ± 1.38	0.00***
Glucose (mg/dL)	112.28 ± 25.19	188.1 ± 71.42	0.00***
Cholesterol (mg/dL)	164.91 ± 39.89	240.31 ± 42.44	0.00***

**** is P ≤ 0.001 (The difference between the paired measurements IS statistically significant (p = < 0.001). At the 0.05 significance level there is a significant change between the two measurement points.)*

Women with PCOS showed a significantly higher BMI compared with controls (25.67 ± 3.41 versus 21.77 ± 2.42 kg/m²; $p < 0.001$). Significant alterations in reproductive hormone levels were also observed. The mean LH concentration was significantly elevated in the PCOS group (9.07 ± 3.11 versus 4.20 ± 1.56 mIU/mL; $p < 0.001$), whereas FSH levels were significantly lower (4.01 ± 1.38 versus 6.89 ± 2.44 mIU/mL; $p < 0.001$). Furthermore, fasting glucose and total cholesterol levels were significantly higher among women with PCOS compared with healthy controls ($p < 0.001$ for both parameters).

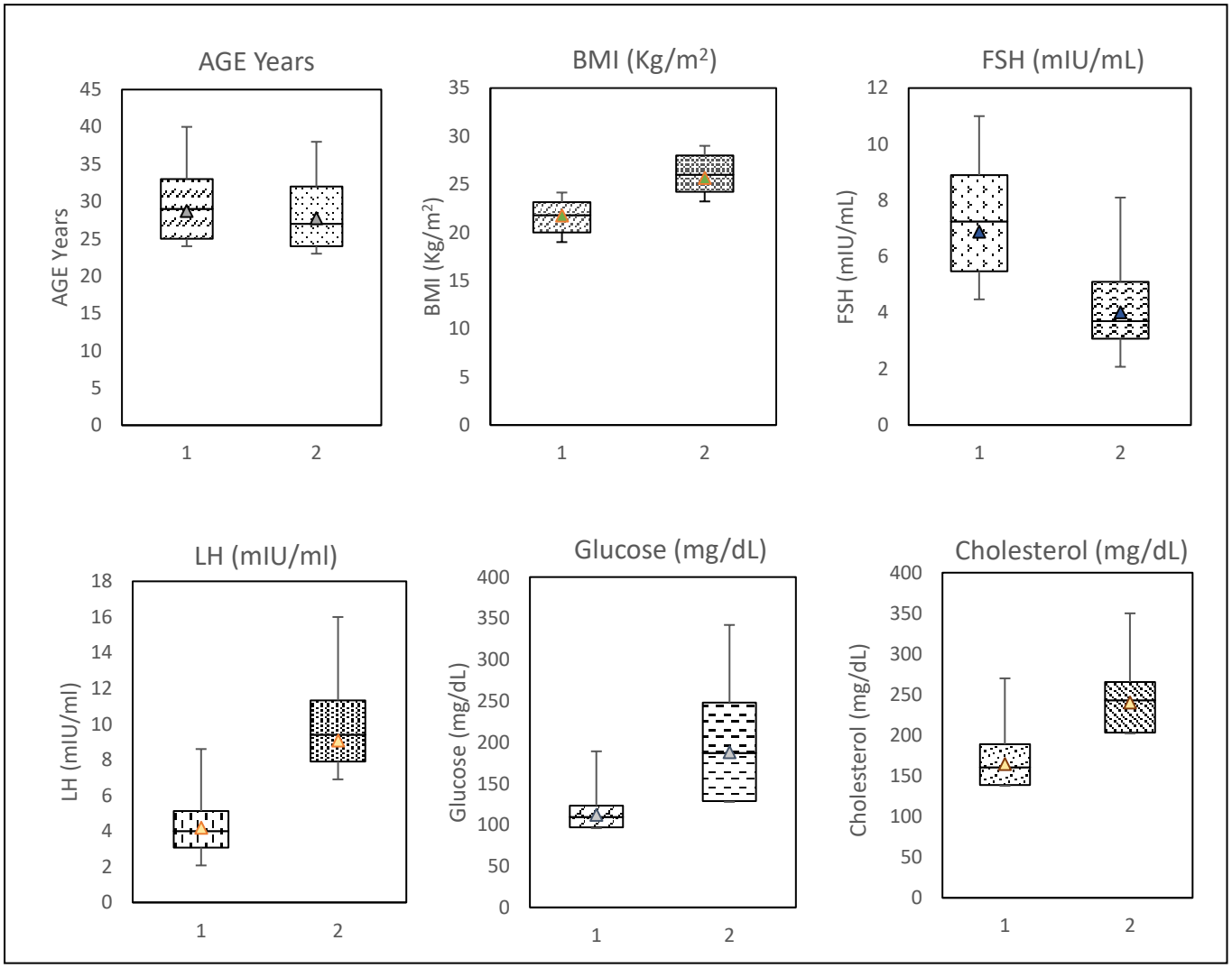

Figure 1: Distribution of age, BMI, Hormonal and biochemical Parameters among Control and PCOS women

Box and Whisker plots showing the distribution of age, body mass index (BMI), Luteinizing hormone (LH), Follicle Stimulating hormone (FSH), total Cholesterol and glucose levels. 1- Controls, 2 - PCOS. Mean values are indicated separately.

