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Генетические ассоциации между полиморфными локусами генов ферментов антиоксидантной защиты GPX4 (rs713041), GSTP1 (rs1695) и PON1 (rs662) и синдромом поликистозных яичников у российских женщин

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Введение. Синдром поликистозных яичников (СПКЯ) является распространенным и сложным эндокринологическим заболеванием, с различными молекулярными фенотипами и коморбидными состояниями. Многочисленные исследования указывают на окислительный стресс как на ключевой фактор в развитии СПКЯ.
Цель: исследовать ассоциации между полиморфными локусами генов ферментов антиоксидантной защиты *GPX4* (rs713041), *GSTP1* (rs1695) и *PON1* (rs662) и риском развития СПКЯ.
Методы: генотипирование проводили аллель специфическим методом ПЦР в реальном времени.
Результаты. Анализ результатов генотипирования показал, что минорные аллели полиморфных локусов генов *GPX4* (rs713041) и *PON1* (rs662) ассоциированы с повышенным риском развития СПКЯ. В частности, наличие генотипа TT гена *GPX4* (rs713041) и хотя бы одной копии аллеля C гена *PON1* (rs662) было ассоциированно с повышенной предрасположенностью к СПКЯ.
Выводы. Полиморфные варианты генов *GPX4* (rs713041) и *PON1* (rs662) могут служить факторами риска развития СПКЯ.

Ключевые слова: СПКЯ, синдром поликистозных яичников, полиморфный локус, антиоксидантный фермент, *GPX4, GSTP1, PON1*.

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Genetic Associations between polymorphic loci in the antioxidant enzyme genes GPX4 (rs713041), GSTP1 (rs1695), and PON1 (rs662) and Polycystic Ovary Syndrome in Russian women

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Background. Polycystic ovary syndrome (PCOS) is a common and complex endocrinologic disease, with various molecular phenotypes and comorbid conditions. Numerous studies have highlighted oxidative stress as a pivotal factor in the development of PCOS.
Aim: to investigate the associations between polymorphic loci of the genes of antioxidant defense enzymes *GPX4* (rs713041), *GSTP1* (rs1695) and *PON1* (rs662) and the risk of developing PCOS.
Methods. Genotyping analysis was performed by allele-specific method using real-time PCR.
Results. Genotyping analysis revealed that the minor alleles of *GPX4* (rs713041) and *PON1* (rs662) polymorphic loci were associated with an increased risk of PCOS development. Specifically, the presence of the TT genotype of *GPX4* (rs713041) and having at least one copy of the mutant allele of *PON1* (rs662) were associated with elevated susceptibility to PCOS.

Conclusions. Polymorphic variants of *GPX4* (rs713041) and *PON1* (rs662) genes might be a risk factor for PCOS development.
Keywords. PCOS, Polycystic ovary Syndrome, polymorphic locus, antioxidant enzyme, *GPX4, GSTP1, PON1*.

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Introduction

Polycystic ovary syndrome (PCOS) is a prevalent multifaceted endocrinological disorder that extends beyond reproductive implications, affecting the entire physiological system. It is often characterized by obesity and various metabolic disorders such as dyslipidemia, hyperinsulinemia, and hyperandrogenism. PCOS elevates the risk of insulin resistance, type 2 diabetes, and cardiovascular complications. While the exact origin of PCOS remains uncertain, hyperandrogenism and insulin resistance are widely regarded as primary factors, perpetuating each other in a detrimental cycle along with other contributing factors. Numerous studies highlights the presence of prolonged oxidative stress imbalance and chronic low-grade inflammation in PCOS patients [1].

Oxidative stress (OS) is a condition in which the balance between free radicals and the body's ability to effectively neutralize them is disturbed. OS has been found to play a critical role in the pathophysiology of PCOS, influencing its onset and progression. A meta-analysis has confirmed elevated levels of OS markers in women with PCOS, as well as decreased levels of antioxidant parameters [1]. OS alters ovarian steroidogenesis towards increasing androgen production, leading to follicular atresia. It affects key processes in folliculogenesis and oocyte development, which can have a significant impact on a woman's reproductive function [2]. The question to what extent OS and inflammation are causally related to PCOS remains open. It is generally recognized that genetic variability in key antioxidant enzymes may determine an individual's ability to protect against OS and its susceptibility to inflammation and oxidative stress. Several levels of antioxidant defense mechanisms have been identified, including antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), glutathione S-transferase P1 (GSTP1) and paraoxonase-1 (PON1), as well as non-enzymatic mechanisms such as antioxidants and metal-binding proteins.

