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Association of *FTO* gene variants rs9939609 and rs1421085 with polycystic ovary syndrome

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Abstract

Background: Polycystic ovary syndrome (PCOS) is among the most common complex genetic endocrinopathy, and its etiology and pathophysiology remain controversial. *FTO* is a large highly polymorphic gene and was coined as the first locus associated with adiposity. The association of the intronic variant *FTO* rs9939609 or *FTO* rs1421085 with PCOS has been controversial and unclear, mainly due to ethnic differences among populations. The present study aims to investigate the association of FTO rs9939609 or FTO rs1421085 polymorphisms with PCOS in Saudi Arabian women.

Results: A total of 98 PCOS patients and 99 healthy females were included in this study. PCR and genotyping (TaqMan®SNP Genotyping Assay) were employed. For *FTO* rs9939609, the genotype *TA* and the recessive model (*TA* + *AA*) in PCOS patients were significantly different compared with control subjects ($p = 0.008$ and $p = 0.007$, respectively). The allele frequency of the *FTO* rs9939609 gene variant was associated significantly ($p = 0.027$) with PCOS, suggesting that the A allele is a risk factor for PCOS susceptibility. However, for the *FTO* rs1421085 variant, the genotype and allele distributions did not differ significantly between PCOS patients and controls ($p > 0.05$).

Conclusions: This is the first report to study the association of *FTO* rs9939609 and *FTO* rs1421085 with PCOS in Saudi women. Results suggest that the *FTO* rs9939609 gene variant could be a genetic predisposing factor for PCOS Saudi women.

Keywords: Polycystic ovary syndrome, Fat mass and obesity-associated gene, PCOS, *FTO*, Polymorphism, Obesity, Adiposity

Introduction

Polycystic ovary syndrome (PCOS) is among the most common complex genetic endocrinopathy, and its etiology and pathophysiology remain controversial [1]. PCOS is characterised by variable metabolic and reproductive abnormalities [2–4]. Symptoms include menstrual irregularities, infertility, anovulation, elevated serum androgens, sexual dysfunction, and obesity [5, 6]. The prevalence rates of PCOS may vary according to the differences in the attributes of the study population. Worldwide, according to the generally preferred revised Rotterdam diagnostic criteria [7, 8], the prevalence rate of PCOS is between 8 and 13% in women of reproductive age [9] and 6–18% in adolescent girls [10]. To date, there is no specific gene that has been recognised for the onset of PCOS [11, 12].

Obesity is one of the factors that exasperate PCOS, and there is a general agreement that obesity is associated with the risk of developing the clinical and endocrine features of PCOS [13, 14]. Almost 38%-88% of PCOS, women are either overweight or obese [15–17]. The clinical observations have led to believe that the level of BMI can reflect the degree of severity of symptoms in PCOS patients. During adolescence, it appears that the most common precipitant of PCOS symptoms is ordinary obesity [18, 19]. Modest reductions in weight have proven to improve many symptoms in PCOS patients, such as menstrual regularity, fertility, and improving quality of life.

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This suggests that obesity is an important contributor to PCOS etiology [13–15, 19–21].

The ubiquity expressed fat mass and obesity-associated (*FTO*) gene was reported to be associated with obesity genetics [22]. *FTO* is a large highly polymorphic gene that located in chromosome *16q12.2*. *FTO* was coined as the first locus associated with adiposity [22–25]. The associations of the intronic variant *FTO* rs9939609 (T>A) or *FTO* rs1421085 (T>C) with PCOS had been controversial and unclear mainly due to ethnic differences among populations [21, 26–30]. The study aims to investigate the association between two variants of the *FTO* gene (rs9939609 and rs1421085) with PCOS in Saudi women to estimate the possible role of *FTO* gene variants in PCOS susceptibility and severity in respect to obesity. To date, there is no information regarding the association of these two variants in the Saudi population.

Materials and methods

Study design and subjects

A retrospective case–control study design was undertaken. Ninety-eight (98) Saudi Arabian women (31.05 ± 0.59 years) who had been diagnosed with PCOS were recruited from the outpatient clinic at King Khaled University Hospital, Riyadh, Saudi Arabia. Diagnosis of PCOS patients was based on the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) diagnostic criteria [31]. Based on the joint ESHRE/ASRM agreement meeting, a refined definition of PCOS was produced that included the presence of two out of the following three criteria: (1) oligo- and/or anovulation, (2) hyperandrogenism, and (3) polycystic ovaries (PCO) morphology detected by ultrasound or pelvic imaging [32, 33]. Additionally, the criteria for patients' selection were the absence of Cushing's syndrome, congenital adrenal hyperplasia, androgen-secreting tumor, hyperprolactinemia, diabetes, thyroid dysfunction, and the absence of respiratory infection and cardiovascular diseases. Ninety-nine healthy non-smoker Saudi Arabian women were chosen to serve as controls. All participants were residents of the region of Riyadh Governorate. All participants signed an informed consent that was approved by the Medical Ethics Committee of King Khalid University Hospital (KKUH). The study protocol was approved by the Institutional Review Board (IRB) of King Saud University, Riyadh, Saudi Arabia.