The genotype distribution of the FTO rs9939609 polymorphism is presented in Table 2. The TT genotype was observed in 38.75% of controls and 27.5% of PCOS cases, whereas the heterozygous TA genotype was observed in 41.25% and 50.0% of controls and PCOS cases, respectively. The AA genotype was present in 20.0% of controls and 22.5% of PCOS cases.

Although the TA genotype showed a numerically higher odds ratio for PCOS compared with the TT reference genotype (OR = 1.71; 95% CI: 0.84–3.49), this association was not statistically significant (p = 0.141). Similarly, the AA genotype did not show a significant association with PCOS susceptibility (OR = 1.59; 95% CI: 0.67–3.77; p = 0.297).

Table 2: Genotype and Allelic frequency of the FTO (rs9939609) SNP A>T gene polymorphisms in PCOS and Controls

Frequency			OR (95% CI)	χ^2	*P* - value
	Control (n=80)	PCOS n=(80)			
Genotype					
TT	31 (38.75)	22 (27.5)	1.00 (Reference)		
TA	33 (41.25)	40 (50)	1.71 (0.84-3.49)	2.17	0.141
AA	16 (20)	18 (22.5)	1.59 (0.67-3.77)	1.09	0.297
Dominant Model					
TT	31 (38.75)	22 (27.5)	1.00 (Reference)		
TA+AA	49 (61.25)	58 (72.5)	1.67 (0.86-3.25)	2.29	0.131
Recessive Model					
TT + TA	64 (80.00)	62 (77.50)	1.00 (Reference)		
AA	16 (20.00)	18 (22.50)	1.16 (0.54-2.48)	0.15	0.699
Allelic Model					
T	95 (59.38%)	65 (40.63%)	1.00 (Reference)		
A	84 (52.50%)	76 (47.50%)	1.32 (0.85-2.06)	1.53	0.215

OR- Odds Ratio, CI – Confidence interval, Recessive indicates AA vs. TA, TT, Dominant indicates TT vs. TA, AA, χ^2 - Chi Square, p - Values are from Pearson's chi-square test ($p<0.05$)

Under the dominant genetic model, carriers of the A allele (TA + AA) demonstrated an increased but statistically non-significant risk of PCOS compared with the TT genotype (OR = 1.67; 95% CI: 0.86–3.25; p = 0.131). Likewise, the recessive model did not reveal a significant association between the AA genotype and PCOS risk (OR = 1.16; 95% CI: 0.54-2.48; p = 0.699). The allelic comparison also demonstrated no statistically significant association between the rs9939609 alleles and PCOS susceptibility (OR = 1.32; 95% CI: 0.85–2.06; p = 0.215).

Overall, the findings demonstrate significant differences in BMI, LH, FSH, glucose and cholesterol between women with PCOS and healthy controls. However, the FTO rs9939609 polymorphism was not significantly associated with susceptibility to PCOS in the present South Indian study population.

DISCUSSION

Polycystic ovary syndrome (PCOS) is a complex endocrine and metabolic disorder characterized by considerable heterogeneity in its reproductive, hormonal and metabolic manifestations. In the present study, women with PCOS demonstrated significantly higher BMI, LH, fasting glucose and total cholesterol levels, together with significantly lower FSH concentrations compared with healthy controls. These findings support the established concept that PCOS is associated with both reproductive dysfunction and significant metabolic abnormalities [4, 11].

The significantly higher BMI observed among women with PCOS is consistent with the well-established relationship between excess adiposity and PCOS. Obesity may influence the development and progression of PCOS by aggravating insulin resistance, hyperinsulinaemia and hyperandrogenism [21]. Although obesity is not present in all women with PCOS, increased adiposity and particularly abdominal fat accumulation are important contributors to metabolic dysfunction and adverse reproductive outcomes [21]. In the present study, the significantly elevated glucose and cholesterol levels in the PCOS group further indicate the presence of metabolic disturbances. PCOS is increasingly recognized as a metabolic as well as reproductive disorder, and insulin resistance may occur independently of obesity in affected women [11].

The hormonal profile observed in the present study, characterized by significantly elevated LH and reduced FSH concentrations, is consistent with the dysregulation of the hypothalamic-pituitary-ovarian axis commonly associated with PCOS. Altered gonadotropin secretion contributes to increased ovarian androgen production and impaired follicular maturation, resulting in ovulatory dysfunction and other reproductive manifestations of the syndrome [4].