GPX4 is glutathione peroxidase 4, a component of the thiol-dependent antioxidant system. The *GPX4* gene, located on chromosome 19p13.3. GPX neutralizes hydroperoxides and hydrogen peroxide through the involvement of glutathione (GSH). Uniquely, GPX4 reduces hydroperoxides in complex lipids, protecting membranes from peroxidation and cell death. Its role in the human body is invaluable, including maintaining mitochondrial function, regulating inflammation, and supporting immunity. GPX4 is classified as a selenoprotein with the importance of the SECIS sequence for selenocysteine incorporation. It has been suggested that subtle genetic variations in this sequence may influence gene activity and enzyme function. The most studied polymorphic locus in this region is rs713041 (C718T), which is substitution located at position 718 of the *GPX4* gene mRNA in the 3'-UTR. This polymorphic locus has demonstrated functionality in regulating *GPX4* translation by altering the affinity of the Sec insertion machinery for its SECIS element, potentially altering the efficiency of selenocysteine incorporation into GPX4 [3]. Rs713041 has been implicated in various diseases, including prostate and breast cancer [4,5], autoimmune thyroid disorders [6], and endometriosis [7]. However, its association with PCOS has not been studied yet.

Glutathione S-transferase pi 1 (GSTP1) represents a major member of the glutathione S-transferase family, providing about 90% of the enzymatic activity. These enzymes participate in cytosolic phase II metabolism by promoting the conjugation of glutathione to reactive electrophilic compounds. This process renders the compounds water-soluble, facilitating their excretion. The *GSTP1* gene, located on chromosome 11q13, is highly polymorphic. Mutations in *GSTP1* can lead to altered antioxidant responses, particularly in the defense of cell membranes against lipid peroxidation. Polymorphic loci in *GSTP1* have been associated with various cancers including breast and prostate cancer [8,9]. The rs1695 (A>G) polymorphic locus, by affecting the active site of the enzyme, may alter its enzymatic activity and substrate specificity [8]. Carriers of the rs1695 mutant allele (G) have an increased

risk of developing cancer, especially tobacco smokers [10]. In addition, rs1695 may be associated with the risk of type 2 diabetes, obesity, and systemic lupus erythematosus [11,12]. The impact of rs1695 on reproductive diseases, including PCOS, has not been studied yet.

Paraoxonase 1 (PON1), encoded by the *PON1* gene and located on chromosome 7q21.3, is a calcium-dependent antioxidant enzyme that circulates in the blood and cooperates with high-density lipoprotein (HDL) cholesterol. This enzyme is synthesized primarily in the liver but is also present in various tissues including the brain, heart, kidney, and intestine. PON1 has multiple functions including paraoxonase, arylesterase, lactonase and ester hydrolase activities. Its role as a cardioprotective enzyme is demonstrated by preventing oxidative modifications of LDL, degrading lipid peroxides, and inhibiting inflammatory processes. In addition, PON1 promotes insulin biosynthesis, enhances glucose uptake, and exhibits antioxidant and anti-inflammatory properties [13]. Reduced PON1 activity is associated with an increased risk of diseases including type 2 diabetes, cardiovascular atherosclerotic diseases and PCOS [14–16]. Various polymorphic loci in the *PON1* gene, such as rs854560 (L55M), rs662 (Q192R) and rs705379 (-108 C/T), affect its expression, stability and activity, which may affect the risk of diseases including PCOS.

In this study, we aimed at investigation the role of rs713041, rs1695, and rs662 in the *GPX4*, *GSTP1*, and *PON1* genes, respectively, in the risk of PCOS development.

Methods

1. Study subjects

In this case-control study, a total of 181 women were enrolled. Among them, 66 women had been diagnosed with PCOS, and 115 women - as a comparison group. These women underwent assisted reproductive technologies (ART) treatment at the Center for Human Reproduction and IVF in Rostov-on-Don, Russia, between 2021 and 2023. PCOS diagnosis was based on the Rotterdam criteria, which required the presence of at least two of the following three criteria: 1) clinical or biochemical confirmation of hyperandrogenism, 2) oligo- or anovulation, and 3) ultrasonographic evidence of polycystic ovarian morphology, characterized by the presence of more than 12 follicles (2-9 mm in diameter) in each ovary, or a total of 20 antral follicles across both ovaries, or an enlarged ovary with a volume exceeding 10 ml. The comparison group included women who entered the IVF/ICSI program due to «male factor» infertility. Patients in both groups with and without PCOS were comparable in age, body mass index, and hormonal stimulation protocol (protocol with gonadotropin-releasing hormone antagonists). Inclusion criteria: age less than 45 years, absence of severe extragenital pathology, embryo transfer in a superovulation cycle. Exclusion criteria: age 45 years and older, X-linked genetic syndromes causing oocytic infertility, presence of severe extragenital pathology or endocrinological pathologies such as hyperprolactinemia, Cushing's disease, adrenal hyperplasia, or ovarian tumors.

