



Original article

# Genetic contribution between *APE1* variants in polycystic ovarian syndrome

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## ABSTRACT

**Introduction:** Polycystic Ovarian Syndrome (PCOS) has been identified as a gynecological, hormonal, and metabolic condition in women of reproductive age. Genetic studies can contribute to understand the pathogenesis of PCOS; which can be beneficial in early diagnosis and long-term management of the disease. Apurinic/apyrimidinic endonuclease 1 (*APE1*) has been related in the literature to polycystic ovarian syndrome.

**Aim:** The purpose of this study was to investigate the effects of –656 T > G and 1349 T > G single nucleotide polymorphisms (SNPs) in the *APE1* gene in Saudi women with PCOS.

**Methods:** This study includes 100 PCOS women and 100 healthy controls were genotyped for –656 T > G and 1349 T > G SNPs using PCR-RFLP method. Serum sample was used for FBG and lipid profile tests. The obtained biochemical and genotypes data were entered into Excel and utilized for statistical analysis.

**Results:** Clinical data presented in Table 1 was used to calculate the t-tests between PCOS and control subjects and results indicate age, weight, BMI, TG, LDLC and PCOS family history was associated ( $p < 0.0001$ ). Genotype and allele frequencies showed the negative association in –656 T > G SNP (GG vs TT: OR-1.15 (0.61–2.17);  $p = 0.65$  and GG + TG vs TT: OR-1.17 (0.67–2.04);  $p = 0.57$ ) and positive association in 1349 T > G SNP (GG vs TT: OR-3.52 (1.48–8.36);  $p = 0.003$  and GG + TG vs TT: OR-2.84 (1.27–6.31);  $p = 0.008$ ) in *APE1* gene. Anova analysis was not associated with any one of the involved parameters ( $p > 0.05$ ).

**Conclusion:** This study found that the 1349 T > G SNP was related with PCOS in Saudi women. However, the –656SNP had no favorable effect on the *APE1* gene.

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## 1. Introduction

PCOS is a condition that affects women of childbearing age and is caused by a combination of genetic, hormonal, and environmental factors. Symptoms include acne, amenorrhea, hyperandrogenism, hirsutism, obesity, oligomenorrhea, insulin resistance, and infertility. The prevalence of PCOS in female infertility has been confirmed to be 40 % (Nautiyal et al., 2022). Between 40 and 80 % of PCOS women are overweight or obese. Clustering of PCOS in families provides compelling evidence for a genetic predis-

position to the condition. Insulin resistance was found to be common pathway between PCOS and obesity (Henry 2022). PCOS has become very common in global women and is identified as one of the potential risk factors for infertility and has been linked to acne and hirsutism (Abraham Gnanadass et al., 2021). Androgen levels are elevated, ovulation dysfunction is prevalent, and PCOS morphological abnormalities are also present. “Hyperandrogenism with ovulatory dysfunction,” as described by the National Institutes of Health. The prevalence of PCOS in women in their reproductive years is from 6 to 10 %, although it can be as high as double that (Xu and Qiao 2022). The global prevalence of PCOS was found to be between 4 and 21 %, whereas frequency in adolescents ranges from 9.1 to 36 % depending on the diagnostic criteria utilized (Rashid et al., 2022). Stein and Leventhal identified hirsutism, amenorrhea, infertility, enlarged ovaries, obesity, and prolonged anovulation in 1935. In 1990, the World Health Organization included PCOS to the 10th version of the International Classification of Diseases. Unapproved pharmaceuticals were used to treat PCOS patients based on their symptoms

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(Bogari 2020). Large prospective cohorts have indicated development to either pre-diabetes or type 2 diabetic mellitus (T2DM) over the course of years. Because insulin resistance and  $\beta$ -cell dysfunction are common in PCOS women, it is possible to predict the development of T2DM (Livadas et al., 2022). PCOS symptoms are not limited to the gynecological sphere, but also include endocrinological disorders such as metabolic syndrome (MetS), T2DM, hypertension, dyslipidemia, and obesity, which are more common in women with the disease than in those without it (Shetty et al., 2022).