DNA extraction and genotyping

Three millilitres of peripheral blood were collected into ethylenediaminetetraacetic acid (EDTA)-containing tubes. Genomic DNA was extracted from patients and controls' blood [34]. SNP genotyping was performed by the hydrolysis probe method. The TaqMan®SNP Genotyping Assay (Applied Biosystems Inc., USA) was used to analyse the *FTO* rs9939609 and *FTO* rs1421085 variants on an ABI 7500 real-time qPCR System (Applied Biosystems Inc., USA) [35]. Briefly, the assay employs the 5′ nuclease activity of Taq polymerase to generate a fluorescent signal during PCR. For each of the *FTO* rs9939609 and rs1421085 SNPs, two probes were utilised, wild-type and variant allele probes. A 5′ reporter dye (FAM or HEX) and a 3′ quencher dye (Black Hole Quencher (BHQ)) were linked to each probe. The nuclease activity only happens with the perfectly hybridised probes. The ratio of the fluorescent signal for the two reporter dyes is measured and is used as an indication of the sample genotype.

Statistical analysis

Data are reported as mean ± SEM (standard error of the mean). The demographic data of PCOS patients and controls were compared using the *t*-test. A Pearson Chi-Square (χ^2) test and Chi-Square (χ^2) test for trend (Armitage trend test) were used to compare the observed and expected numbers of *FTO* rs9939609 and *FTO* rs1421085 genotypes for PCOS patients and control for the Hardy–Weinberg equilibrium analysis. A Chi-Square test (χ^2) and logistic regression were used to assess the association of the *FTO* rs9939609 and *FTO* rs1421085 gene variants with PCOS. The significance level $p < 0.05$ was considered statistically significant. GraphPad-Prism Software (San Diego, USA) was used for all statistical analyses.

Results

The demographic data of PCOS patients and control subjects are shown in Table 1. No significant differences were observed between PCOS patients and controls in any of the parameters. Hardy–Weinberg equilibrium (HWE) analysis on all subjects revealed that only *FTO* rs1421085 of the control subjects showed a deviation from Hardy–Weinberg equilibrium ($p = 0.012$) with a Pearson Chi-Square (χ^2) test (Table 2). It was reported that when

Table 1 Demographic data of PCOS patients and control subjects

Parameter	Control (n = 99)	PCOS (n = 98)	*p value*
Age (yr)	33.10 ± 0.74	31.50 ± 0.47	0.07
Height (cm)	158.48 ± 0.55	158.41 ± 0.61	0.94
Weight (kg)	70.59 ± 1.53	72.09 ± 1.37	0.47
BMI (kg/m2)	28.16 ± 0.62	28.71 ± 0.51	0.49

Values are Mean ± Standard Error of Mean (SEM)

BMI: body mass index; PCOS: polycystic ovarian syndrome; *p*: significance value. $p < 0.05$ was considered statistically significant

Table 2 Observed and expected values of *FTO* rs9939609 (T>A) and *FTO* rs1421085 (T>C) variants in PCOS patients and controls by Hardy–Weinberg equilibrium

Gene polymorphism		Control				PCOS			
		O	*E*	χ2	*p*	*O*	*E*	χ2	*p*
FTO rs9939609	*TT*	29	32.2	1.77[P] 0.00[A]	0.183[P] >0.999[A]	47	45.1	0.75[P] 0.00[A]	0.385[P] >0.999[A]
	TA	55	48.5			39	42.8		
	AA	15	18.2			12	10.1		
FTO rs1421085	*TT*	32	25.8	6.30[P] 0.00[A]	**0.012[P]*** 0.998[A]	28	27.6	0.03[P] 0.00[A]	0.869[P] 0.995[A]
	TC	37	49.5			48	48.8		
	CC	30	23.8			22	21.6		

PCOS: polycystic ovarian syndrome; *O*: observed data; *E*: expected data; P: Pearson Chi-Square (χ^2) test; A: Chi-Square (χ^2) test for trend (Armitage trend test); *p*: significance value

*Significant difference. $p < 0.05$ was considered statistically significant

the HWE deviation cannot be attributed to genotyping error or selection or non-random mating and may be due to an unknown factor, the Chi-Square (χ^2) test for trend (Armitage trend test) should be used to reduce the chance of false-positive associations [36]. When the Armitage trend test was employed, there was no deviation from Hardy–Weinberg equilibrium ($p = 0.998$).

The analysis of the genotype and allele distributions of *FTO* rs9939609 (T>A) and *FTO* rs1421085 (T>C) variants was performed on PCOS patients and controls (Table 3). For *FTO* rs9939609, the genotype TA in PCOS patients was significantly different when compared with their respective controls ($p = 0.008$). Both TT and AA genotypes exhibited no significant difference in distribution ($p > 0.05$). The recessive model (TA + AA) showed a significant difference ($p = 0.007$), while the dominant model (TT + TA) did not show any significant difference between PCOS patients and controls ($p > 0.05$). Moreover, a significant difference of the alleles was evident in PCOS patients compared with healthy controls ($p = 0.027$), suggesting that the A allele is a risk factor for PCOS susceptibility. However, for the *FTO* rs1421085

Table 3 Genotype and allele frequencies of *FTO* rs9939609 (T>A) and *FTO* rs1421085 (T>C) variants in PCOS patients and controls