All participants provided their informed consent to be part of this study. The study was conducted in compliance with the ethical principles outlined in the Helsinki Declaration and received approval from the local bioethics committee at Southern Federal University (Protocol No. 2 of 17.01.2018).

2. Genotyping of GPX4 (rs713041), GSTP1 (rs1695), and PON1 (rs662)

Peripheral blood samples were collected in EDTA and subsequently stored at -20°C. Genomic DNA was then extracted utilizing the «DNA-extran-1 (EX-509)» kit provided by («Syntol», Russia). Genotyping of *GPX4* (rs713041) and *GSTP1* (rs1695) was conducted using the «SNP-Screen» kits (NP-415-100, NP-429-100) («Syntol», Russia). For genotyping of *PON1* (rs662) the «SNP-EXPRESS» kit (N° s01125-100) («Litech», Russia) was employed. The QuantStudio Real-Time PCR Systems by Applied Biosystems, Thermo Fisher Scientific, United States, were utilized for these analyses.

3. Biochemical and hormonal analysis

Biochemical and hormonal analysis was conducted on morning blood samples obtained from patients following a fasting period of 12-14 hours. The serum was isolated from the blood samples through centrifugation at 3000 rpm for 5 minutes and then stored at -20°C until further analysis. The hormonal analysis was carried out as per established protocols [17]. The insulin level was measured using the Beckman Coulter test systems on the Access 2 automatic analyzer. The glucose level was determined using a LabSystem analyzer from Finland, with reagents sourced from Biocon in Germany. The HOMA-IR index was calculated using the formula: HOMA-IR = fasting insulin (μU/mL) × fasting glucose (mmol/L) / 22.5.

4. Statistical analysis

For our statistical analysis, we employed GraphPad Prism 7. The comparisons of variables were carried out

using Mann–Whitney U test. The variables were presented as median (25%, 75% percentiles) for each group. In comparing genotypic and allelic frequencies between the PCOS and the comparison group, we utilized Fisher's exact test instead of the chi-square test, as it provides a more accurate P-value calculation with a small sample size. Statistical significance was determined at $p < 0.05$.

Results

1. Hormonal profiles in blood serum of PCOS patients and the comparison group

Table 1 illustrates the hormonal profiles of both PCOS patients and healthy women. Our assessment included measurements of total and free testosterone, dehydroepiandrosterone (DHEA), and dehydroepiandrosterone sulfate (DHEA-S) in both groups. As anticipated, the PCOS group exhibited significantly elevated levels of serum total and free testosterone, as well as DHEA, compared to the comparison group. However, the variance in DHEA-S levels between PCOS patients and the comparison group was not statistically significant. Additionally, markers such as LH, LH/FSH ratio, anti-mullerian hormone (AMH), and BMI were notably higher in the PCOS group. Moreover, PCOS patients demonstrated a significant increase in 17-OH-progesterone, insulin levels, and HOMA-IR, while levels of FSH and SHBG were significantly lower compared to the comparison group. Nonetheless, no significant differences were observed in estradiol, progesterone, and glucose levels between the two groups.

2. Association of polymorphic loci of GPX4 (rs713041), GSTP1 (rs1695), and PON1 (rs662) genes with PCOS risk

We determined the genotypic and allelic frequencies for *GPX4* (rs713041), *GSTP1* (rs1695), and *PON1* (rs662) in Russian women. The data are summarized in **Table 2**. The genotypic distributions for all three polymorphic loci were in accordance with the Hardy–Weinberg equilibrium ($p > 0.05$).