There is a strong correlation between environmental and genetic factors, and vice versa, when it comes to disease. Both environmental and genetic factors have a role in PCOS. Although the genetic etiology of PCOS varies within and within families, a common pathway can be found. Patients from the same family have varying levels of genetic vulnerability to disease. It is therefore possible to uncover possible correlations by conducting large population-based case-control studies and genome-wide association studies (GWAS). In order to uncover possible correlations in which PCOS is known to be polygenic and multifactorial syndromic disorder, population-based case-control studies and GWAS are beneficial (Khan et al., 2019). The human *APE1* gene is engaged in the base excision repair process and is found on chromosome 14q11.2-q12. The *APE1* gene is made up of five exons totaling 2.21 kb. A total of 18 SNPs were found in the *APE1* gene, with Asp148Glu (rs3136820) being the most prevalent. *APE1* generates normal 3'-hydroxyl nucleotide termini from oxidized DNA by hydrolyzing 3'-blocking fragments (Gu et al., 2011). Another significant *APE1* gene SNP, 656 T > G (rs1760944), is found in the promoter region (Yousefi et al., 2015). Limited studies have addressed the relation between specific SNPs in gynecological complications such as female infertility (Mashayekhi et al., 2016) and PCOS (Gulbay et al., 2017). Apart from this, the prevalence of PCOS was found to be 53.7 % in Saudi Arabia (Guraya 2013). As a result, the current study sought to investigate the relationship between -656 T > G and 1349 T > G polymorphisms in the *APE1* gene and PCOS in Saudi women.

## 2. Materials and methods

### 2.1. Ethical concerns

Ethical committee has approved this study within hospital premises. Two hundred Saudi women who took part in this study signed an informed consent form before taking part. This study protocol complied with both original and updated version of the Helsinki Declaration.

### 2.2. Deigned of Saudi women

Based on predetermined inclusion and exclusion criteria, two hundred Saudi women participated in this study. The Saudi women were extracted into 100 PCOS patients and remaining 100 women as control participants. These 200 Saudi women came from the KCUH Gynec department. This study recruitment was carried out for 10 months starting from January 2021-November 2021 in the hospital premises. Inclusion criteria of PCOS women is based on Rotterdam criteria (Eshre and Group 2004), oligo-or-anovulation and polycystic ovaries and women who does not meet under Rotterdam criteria is confirmed as exclusion criteria of PCOS women (Kawwass et al., 2010). Saudi women with normal ovulation are confirmed as inclusion criteria of control subjects and exclusion criteria will be confirmed based on fertile subjects, ovarian lesions and family history associated with PCOS. Pregnant women and women with other metabolic diseases were excluded from both

the PCOS and control groups in this study. Participant information was acquired.

### 2.3. Ergonomic assessments

Age and body mass index (BMI) (Alshammary and Khan 2021)-data were collected for 200 women. A blood sample of 4 mL was obtained in a plain tube and a blood sample of 2 mL was collected in an EDTA tube.

### 2.4. Biochemical and genotyping analysis

The FBG and lipid profile were measured using a plain blood sample (Alharbi et al., 2021), and the genomic DNA was isolated using a Qiagen kit and methodology. The genomic DNA was converted into 20 ng using NanoDrop spectrophotometer. PCR-RFLP analysis was implemented in this study. A couple of SNPs (-656 T > G and 1349 T > G) was adopted from the previous studies among PCOS women (Gulbay et al., 2017). Using a PCR master kit, double-distilled purified water, primers (+/-), and DNA template, genotyping analysis and PCR conditions was performed (Khan et al., 2015). PCR products were electrophoretically separated on a 2 % agarose gel stained with ethidium bromide. RFLP analysis was carried out. Electrophoresis was carried out. Table 1 lists the primers, band sizes, and restriction enzymes.

### 2.5. Statistical analysis

SPSS software was used for statistical analysis (v.25). When applicable, baseline features of PCOS women and controls were examined using independent sample t-tests (Table 2).  $\chi^2$  goodness of fit tests were used to look for evidence of a departure from Hardy Weinberg equilibrium (HWE) at the -656 T > G and 1349 T > G SNPs in the *APE1* gene (Table 3). Adjusted odds ratios (ORs) with 95 % confidence intervals (CIs) were calculated using multiple logistic regression analysis to determine the correlation between allele, genotype, and various genetic model frequencies for *APE1* SNPs and the risk of PCOS (Table 4). ANOVA (one-way; Table 5) analysis was done between baseline parameters and the *APE1* gene SNPs -656 T > G and 1349 T > G (Khan et al., 2019). A p value of < 0.05 was deemed statistically significant (p < 0.05).