Gene polymorphism		Control	PCOS	Control versus PCOS		
		n (%)	n (%)	OR (95% CI)	χ^2	*p*
FTO rs9939609 Genotype	*TT*	29 (29.3)	47 (48.0)	2.03 (0.83–4.93)	2.46	0.116
	TA	55 (55.6)	39 (39.8)	0.44 (0.24–0.81)	6.96	**0.008***
	AA	15 (15.2)	12 (12.2)	0.50 (0.20–1.20)	2.46	0.116
	TT + TA	84 (84.8)	86 (87.8)	1.30 (0.57–2.90)	0.35	0.553
	TA + AA	70 (70.7)	51 (52.0)	0.45 (0.25–0.81)	7.24	**0.007***
Allele	*T*	113 (57.1)	133 (67.9)	0.63 (0.42–0.95)	4.89	**0.027***
	A	85 (42.9)	63 (32.1)	1.59 (1.05–2.40)		
		n = 99	n = 98			
FTO rs1421085 Genotype	*TT*	32 (32.3)	28 (28.6)	1.20 (0.57–2.52)	0.21	0.644
	TC	37 (37.4)	48 (49.0)	1.48 (0.76–2.90)	1.36	0.244
	CC	30 (30.3)	22 (22.4)	0.84 (0.40–1.77)	0.21	0.644
	TT + TC	69 (69.7)	76 (77.6)	1.50 (0.80–2.85)	1.56	0.211
	TC + CC	67 (67.7)	70 (71.4)	1.20 (0.65–2.20)	0.33	0.567
Allele	*T*	101 (51.0)	104 (53.1)	0.92 (0.62–1.37)	0.17	0.684
	C	97 (49.0)	92 (46.9)	1.10 (0.73–1.61)		
		n = 99	n = 98			

n: Number of individuals; PCOS: polycystic ovarian syndrome; OR: odds ratio; CI: confidence interval; χ^2: Chi-Square; *p*: significance value

*Significant difference. $p < 0.05$ was considered statistically significant

variant, the genotype and allele distributions did not differ significantly between PCOS patients and controls.

Discussion

FTO was identified in 2007 as a sensitive gene for obesity. The intron 1 region of the *FTO* gene received extensive attention due to the harbouring of multiple polymorphisms that were strongly associated with BMI, waist circumference, hip circumference, body fat rate, energy intake, type 2 *diabetes mellitus* (T2DM), and obesity [22, 24, 37, 38]. *FTO* is involved in various cellular processes, including fatty acid metabolism, DNA repair, and posttranslational modifications [39]. Although *FTO* is expressed in the liver, pancreas, muscles, and adipose tissue [40], the highest expression of the *FTO* gene is in the region that controls energy balance in the hypothalamus implying its crucial role in regulating energy metabolism and appetite [39]. The involvement of *FTO* polymorphisms with BMI was first reported in diabetic European people. Among the first reported BMI-related *FTO* variants was the rs9939609 variant [22, 34]. Recent studies have associated the rs9939609 with higher obesity risks in other populations (Chinese, Brazilian, and Iranian populations) [41–43]. It is also associated with increased waist circumference and BMI in Brazilian young individuals [44], increased metabolic syndrome predisposition in Chinese subjects, and distribution of adipose tissue in the Italian subjects [45, 46]. Furthermore, multiple polymorphisms in the first intronic region of *FTO* have been correlated with the risk of cancers. Again, the classic *FTO* rs9939609 was associated with breast, lung, prostate, endometrial, renal, and pancreatic cancers. The association between the *FTO* variants and a wide spectrum of diseases may suggest another role beyond the involvement with BMI [39]. Increasing evidence suggests that *FTO* can be a main genetic factor in predisposing to PCOS, primarily via its role in BMI and obesity, and secondarily with manipulating hyperandrogenemia and metabolic parameters [6, 39, 47].

PCOS is a metabolic disorder that is closely related to insulin resistance [48], T2DM [49], obesity [14], metabolic syndrome [4], and premature arteriosclerosis [50]. No surprise that genes affecting T2DM and obesity, such as *FTO*, are regarded as important candidate genes for PCOS. Obesity is found in approximately 50% of PCOS patients. Indeed, as reported previously, *FTO* is associated and has a profound influence on PCOS [6, 39, 51, 52].

The major finding of the present study is that the first intronic *FTO* rs9939609 gene variant is associated with PCOS in Saudi Arabian women. However, one must be careful because the presence of an association does not mean causation. The rs9939609 gene variant is strongly conserved across species, the most extensively studied *FTO* variant, and was previously reported to be associated with PCOS in the Korean [23, 24, 38, 53], Chinese [38, 54–56], UK patients of British/Irish origin [57], SriLankan [21, 58], Brazilian [34], Turkish [27], and Tunisian populations [59]. Thus, the finding of the present study, along with, the findings of previous studies suggest that the *FTO* rs9939609 gene variant might have a positive association with the presence of PCOS. Additionally, to the aim to investigate the association of rs9939609 with a larger population of PCOS patients, Liu et al. (2017) performed a meta-analysis that involved 5010 PCOS subjects and 5300 controls. The studies used for the meta-analysis were conducted in Brazil, United Kingdom, China, and Korea and suggested that the *FTO* rs9939609 gene variant is associated with PCOS risk [60]. An interesting meta-analysis by Cai et al. (2014) revealed that *FTO* rs9939609 might not be associated with PCOS in Caucasian patients. However, the association was highly significant in PCOS East Asians, which is independent of BMI [61]. On the contrary, rs9939609 was not significantly associated with PCOS itself in Korean women. However, the variant may have a gene dose effect, via an association with obesity, in predisposition to PCOS [62].