A significant difference was observed in the genotype distribution of *GPX4* (rs713041), since TT genotype was more frequently observed in patients (27.3%) than in comparison group (13.9%), ($p = 0.0310$). Although the T allele frequency was higher in PCOS (49.2%) compared

Таблица 1. Гормональный профиль в сыворотке крови больных СПКЯ и в группе сравнения

Table 1. Hormonal profiles in blood serum of PCOS patients and the comparison group

	COMPARISON GROUP	PCOS	P-value
BMI (kg/m²)	21 (20-23)	24 (22-29)	**<0,001**
Total testosterone (nmol/l)	1,2 (0,9-1,7)	1,8 (0,7-3,2)	**0,0001**
Free testosterone (pmol/l)	3,12 (1,5-8,4)	5,55 (0,8-8,7)	**0,0181**
DHEA (ng/ml)	3,9 (3,4-6,0)	4,8 (3,2-6,8)	**0,0466**
DHEA-S (µg/ml)	2,7 (1,7-4,4)	2,8 (1,7-4,2)	0,877
Estradiol (pmol/l)	188 (134-242)	186 (140-514)	0,523
Progesterone (nmol/l)	1,3 (0,4-2,5)	1,6 (0,7-3,2)	0,224
FSH (IU/l)	7,0 (6,1-8,5)	6,0 (5,1-7,5)	**0,002**
LH (IU/l)	5,4 (3,9-7,8)	7,3 (4,1-10,9)	**0,023**
LH/FSH	0,78 (0,62-1,04)	1,16 (0,8-1,82)	**<0,0001**
17-OH progesterone (ng/ml)	2,2 (1,6-2,7)	3,2 (2,3-4,3)	**0,003**
AMH (ng/ml)	2,7 (2,0-3,4)	8,9 (6,3-13,7)	**<0,001**
SHBG (nmol/l)	81 (56-96)	43 (29-56)	**0,001**
Insulin (µIU/ml)	4,4 (4,0-5,2)	7,2 (5,2-13,1)	**0,004**
Glucose (mmol/l)	4,5 (4,4-5,4)	5,1 (4,6-5,6)	0,302
HOMA-IR	1,1 (0,6-1,1)	1,7 (1,2-3,0)	**0,002**

Abbreviations: BMI body mass index; DHEA dehydroepiandrosterone; DHEA-S dehydroepiandrosterone sulfate; FSH follicle-stimulating hormone; LH luteinizing hormone; AMH anti-mullerian hormone; SHBG sex hormone binding globulin; HOMA-IR insulin resistance level.

to (39.1%) the comparison group. This difference was not significant (p = 0.0773).

A significant difference was observed in the allelic distribution of the polymorphic locus *PON1* (rs662) (p = 0.0423). The frequency of the C allele was higher in PCOS (43.9%) compared to the comparison group (33%). Moreover, the genotypes (CC+TC) were found to be more frequent among PCOS patients (p = 0381). For *GSTP1* (rs1695) genotyping, it was found that the frequency of AG and GG genotypes was higher in patients with PCOS compared to the comparison group. Additionally, the frequency of minor allele was also elevated (34.48%) in PCOS patients compared to the comparison group (27%). However, these differences did not reach statistical significance (P > 0.05).

Discussion

Polycystic Ovary Syndrome presents a multifaceted challenge within reproductive health, characterized by a spectrum of hormonal, metabolic, and physiological irregularities. Despite various hypotheses proposed over the years regarding the immediate physiological origins of PCOS, the precise pathophysiological pathway initiating the syndrome remains elusive due to its heterogeneity. Hyperandrogenism synergizes with insulin resistance, creating a cyclical dynam-

Таблица 2. Частоты генотипов и аллелей *GPX4* (rs713041), *GSTP1* (rs1695) и *PON1* (rs662) у больных СПКЯ и в группе сравнения
Table 2. The genotypic and allelic frequencies for *GPX4* (rs713041), *GSTP1* (rs1695), and *PON1* (rs662) in PCOS patients and comparison group

		PCOS N (%)	COMPARISON GROUP N (%)	P	OR (95% CI)
***GPX4* (rs713041)**	Genotype			0.0842	
	CC	19 (28.8)	41 (35.65)	-	
	CT	29 (43.9)	58 (50.43)		
	TT	18 (27.3)	16 (13.91)	0.0310	2.32 (1.094 - 5.045)
	CT+TT	47	74	0.4129	1.371 (0.719 - 2.641)
	Allele				
	C	67 (50.8)	140 (60.9)	-	
	T	65 (49.2)	90 (39.1)	0.0773	1.509 (0.975 - 2.343)
***GSTP1* (rs1695)**	Genotype			0.2591	
	AA	29 (43.94)	61 (53)	-	
	AG	28 (42.42)	46 (40)		
	GG	9 (13.64)	8 (7)	0.1832	2.15 (0.8266 -5.916)
	AG+GG	36	54	0.3519	1.402 (0.7492 - 2.54)
	Allele				
	A	86 (65.15)	168 (73)	-	
	G	46(34.85)	62 (27)	0.1496	1.435 (0.91 -2.302)
***PON1* (rs662)**	Genotype			0.0825	
	TT	18 (27.3)	50 (43.5)	-	
	TC	38 (57.6)	54 (47)		
	CC	10 (15.1)	11 (9.5)	0.3350	1.688 (0.6568 - 4.155)
	TC+CC	48	65	0.0381	2.051 (1.085 - 3.992)
	Allele				
	T	74 (56.1)	154 (67)	-	
	C	58 (43.9)	76 (33)	0.0423	1.588 (1.033 - 2.439)

ic of mutual reinforcement that contributes to the onset and progression of PCOS. This interplay involves oxidative stress and chronic low-grade inflammation among other factors.