## 3. Results

### 3.1. Basic information of Saudi women

One hundred PCOS women and one hundred control subjects were collected from KCUH for this study. The 200 women participating in this study were all of Saudi origin. Table 2 provides the clinical and biochemical information. The mean age was  $29.63 \pm 5.42$  in PCOS women and  $29.14 \pm 5.18$  in controls. No significant difference was found among PCOS women and controls in terms of age (p = 0.51), height (p = 0.75) FBG (p = 0.69), TC (n = 0.21) and HDLC (p = 0.52). A strong significant association was observed in weight, BMI, TG and LDLC (p < 0.0001) when compared between PCOS and control women.

### 3.2. HWE and genotyping analysis of *APE1* gene

The findings indicate that both rs1760944 (-656 T > G) and rs1130409 (1349 T > G) SNPs were found on chromosome 14q11.2. The 1349 T > G SNP is involved in protein coding. Except for PCOS women with -656 T > G, significant difference in rs1760944 (-656 T > G) and rs1130409 (1349 T > G) SNPs in the *APE1* gene was detected between cases and controls (Table 3).

**Table 1**  
Details of SNPs, Primers and RFLPs used in this study.

Gene	Mutation	rsnumber	Forward Primers	Reverse Primers	PCR	Enzyme	Band Size
APE1	-656 T > G	rs1760944	CTCCTAACCCGAGCACAAAG	CTAACTGCCAGCGAGGCCA	371 bp	HpyCH4III	T-280/91; G-258/91/22
APE1	1349 T > G	rs1130409	CTGTTTCATTCTATAGGCTA	AGGAACTTGCGAAAGGCTTC	164 bp	Bfal	T-164 bp; G-144/20 bp

**Table 2**  
Demographic factors between PCOS women and control subjects.

	PCOS (n = 100)	Controls (n = 100)	P value
Age (Years)	29.63 ± 5.42	29.14 ± 5.18	0.51
Weight (kgs)	77.63 ± 9.40	62.14 ± 8.18	<0.0001
Height (cms)	156.79 ± 4.76	156.58 ± 4.58	0.75
BMI (Kg/m <sup>2</sup> )	31.37 ± 3.90	25.30 ± 3.01	<0.0001
FBG (mmol/L)	5.12 ± 0.76	5.08 ± 0.67	0.69
TC (mmol/L)	1.79 ± 1.07	1.61 ± 0.98	0.21
TG (mmol/L)	5.06 ± 1.06	2.24 ± 0.26	<0.0001
HDLc (mmol/L)	0.63 ± 0.23	0.61 ± 0.21	0.52
LDLc (mmol/L)	3.61 ± 0.90	2.58 ± 0.64	<0.0001
Family History	33 (33 %)	00 (0 %)	<0.0001

**Table 3**  
Output of HWE analysis between T656G and T1349G variants in APE1 gene.

rs1760944	HWE	χ <sup>2</sup>	P value
Controls	0.13	0.07	0.78
Cases	0.42	37.05	0.00001
rs1130409	HWE	χ <sup>2</sup>	P value
Controls	0.52	1.61	0.20
Cases	0.66	0.48	0.48

**Table 4**  
Genotype and allele distribution between T656G and T1349G variants in APE1 gene.

rs1760944 (-T656G)	PCOS (n = 100)	Controls (n = 100)	ORs (95 %CI)	P value
TT Genotype	49 (49 %)	53 (53 %)	Reference	Reference
TG Genotype	19 (19 %)	17 (17 %)	1.20 (0.56–2.58)	0.62
GG Genotype	32 (32 %)	30 (30 %)	1.15 (0.61–2.17)	0.65
Dominant Model	51 (51 %)	47 (47 %)	1.17 (0.67–2.04)	0.57
Co-dominant Model	19 (19 %)	17 (17 %)	1.14 (0.55–2.35)	0.71
Recessive Model	32 (32 %)	30 (30 %)	1.09 (0.60–2.00)	0.75
T allele	117 (58.5 %)	123 (61.5 %)	Reference	Reference
G allele	83 (41.5 %)	77 (38.5 %)	1.13 (0.75–1.69)	0.54
rs1130409 (T1349G)	PCOS (n = 100)	Controls (n = 100)	ORs (95 %CI)	P value
TT Genotype	10 (10 %)	26 (26 %)	Reference	Reference
TG Genotype	48 (48 %)	44 (44 %)	2.83 (1.22–6.54)	0.01
GG Genotype	42 (42 %)	31 (31 %)	3.52 (1.48–8.36)	0.003
Dominant Model	90 (90 %)	76 (76 %)	2.84 (1.27–6.31)	0.008
Co-dominant Model	48 (48 %)	44 (44 %)	1.17 (0.67–2.05)	0.57
Recessive Model	42 (42 %)	31 (31 %)	1.61 (0.90–2.88)	0.10
T allele	68 (34 %)	96 (48 %)	Reference	Reference
G allele	132 (66 %)	104 (52 %)	1.79 (1.19–2.68)	0.004