Several reports had confirmed that the *FTO* rs9939609 gene variant impacted body fat contents hence BMI from multiple biological pathways [27, 28, 63]. Furthermore, other studies have reported a positive association between the rs9939609 variant with other PCOS-associated phenotypes [38]. In a cohort of PCOS women from a Polish population, the rs9939609 variant may have a higher impact on obesity and related traits in PCOS [48, 64]. It was reported that there is a correlation between rs9939609 and insulin resistance in PCOS subjects. And the effect size of the rs9939609 variant on BMI in PCOS was greater than that of controls of the same age range in the German population [65]. To the aim to investigate the impact of the *FTO* rs9939609 on metabolic and endocrine parameters in PCOS patients, Wehr *et al.*, (2010) demonstrated that rs9939609 influenced the anthropometric parameters and hyperandrogenemia and in PCOS women, indicating an important role of this variant not only in T2DM and obesity but also in hyperandrogenism in Austrian women with PCOS [66].

The second finding of the present study was that the *FTO* rs1421085 gene variant was not associated with PCOS in Saudi Arabian women residing in the Riyadh region. Few studies investigated the association of the rs1421085 variant with PCOS compared to studies on rs9939609. *FTO* rs1421085 gene variant was not a contributing factor for the development of PCOS in Korean patients [67]. In addition, the findings of this study

are consistent with previously reported data, the *FTO* rs1421085 variant had no association with PCOS in cohorts of 212 Chinese and 207 Romanian women compared with 198 and 100 of matched controls, respectively [68, 69]. On the contrary, in another study in Korea that included 432 patients with PCOS and 927 controls, the *FTO* rs1421085 variant was associated with PCOS in young Korean women [38]. And, in another study that involved 750 PCOS individuals of European origin and 1567 control subjects (BMI-matched), out of the 92 investigated BMI-risk polymorphisms, the association of rs1421085 with BMI was stronger in PCOS women. None of the other investigated variants were associated individually with PCOS [51]. Furthermore, rs1421085 was found to be associated with impaired fasting glucose in PCOS patients in a Central European population [69].

The first intronic *FTO* rs1421085 gene variant was first found to be associated with obesity [24]. However, it was not clear whether the *FTO* rs1421085 variant was associated with overfat or overweight. An overweight reflects an increase in total body mass (calculated BMI), including lean contents and fat contents. Whereas an overfat will reflect elevated fat contents which cannot be accurately estimated using the calculated BMI. It is very important to realise that many SNPs in the *FTO* gene are co-inherited with a wide range of expressing the proportion of fat content to lean content for a given increase in body weight. Additionally, body fat is excessive in PCOS [18]. The results of previous studies regarding the *FTO* rs1421085 gene variant had not been clear nor yielded a repeatable association with obesity rather than BMI alone. 362,129 SNPs of the *FTO* gene were tested in African Americans for association with obesity-related traits. The rs9939609 gene variant was associated with obesity, and this was not the case for the *FTO* rs1421085 gene variant [37]. The *FTO* rs9939609 polymorphism might influence the baseline lipid oxidation in PCOS patients which may explain the impact of the variant on BMI in PCOS patients [64]. However, Li et al. (2013) reported that the variant rs9939609 was associated with PCOS patients in obese, as well as, in non-obese Chinese women [70]. Other studies are needed to investigate the association of the *FTO* rs1421085 variant with PCOS in women of reproductive age in different populations.

In a meta-analysis study that included twelve studies published from 2008 to 2015, and included a total of 6287 PCOS patients and 6667 controls for assessing the association with rs9939609, and 1549 PCOS patients and 1611 controls for assessing the association with rs1421085, the *FTO* rs9939609 gene variant was significantly associated with PCOS. However, the association between rs1421085 and PCOS needed further confirmation as reported by the authors. These studies were performed in USA, Brazil, UK, France, Romania, China, and Korea [71]. In another systematic review and meta-analysis that included seven studies describing eight distinct PCOS cohorts in which seven of the cohorts were genotyped for rs9939609 and one for rs1421085, and included 2548 PCOS women (sample size ranged from 136 to 469), *FTO* variants showed a statistically larger effect in PCOS cohorts than in the reference groups [22, 72]. The studies were conducted in USA, Austria, Czech Republic, Germany, Poland, France, Romania, and UK [55]. A recent meta-analysis on the associations of *FTO* variants with PCOS, which included forty-six studies, revealed that rs9939609 is significantly associated with PCOS (7629 PCOS vs 10511 controls) which was not the case for the rs1421085 variant (1256 PCOS vs 1638 controls). The meta-analysis proved that the rs9939609 variant may serve as a predisposing factor for PCOS, especially for Asians [1]. Very recently, it was reported that the *FTO* rs9939609 variant may increase susceptibility to PCOS development independent from serum adipocytokine levels [47].