The present study did not demonstrate a statistically significant association between the FTO rs9939609 polymorphism and susceptibility to PCOS. Although the TA and AA genotypes showed numerically increased odds ratios compared with the TT genotype, the associations were not statistically significant. Similarly, no significant association was observed under the dominant, recessive or allelic genetic models. Therefore, the findings of the present study do not support an independent association between FTO rs9939609 and PCOS susceptibility in the South Indian women investigated.

The FTO gene is one of the most extensively investigated genetic loci in relation to body mass index and obesity. Variants in the FTO gene were identified through genome-wide association studies as important determinants of body weight and obesity susceptibility [22]. Because obesity and metabolic dysfunction are common features of PCOS, the FTO rs9939609 polymorphism has subsequently been investigated as a potential genetic factor contributing to PCOS susceptibility. However, the results of individual studies and pooled analyses have been inconsistent.

A meta-analysis by Cai et al. [23] evaluated the association between FTO rs9939609 and PCOS susceptibility and reported that the association in the overall population was weak and unstable following sensitivity analysis. Their subgroup analysis demonstrated a significant association among East Asian populations but not among Caucasian

populations, suggesting that the effect of the FTO variant may vary according to ethnic background. This observation is particularly relevant to the present study, as the absence of a significant association in South Indian women may similarly reflect population-specific genetic differences.

In contrast, a subsequent systematic review and meta-analysis by Liu et al. [24], involving 5,010 PCOS patients and 5,300 controls, reported a significant association between the FTO rs9939609 A/T polymorphism and PCOS susceptibility under several genetic models. The authors reported that the A allele was associated with an increased risk of PCOS and concluded that rs9939609 may contribute to disease susceptibility. The difference between the findings of Liu et al. [24] and those of the present study may be attributable to differences in ethnicity, sample size, genetic background and environmental influences.

The discrepancy between the available meta-analyses further emphasizes the complexity of the association between FTO rs9939609 and PCOS. Cai et al. [23] concluded that the overall association was not robust and appeared to be influenced by ethnicity, whereas Liu et al. [24] reported significant associations across multiple genetic models. Therefore, the contribution of FTO rs9939609 to PCOS susceptibility may not be uniform across populations. Such inconsistencies are particularly important when interpreting genetic association studies in ethnically diverse populations such as those in India.

The absence of a statistically significant association in the present study may also be explained by the relatively modest sample size. Genetic variants contributing to complex diseases often exert relatively small effects, and a study involving 80 cases and 80 controls may have limited statistical power to detect small or moderate genetic associations. The relatively wide confidence intervals observed for the genotype comparisons in the present study also suggest limited precision in estimating the true effect size.

Importantly, the absence of a direct association between FTO rs9939609 and PCOS susceptibility does not necessarily exclude a role for FTO in the metabolic phenotype of PCOS. The FTO locus may influence PCOS indirectly through its effects on adiposity, body weight regulation and energy metabolism. This interpretation is supported by the present observation of significantly increased BMI among women with PCOS, despite the absence of a statistically significant difference in the rs9939609 genotype distribution between cases and controls. Previous evidence indicates that FTO variants may be more strongly associated with obesity-related phenotypes than with PCOS itself [22].

The present findings therefore support the multifactorial nature of PCOS, in which disease development is likely to result from complex interactions between multiple genetic factors, obesity, insulin resistance and environmental influences. A single nucleotide polymorphism is unlikely to independently explain the complex pathogenesis of PCOS. Future studies involving larger and ethnically diverse Indian populations should investigate rs9939609 together with other obesity-related and PCOS susceptibility genes. Furthermore, analyses adjusted for BMI, insulin resistance, androgen levels and different PCOS phenotypes may help to distinguish whether FTO contributes directly to PCOS susceptibility or primarily modifies its metabolic characteristics.

Overall, the present study demonstrates significant hormonal and metabolic alterations among women with PCOS, including increased BMI, LH, glucose and cholesterol levels and reduced FSH concentrations. However, the FTO rs9939609 polymorphism was not significantly associated with PCOS susceptibility in the South Indian population studied. These findings suggest that the genetic contribution of FTO to PCOS may be population-specific and may be mediated predominantly through its effects on obesity and metabolic dysfunction rather than acting as a direct independent determinant of PCOS.

CONCLUSION

The present study demonstrated significant hormonal and metabolic differences between women with PCOS and healthy controls, with significantly higher BMI, LH, glucose and cholesterol levels and significantly lower FSH levels observed in women with PCOS. These findings confirm the coexistence of reproductive and metabolic abnormalities in PCOS. However, the FTO rs9939609 polymorphism showed no statistically significant association with PCOS susceptibility under genotype, dominant, recessive or allelic models. The findings suggest that the influence of FTO on PCOS may vary according to ethnicity and metabolic background. Further studies involving larger South Indian populations are required to clarify the contribution of FTO gene variants to the genetic and metabolic pathogenesis of PCOS.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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