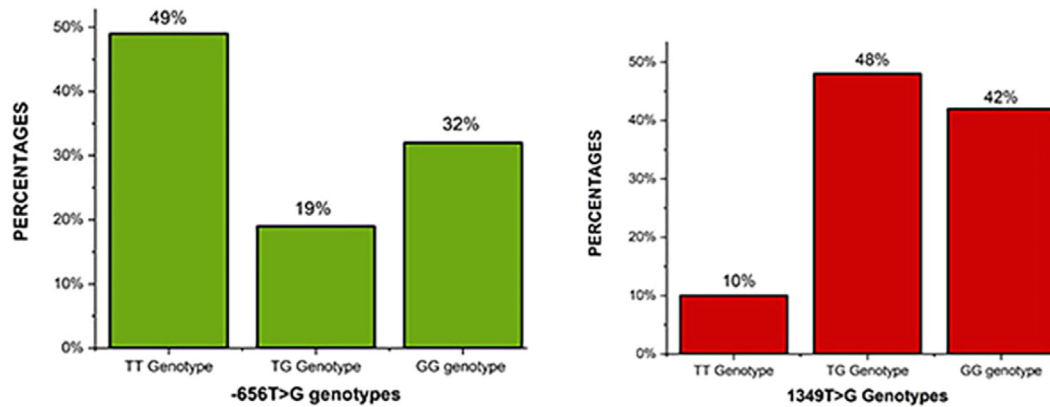
**Table 5**  
Anova analysis between clinical factors and T656G and T1349G variants.

	rs1760944 (-T656G)				rs1130409 (T1349G)			
	TT (n = 49)	TG (n = 19)	GG (n = 32)	P value	TT (n = 10)	TG (n = 48)	GG (n = 42)	P Value
Age	29.34 ± 5.55	29.36 ± 5.41	30.21 ± 5.34	0.76	30.20 ± 6.09	29.60 ± 5.73	29.52 ± 5.00	0.93
Weight	77.21 ± 9.24	76.57 ± 9.00	78.96 ± 10.00	0.61	78.17 ± 6.45	76.82 ± 11.11	78.47 ± 7.82	0.70
Height	156.42 ± 5.14	157.31 ± 3.92	157.05 ± 4.70	0.73	157.40 ± 4.67	156.10 ± 4.41	157.44 ± 5.15	0.37
BMI	31.37 ± 2.88	30.76 ± 2.72	31.71 ± 3.59	0.57	31.39 ± 1.63	31.25 ± 3.54	31.49 ± 2.83	0.93
FBG	5.16 ± 0.74	5.11 ± 0.52	5.05 ± 0.91	0.81	4.87 ± 0.61	5.10 ± 0.63	5.19 ± 0.91	0.48
TC	1.78 ± 0.97	1.70 ± 1.12	1.85 ± 1.23	0.89	2.20 ± 1.28	1.66 ± 0.88	1.84 ± 1.22	0.32
TG	4.95 ± 1.11	5.03 ± 0.96	5.24 ± 1.07	0.49	5.12 ± 0.67	5.03 ± 1.00	5.08 ± 1.22	0.95
HDLc	0.64 ± 0.25	0.68 ± 0.21	0.59 ± 0.21	0.38	0.65 ± 0.25	0.64 ± 0.22	0.62 ± 0.25	0.89
LDLc	3.50 ± 0.97	3.58 ± 0.82	3.80 ± 0.84	0.34	3.47 ± 0.65	3.64 ± 0.89	3.62 ± 0.98	0.86