Although the diagnostic criteria for PCOS do not include obesity [14, 73], the Northern Finland Birth Cohort (NFBC) reported a significant association between BMI and PCOS at all ages. The outcome of weight loss has shown that it can lead to clinically meaningful improvements of PCOS manifestations [17, 74, 75]. Weight gain and obesity often result in clinical and biochemical manifestation in women who are genetically susceptible to the development of PCOS [17]. On the contrary, the increased prevalence of PCOS in obese and overweight women was independent of the presence or absence of the metabolic syndrome of PCOS [76, 77]. The co-occurrence of PCOS and obesity may be attributed to a contributing genetic predisposition and a significant inherited etiology as suggested by evidence from family-based studies [38, 66, 78]. Obesity may be an important contributor to PCOS but is not one of the main etiologic defects leading to this disease [77, 79].

Conclusion

This is the first report to study the association of *FTO* rs9939609 and *FTO* rs1421085 with PCOS in Saudi women. *FTO* rs9939609 gene variant is significantly associated with PCOS patients, while *FTO* rs1421085 exhibited no significant difference. Results suggest that the *FTO* rs9939609 gene variant could be a genetic predisposing factor for PCOS Saudi women. A discrepancy between populations is evident, and further studies on other and large populations to evaluate the association between these two SNPs and the risk of PCOS are highly required.

Limitations

(1) The study employed only two genetic variants of the *FTO* gene. Other variants of the *FTO* gene should be considered in future studies. (2) The study was restricted to Saudi Arabian women. Further studies are required in other populations. (3) Biochemical and clinical parameters including hyperandrogenism or serum testosterone levels, and modified Ferriman-Gallwey (mFG) score have been assessed for the study population, for the purpose of complete PCOS diagnosis, before the recruitment of PCOS patients for this study. And these data are not available with the authors. (4) The results need to be confirmed in larger samples.

Abbreviations

ASRM: American Society for Reproductive Medicine; BMI: Body mass index; CI: Confidence interval; EDTA: Ethylenediaminetetraacetic acid; ESHRE: European Society for Human Reproduction and Embryology; FTO: Fat mass and obesity-associated; HWE: Hardy–Weinberg equilibrium; IRB: Institutional Review Board; KKUH: King Khalid University Hospital; NFBC: Northern Finland Birth Cohort; PCO: Polycystic ovaries; PCOS: Polycystic ovary syndrome; PCR: Polymerase chain reaction; SEM: Standard error of the mean; SNP: Single nucleotide polymorphism; T2DM: Type 2 *Diabetes mellitus*.

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Authors' contributions

All authors listed have made a substantial and intellectual contribution to the work and approved it for publication. AAA and HMA were involved in data acquisition and methodology. HMA was involved in formal analysis and literature search. AFA and ZAB contributed to the supervision and project administration. AFA, ZAB, and MIK have made substantial contributions to the conception, design of the work, analysis, and interpretation of data. AFA and MIK contributed to the manuscript preparation, editing, and review. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

All participants signed an informed consent that was approved by the Medical Ethics Committee of King Khalid University Hospital (KKUH). The study protocol was approved by the Institutional Review Board (IRB) of King Saud University, Riyadh, Saudi Arabia.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

1. Wang X, Wang K, Yan J, Wu M (2020) A meta-analysis on associations of FTO, MTHFR and TCF7L2 polymorphisms with polycystic ovary syndrome. Genomics 112(2):1516–1521
2. Dumesic DA, Oberfield SE, Stener-Victorin E, Marshall JC, Laven JS, Legro RS (2015) Scientific statement on the diagnostic criteria, epidemiology, pathophysiology, and molecular genetics of polycystic ovary syndrome. Endocr Rev 36(5):487–525
3. Witchel SF, Oberfield SE, Peña AS (2019) Polycystic ovary syndrome: pathophysiology, presentation, and treatment with emphasis on adolescent girls. J Endocr Soc 3(8):1545–1573
4. Sanchez-Garrido MA, Tena-Sempere M (2020) Metabolic dysfunction in polycystic ovary syndrome: pathogenic role of androgen excess and potential therapeutic strategies. Mol Metab. 35:100937
5. Mayrhofer D, Hager M, Walch K, Ghobrial S, Rogenhofer N, Marculescu R et al (2020) The prevalence and impact of polycystic ovary syndrome in recurrent miscarriage: a retrospective cohort study and meta-analysis. J Clin Med 9(9):2700
6. Dapas M, Lin FTJ, Nadkarni GN, Sisk R, Legro RS, Urbanek M et al (2020) Distinct subtypes of polycystic ovary syndrome with novel genetic associations: an unsupervised, phenotypic clustering analysis. PLoS Med 17(6):e1003132
7. Sirmans SM, Pate KA (2013) Epidemiology, diagnosis, and management of polycystic ovary syndrome. Clin Epidemiol 18(6):1–13
8. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group (2004) Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril 81(1):19–25
9. Bozdag G, Mumusoglu S, Zengin D, Karabulut E, Yildiz BO (2016) The prevalence and phenotypic features of polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod 31(12):2841–2855
10. Çoban Ö, Tulacı Ö, Adanır AS, Önder A (2019) Psychiatric disorders, self-esteem, and quality of life in adolescents with polycystic ovary syndrome. J Pediatr Adolesc Gynecol 32(6):600–604
11. Ganie MA, Rashid A, Sahu D, Nisar S, Wani IA, Khan J (2020) Prevalence of polycystic ovary syndrome (PCOS) among reproductive age women from Kashmir valley: a cross-sectional study. Int J Gynaecol Obstet 149(2):231–236
12. Tan J, Hao X, Zhao T, Ying J, Li T, Cheng L (2020) Association between long-chain non-coding RNA SRA1 gene single-nucleotide polymorphism and polycystic ovary syndrome susceptibility. J Assist Reprod Genet 37(10):2513–2523
13. Cupisti S, Kajaia N, Dittrich R, Duezenli H, Beckmann MW, Mueller A (2008) Body mass index and ovarian function are associated with endocrine and metabolic abnormalities in women with hyperandrogenic syndrome. Eur J Endocrinol 158(5):711–719
14. Chen J, Shen S, Tan Y, Xia D, Xia Y, Cao Y et al (2015) The correlation of aromatase activity and obesity in women with or without polycystic ovary syndrome. J Ovarian Res 8:11
15. Chitme HR, Al Azawi EAK, Al Abri AM, Al Busaidi BM, Salam ZKA, Al Taie MM et al (2017) Anthropometric and body composition analysis of infertile women with polycystic ovary syndrome. J Taibah Univ Med Sci 12(2):139–145
16. Munawar Lone N, Babar S, Sultan S, Malik S, Nazeer K, Riaz S (2020) Association of the CYP17 and CYP19 gene polymorphisms in women with polycystic ovary syndrome from Punjab, Pakistan. Gynecol Endocrinol 37:456–461
17. Barber TM, Hanson P, Weickert MO, Franks S (2019) Obesity and polycystic ovary syndrome: implications for pathogenesis and novel management strategies. Clin Med Insights Reprod Health 13:1179558119874042
18. Rosenfield RL (2020) Current concepts of polycystic ovary syndrome pathogenesis. Curr Opin Pediatr 32(5):698–706

19. Rosenfield RL, Ehrmann DA (2016) The pathogenesis of polycystic ovary syndrome (PCOS): the hypothesis of PCOS as functional ovarian hyperandrogenism revisited. Endocr Rev 37(5):467–520
20. Tan S, Scherag A, Janssen OE, Hahn S, Lahner H, Dietz T et al (2010) Large effects on body mass index and insulin resistance of fat mass and obesity associated gene (FTO) variants in patients with polycystic ovary syndrome (PCOS). BMC Med Genet 11:12
21. Branavan U, Wijesundera S, Chandrasekaran V, Arambepola C, Wijeyaratne C (2020) In depth analysis of the association of FTO SNP (rs9939609) with the expression of classical phenotype of PCOS: a Sri Lankan study. BMC Med Genet 21(1):30
22. Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM et al (2007) A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science 316(5826):889–894
23. Chang Y-C, Liu P-H, Lee W-J, Chang T-J, Jiang Y-D, Li H-Y et al (2008) Common variation in the fat mass and obesity-associated (FTO) gene confers risk of obesity and modulates BMI in the Chinese population. Diabetes 57(8):2245–2252
24. Dina C, Meyre D, Gallina S, Durand E, Körner A, Jacobson P et al (2007) Variation in FTO contributes to childhood obesity and severe adult obesity. Nat Genet 39(6):724–726
25. Fawcett KA, Barroso I (2010) The genetics of obesity: FTO leads the way. Trends Genet 26(6):266–274
26. Meng Y, Lohse B, Cunningham-Sabo L (2020) Sex modifies the association between the CLOCK variant rs1801260 and BMI in school-age children. PLoS ONE 15(8):e0236991
27. Ağagündüz D, Gezmen-Karadağ M (2019) Association of FTO common variant (rs9939609) with body fat in Turkish individuals. Lipids Health Dis 18(1):212
28. Ursu RI, Badiu C, Cucu N, Ursu GF, Craciunescu I, Severin E (2015) The study of the rs9939609 FTO gene polymorphism in association with obesity and the management of obesity in a Romanian cohort. J Med Life 8(2):232–238
29. Mačeková S, Bernasovský I, Gabriková D, Bôžiková A, Bernasovská J, Boroňová I et al (2012) Association of the FTO rs9939609 polymorphism with obesity in Roma/Gypsy population. Am J Phys Anthropol 147(1):30–34
30. Saad E, El Sebai A, Maher M, Heikal A (2020) Study of the common variant rs9939609 of FTO gene polymorphism in Polycystic Ovary Syndrome. Med Sci 24(106):3845–3854
31. Fauser BCJM, Tarlatzis BC, Rebar RW, Legro RS, Balen AH, Lobo R et al (2012) Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. Fertil Steril 97(1):28–38
32. Tsikouras P, Spyros L, Manav B, Zervoudis S, Poiana C, Nikolaos T et al (2015) Features of polycystic ovary syndrome in adolescence. J Med Life 8(3):291
33. Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L et al (2018) Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Clin Endocrinol 89(3):251–268
34. Ramos RB, Spritzer PM (2015) FTO gene variants are not associated with polycystic ovary syndrome in women from Southern Brazil. Gene 560(1):25–29
35. Zhong L, Xie YZ, Cao TT, Wang Z, Wang T, Li X et al (2016) A rapid and cost-effective method for genotyping apolipoprotein E gene polymorphism. Mol Neurodegener 11:2
36. Szeszko JS, Howson JMM, Cooper JD, Walker NM, Twells RCJ, Stevens HE et al (2006) Analysis of polymorphisms of the Interleukin-18 gene in type 1 diabetes and Hardy–Weinberg equilibrium testing. Diabetes 55(2):559
37. Scuteri A, Sanna S, Chen W-M, Uda M, Albai G, Strait J et al (2007) Genome-wide association scan shows genetic variants in the FTO gene are associated with obesity-related traits. PLoS Genet 3(7):e115
38. Song DK, Lee H, Oh J-Y, Hong YS, Sung Y-A (2014) FTO gene variants are associated with PCOS susceptibility and hyperandrogenemia in young Korean Women. Diabetes Metab J 38(4):302–310
39. Lan N, Lu Y, Zhang Y, Pu S, Xi H, Nie X et al (2020) FTO—a common genetic basis for obesity and cancer. Front Genet 11:559138
40. Stratigopoulos G, Padilla SL, LeDuc CA, Watson E, Hattersley AT, McCarthy MI et al (2008) Regulation of *Fto/Ftm* gene expression in mice and humans. Am J Physiol-Regul Integr Comp Physiol 294(4):R1185–R1196