3.3. Genotype distribution between PCOS women and control subjects

Table 4 shows the genotype distribution and allele frequencies of the -656 T > G and 1349 T > G SNPs in PCOS women and controls. In the -656 T > G SNP, PCOS women had genotype frequencies of 49 %, 19 %, and 32 % as TT, TG, and GG, respectively Fig. 1, while controls had genotype frequencies of 53 %, 17 %, and 30 % as TT, TG, and GG, respectively. The dominant allele (T) was found to be present in 58.5 % of PCOS women and 61.5 % of controls, whereas the minor allele (G) was found to be present in 41.5 % of PCOS women and 38.5 % of controls. There was no correlation between PCOS women and control participants in terms of allele frequency (OR-1.13 [95 %CI:0.75–1.69]; p = 0.54), genotype (TG vs TT: OR-1.20 [95 %CI: 0.56–2.58]; p = 0.62 and GG vs TT: OR-1.15 [95 %CI: 0.61–2.17]; p = 0.65), or genetic models such as dominant (OR-1.17 [95 %CI: 0.67–2.17]; p = 0.57), co-dominant (OR-1.14 [95 %CI: 0.55–2.35]; p = 0.71), and recessive models (OR-1.09 [95 %CI: 0.60–2.00]; p = 0.75).

The 1349 T > G SNP was found to be associated to allele (OR-1.79 [95 %CI: 1.19–2.68]; p = 0.004), genotype (TG vs TT: OR-2.83 [95 %CI: 1.22–6.54]; p = 0.01 and GG vs TT: OR-3.52 [95 %CI: 1.48–8.36]; p = 0.003), and dominant models (OR-2.84 [95 %CI:



## -656T>G and 1349T>G genotypes in APE1 gene

Fig. 1. Genotype frequencies between -656 T > G and 1349 SNPs in PCOS women.

1.27–6.31);  $p = 0.008$ ). However, neither co-dominant (OR-1.17 [95 %CI: 0.67–2.05];  $p = 0.57$ ) nor recessive models were (OR-1.61 [95 %CI: 0.90–2.88];  $p = 0.10$ ) associated. PCOS women had 66 % of the G allele and 34 % of the T allele, while controls had 52 % of the G allele and 48 % of the T allele. In PCOS women, the genotype frequencies were 10 %, 48 %, and 42 % as TT, TG, and GG genotypes (Figure-1), respectively, whereas in controls, the genotype frequencies were 26 % as TT, 44 % as TG, and 31 % as GG genotypes.

### 3.4. Anova analysis between APE1 variants and Table 1

Anova analysis was conducted in Table 5 in this study between genotypes involving TT, TG, and GG in -656 T > G and 1349 T > G SNPs and clinical and biochemical factors include age, height, weight, BMI, FBG, TC, TG, HDLC, and LDLC levels in PCOS women. No significant association was found between -656 and 1349 SNPs ( $p < 0.05$ ). FBG ( $5.16 \pm 0.74$ ) was found to be higher in the TT genotype at the -656 SNP, whereas height ( $157.31 \pm 3.92$ ) and HDLC ( $0.68 \pm 0.21$ ) were found to be elevated in the TG genotype and age ( $30.21 \pm 5.34$ ), weight ( $78.96 \pm 10.00$ ), BMI ( $31.71 \pm 3.59$ ), TC ( $1.85 \pm 1.23$ ), TG ( $5.24 \pm 1.07$ ), and LDLC ( $3.80 \pm 0.84$ ) were found to be elevated in the GG genotype. Among 1349 T > G SNP, age ( $30.20 \pm 6.09$ ), TC ( $30.20 \pm 6.09$ ), TG ( $5.12 \pm 0.67$ ), and HDLC ( $0.65 \pm 0.25$ ) were found to be higher values in the TT genotype, LDLC ( $3.64 \pm 0.89$ ) was found to be higher in TG genotype, and weight ( $78.47 \pm 7.82$ ), height ( $157.44 \pm 5.15$ ), BMI ( $31.49 \pm 2.83$ ), and FBG ( $5.19 \pm 0.91$ ) were found to be significantly higher in the GG genotype.

## 4. Discussion

The purpose of this study is to examine the effects of the APE1 -656 T > G and -1349 T > G SNPs in the predisposition to PCOS women in Saudi Arabia. The APE1 gene is a key regulator of the frontline base excision repair pathway, which may be employed to repair DNA damage processes. The APE1 gene has been linked to a variety of human diseases, including cancer (Liu et al., 2021), male (Yousefi et al., 2015) and female infertilities (Mashayekhi et al., 2016) and PCOS (Gulbay et al., 2017). The human APE1 gene is 318 amino acid protein and 3 kb in size, found on chromosome 14, with 4 introns and 5 exons. APE1 is a numerous oxidation reduction factors as well as other repair pathways such as DNA repair, transcription factor activity modulation, apoptosis, redox

homeostasis, and maturation related multifunctional protein. DNA repair systems are damaged in monocytes, and APE1 plays an important function in those cells in other ways (Betlej et al., 2020). Kaur was identified Asp148Glu SNP (Kaur and Kaur 2018).