41. da Fonseca ACP, Abreu GM, Zembrzuski VM, Campos Junior M, Carneiro JRI, Nogueira Neto JF et al (2019) The association of the fat mass and obesity-associated gene (FTO) rs9939609 polymorphism and the severe obesity in a Brazilian population. DMSO 12:667–684
42. Jiang Y, Mei H, Lin Q, Wang J, Liu S, Wang G et al (2019) Interaction effects of FTO rs9939609 polymorphism and lifestyle factors on obesity indices in early adolescence. Obes Res Clin Pract 13(4):352–357
43. Mehrdad M, Fardaei M, Fararouei M, Eftekhari MH (2020) The association between FTO rs9939609 gene polymorphism and anthropometric indices in adults. J Physiol Anthropol 39(1):14
44. Reuter CP, Rosane De Moura Valim A, Gaya AR, Borges TS, Klinger EI, Possuelo LG et al (2016) FTO polymorphism, cardiorespiratory fitness, and obesity in Brazilian youth: polymorphism, cardiorespiratory fitness, and obesity. Am J Hum Biol 28(3):381–386
45. Merra G, Gualtieri P, Cioccoloni G, Falco S, Bigioni G, Tarsitano MG et al (2020) FTO rs9939609 influence on adipose tissue localization in the Italian population. Eur Rev Med Pharmacol Sci 24(6):3223–3235
46. Wang D, Wu Z, Zhou J, Zhang X (2020) Rs9939609 polymorphism of the fat mass and obesity-associated (FTO) gene and metabolic syndrome susceptibility in the Chinese population: a meta-analysis. Endocrine 69(2):278–285
47. Beyazit F, Hiz MM, Turkon H, Unsal MA (2021) Serum spexin, adiponectin and leptin levels in polycystic ovarian syndrome in association with FTO gene polymorphism. Ginekol Polska. 92:682–688
48. Kowalska I, Malecki MT, Straczkowski M, Skupien J, Karczewska-Kupczewska M, Nikolajuk A et al (2009) The FTO gene modifies weight, fat mass and insulin sensitivity in women with polycystic ovary syndrome, where its role may be larger than in other phenotypes. Diabetes Metab 35(4):328–331
49. Legro RS (1999) Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. J Clin Endocrinol Metab 84(1):165–169
50. Talbott EO, Guzick DS, Sutton-Tyrrell K, McHugh-Pemu KP, Zborowski JV, Remsberg KE et al (2000) Evidence for association between polycystic ovary syndrome and premature carotid atherosclerosis in middle-aged women. ATVB 20(11):2414–2421
51. Brower MA, Hai Y, Jones MR, Guo X, Chen YI, Rotter JI et al (2019) Bidirectional Mendelian randomization to explore the causal relationships between body mass index and polycystic ovary syndrome. Hum Reprod 34(1):127–136
52. Zhao H, Lv Y, Li L, Chen Z-J (2016) Genetic studies on polycystic ovary syndrome. Best Pract Res Clin Obst Gynaecol 37:56–65
53. Hotta K, Nakata Y, Matsuo T, Kamohara S, Kotani K, Komatsu R et al (2008) Variations in the FTO gene are associated with severe obesity in the Japanese. J Hum Genet 53(6):546–553
54. Yuan H, Zhu G, Wang F, Wang X, Guo H, Shen M (2015) Interaction between common variants of FTO and MC4R is associated with risk of PCOS. Reprod Biol Endocrinol 13(1):55
55. Consortium G, Wojciechowski P, Lipowska A, Rys P, Ewens KG, Franks S et al (2012) Impact of FTO genotypes on BMI and weight in polycystic ovary syndrome: a systematic review and meta-analysis. Diabetologia 55(10):2636–2645
56. Yan Q, Hong J, Gu W, Zhang Y, Liu Q, Su Y et al (2009) Association of the common rs9939609 variant of FTO gene with polycystic ovary syndrome in Chinese women. Endocrine 36(3):377–382
57. Barber TM, Bennett AJ, Groves CJ, Sovio U, Ruokonen A, Martikainen H et al (2008) Association of variants in the fat mass and obesity associated (FTO) gene with polycystic ovary syndrome. Diabetologia 51(7):1153–1158
58. Branavan U, Muneeswaran K, Wijesundera S, Jayakody S, Chandrasekharan V, Wijeyaratne C (2018) Identification of selected genetic polymorphisms in polycystic ovary syndrome in Sri Lankan women using low cost genotyping techniques. PLoS ONE 13(12):e0209830
59. Ben Salem A, Attaoua R, Mtiraoui N, Meddeb S, Kacem O, Ajina M et al (2015) Haplotyping strategy highlights the specificity of FTO gene association with polycystic ovary syndrome in Tunisian women population. Gene 565(2):166–170

60. Liu AL, Xie HJ, Xie HY, Liu J, Yin J, Hu JS et al (2017) Association between fat mass and obesity associated (FTO) gene rs9939609 A/T polymorphism and polycystic ovary syndrome: a systematic review and meta-analysis. BMC Med Genet 18(1):89
61. Cai X, Liu C, Mou S (2014) Association between fat mass- and obesity-associated (FTO) gene polymorphism and polycystic ovary syndrome: a meta-analysis. PLoS ONE 9(1):e86972
62. Kim JJ, Choi YM, Hong MA, Kim JM, Hwang SS, Lee GH et al (2014) Gene dose effect between a fat mass and obesity-associated polymorphism and body mass index was observed in Korean women with polycystic ovary syndrome but not in control women. Fertil Steril 102(4):1143–8.e2
63. Ewens KG, Jones MR, Ankener W, Stewart DR, Urbanek M, Dunaif A et al (2011) FTO and MC4R gene variants are associated with obesity in polycystic ovary syndrome. PLoS ONE 6(1):e16390-e
64. Kowalska I, Adamska A, Malecki MT, Karczewska-Kupczewska M, Nikolajuk A, Szopa M et al (2012) Impact of the FTO gene variation on fat oxidation and its potential influence on body weight in women with polycystic ovary syndrome. Clin Endocrinol 77(1):120–125
65. Tan S, Scherag A, Janssen OE, Hahn S, Lahner H, Dietz T et al (2010) Large effects on body mass index and insulin resistance of fat mass and obesity associated gene (FTO) variants in patients with polycystic ovary syndrome (PCOS). BMC Med Genet 11(1):12
66. Wehr E, Schweighofer N, Möller R, Giuliani A, Pieber TR, Obermayer-Pietsch B (2010) Association of FTO gene with hyperandrogenemia and metabolic parameters in women with polycystic ovary syndrome. Metabolism 59(4):575–580
67. Kim JJ, Choi YM, Cho YM, Hong MA, Chae SJ, Hwang KR et al (2012) Polycystic ovary syndrome is not associated with polymorphisms of the TCF7L2, CDKAL1, HHEX, KCNJ11, FTO and SLC30A8 genes. Clin Endocrinol 77(3):439–445
68. Xue H, Zhao H, Zhao Y, Liu X, Chen Z, Ma J (2015) Association of common variants of FTO in women with polycystic ovary syndrome. Int J Clin Exp Pathol 8(10):13505–13509
69. Attaoua R, Ait El Mkadem S, Radian S, Fica S, Hanzu F, Albu A et al (2008) FTO gene associates to metabolic syndrome in women with polycystic ovary syndrome. Biochem Biophys Res Commun 373(2):230–234
70. Li T, Wu K, You L, Xing X, Wang P, Cui L et al (2013) Common variant rs9939609 in gene FTO confers risk to polycystic ovary syndrome. PLoS ONE 8(7):e66250
71. Liu Y, Chen Y (2017) Fat mass and obesity associated gene polymorphism and the risk of polycystic ovary syndrome: a meta-analysis. Iran J Public Health 46(1):4–11
72. Speliotes EK, Willer CJ, Berndt SI, Monda KL, Thorleifsson G, Jackson AU et al (2010) Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. Nat Genet 42(11):937–948
73. Hahn S, Tan S, Sack S, Kimmig R, Quadbeck B, Mann K et al (2007) Prevalence of the metabolic syndrome in German women with polycystic ovary syndrome. Exp Clin Endocrinol Diabetes 115(2):130–135
74. Ollila M-ME, Piltonen T, Puukka K, Ruokonen A, Järvelin M-R, Tapanainen JS et al (2016) Weight gain and dyslipidemia in early adulthood associate with polycystic ovary syndrome: prospective cohort study. J Clin Endocrinol Metab 101(2):739–747
75. Holte J, Bergh T, Berne CH, Wide L, Lithell H (1995) Restored insulin sensitivity but persistently increased early insulin secretion after weight loss in obese women with polycystic ovary syndrome. J Clin Endocrinol Metab 80(9):2586–2593
76. Sam S (2007) Obesity and polycystic ovary syndrome. Obes Manag 3(2):69–73
77. Alvarez-Blasco F, Botella-Carretero JI, San Millán JL, Escobar-Morreale HF (2006) Prevalence and characteristics of the polycystic ovary syndrome in overweight and obese women. Arch Intern Med 166(19):2081–2086
78. Goodman NF, Cobin RH, Futterweit W, Glueck JS, Legro RS, Carmina E (2015) American Association of Clinical Endocrinologists, American College of Endocrinology, and androgen excess and PCOS society disease state clinical review: guide to the best practices in the evaluation and treatment of polycystic ovary syndrome-part 1. Endocr Pract 21(11):1291–1300
79. Korhonen S, Hippeläinen M, Niskanen L, Vanhala M, Saarikoski S (2001) Relationship of the metabolic syndrome and obesity to polycystic ovary syndrome: a controlled, population-based study. Am J Obstet Gynecol 184(3):289–296

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