The current study results confirmed age, weight, BMI, TG, LDLC and family history are associated in PCOS women ( $p < 0.05$ ) and HWE analysis showed that -656 T > G and 1349 T > G SNPs in the APE1 gene were the same as in the control group ( $p > 0.05$ ). None of the allele and genotype frequencies in the -656 T > G SNP were linked to each other. ( $p > 0.05$ ), whereas, 1349 T > G SNP was found to be associated with allele (OR-1.79 [95 %CI: 1.19–2.68];  $p = 0.004$ ), genotypes (TG vs TT: OR-2.83 [95 %CI: 1.22–6.54];  $p = 0.01$  and GG vs TT: OR-3.52 [95 %CI: 1.48–8.36];  $p = 0.003$ ) and dominant model (OR-2.84 [95 %CI: 1.27–6.31];  $p = 0.008$ ). However, Anova analysis failed to show the association between Table 1 and a couple of SNPs involved in this study ( $p > 0.05$ ). The genotyping analysis of 1349 T > G SNP of current study results was found to be associated with previous studies carried out in PCOS (Gulbay et al., 2017) and female infertility (Mashayekhi et al., 2016). APE1 gene studies were carried out in Saudi Population and confirmed the positive association with 1349 T > G SNP (AlMutairi et al., 2015, Nemer et al., 2018). Unfortunately, limited studies in female populations have been conducted in the APE1 gene, and this is the first study documented in PCOS disease in Saudi Arabia, and it was examined with -656 T > G and 1349 T > G SNPs, and Asp148Glu (1349 T > G) variant was strongly associated with PCOS women. Having a 1349 T > G SNP in APE1 can lead to decreased activity of APE1 in the DNA base excision repair pathway, which increases the risk of polycystic ovary syndrome in carriers. APE1 individuals with the 1349 T > G SNP have reduced APE1 activity in the DNA base excision repair pathway, which contributes to an increased risk of polycystic ovary syndrome. A greater prevalence of human diseases among Asian women is suggested by a previous meta-analysis study (Mohammed Nawi et al., 2021). This study analysis supports the observation by demonstrating that the Glu residue at 148 locations in APE1 enhances the risk of PCOS in Saudi women. The current study discovered and demonstrated that the Glu residue at APE1 position 148 significantly increases the incidence of PCOS in Saudi women.

PCOS is considered as hormonal and metabolic disorder affecting in reproductive aged women causing them ovarian problems. The definition of PCOS can be defined as a hormonal condition that affects women of reproductive age. PCOS, which often begins after

adolescence, causes the emergence of numerous symptoms connected with the hormonal disorder, which causes ovarian issues and leads to egg underdevelopment or hinders its release during ovulation. The pathophysiology of PCOS is elusive, however it is thought to be connected to both inherited and environmental factors. Acne and irregular menstruation were considered to be frequent PCOS symptoms. Obesity and T2DM have been linked to PCOS. All human diseases are connected to a family health history that may be inherited, and genes can be transmitted and detected in individuals who have a greater than average risk of developing human disorders. Family members will inherit common traits via sharing their DNA, environment, lifestyles, and behaviors. The family history of PCOS was found to be 33 % in this study, indicating that one-third of Saudi women were diagnosed, and these women are at risk of developing future complications such as diabetes, cancer, MetS, and endometrial cancer (Helvacı and Yildiz 2020). There is currently no cure for PCOS, however it can be treated with restricted medicines and fertility treatment. The strength of this study was to enroll all Saudi women and studied the couple of important markers in *APE1* gene. The limitations of this study were the selection of 100 PCOS women and 100 controls, as well as the omission of serum concentration.

## 5. Conclusion

Finally, this study confirms as 1349 T > G SNP was associated in PCOS women. However, -656 T > G was not associated. Future studies should be carried out in global population on male and female couples, and the impact of the -656 T > G and 1349 T > G polymorphisms in the *APE1* gene should be investigated using *meta*-analysis.

## Declaration of Competing Interest

The author declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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