Oxidative stress has been a highly researched topic in the last two decades. Several studies have indicated that OS is involved in the development of many diseases, such as diabetes, cancer, cardiovascular diseases, and PCOS [18–20]. Many studies tried to evaluate OS markers in PCOS women [1,21]. In which PCOS patients present with higher levels of OS than controls. Murri et al.'s meta-analysis of 63 studies, involving 4933 PCOS patients and 3671 controls, revealed significantly elevated OS markers in PCOS patients. Additionally, circulating antioxidant markers, such as glutathione and PON1 activity, were decreased [1].

Excessive ROS accumulation in serum or follicular fluid can arise from various sources. One source is disruptions in the electron transport chain within follicular cells, leading to increased ROS production [17]. Prooxidant enzymes like NADPH isoform-oxidases (NOX4, NOX5) also contribute by generating superoxide and hydrogen peroxide [18]. Additionally, the activation of steroidogenic cytochrome P450 enzymes in the ovaries may elevate ROS levels [19]. On the other hand, impaired elimination of ROS by antioxidants, including SOD2, CAT, GPX4, GSTP1, and PON1, can also lead to ROS accumulation. Genetic variations in these antioxidative enzymes can influence an individual's defense against OS and their susceptibility to it [22]. Our research revealed a significant association between the minor alleles of *GPX4* (rs713041) and *PON1* (rs662) polymorphic loci and PCOS development. Individuals with the genotype (TT) of *GPX4* (rs713041) face a significantly higher risk of developing PCOS. Moreover, the frequency of *PON1* (rs662) is notably higher in PCOS patients compared to the comparison group, and the presence of at least one mutant allele of *PON1* (rs662) enhances the risk of PCOS development. However, we did not find a significant association between the polymorphic locus of *GSTP1* (rs1695) and PCOS development.

Rs713041 in *GPX4* represents a C718T substitution at position 718 of the *GPX4* gene mRNA in the 3'-UTR. Rs713041 has been shown to impact *GPX4* translation by modifying the affinity of the Sec insertion machinery for its SECIS element, potentially affecting the efficiency of selenocysteine incorporation into GPX4 [23]. The minor allele of rs713041 (T) has been found to be associated with an elevated risk of various cancers including colorectal, prostate and breast cancer [5,24], as well as an increased risk of stroke and hypertension [3]. This polymorphic variant is associated with the hyperactivation of signaling pathways that produce oxidative stress and inflammation mediators, since the TT genotype amplifies lipid peroxidation, monocyte adhesion, and VCAM-1 expression in endothelial cells, making it a risk factor for cardiovascular disease development [25]. In addition, rs713041 is associated with autoimmune thyroid diseases and multiple sclerosis [6,26]. [27]. In the field of infertility, *GPX4* (rs713041) along with several other alleles were shown to be risk alleles for idiopathic recurrent miscarriage [28]. In pre-eclampsia patients, the T allele of *GPX4* (rs713041) contributes to a hypoxic environment during periods of ischemia and placental reperfusion, leading to the formation of ROS, lipid peroxidation, and endothelial dysfunction [29]. In addition, rs713041 was associated with the severity of the endometriosis [7]. Notably, our research is the first to reveal a significant association of rs713041 with PCOS risk.

RS662 in *PON1* is a T>C substitution that leads to a guanine-to-arginine change at the 192nd amino acid position in the enzyme's active site, affecting PON1's catalytic efficiency. Similar to our findings, the CC genotype is more prevalent in Greek PCOS women and is associated with hyperandrogenemia. Patients with the CC genotype exhibit higher levels of testosterone, Free Androgen Index (FAI), and dehydroepiandrosterone sulfate (DHEAS) compared to those with wild-type or heterozygous genotypes [30]. Moreover, the CC genotype of rs662 remains a significant predictor for PCOS among south-west Chinese women. Patients with the CC or TC genotype exhibit significantly higher waist circumference, fasting insulin, and triglyceride levels.31]] However, studies conducted on Spanish and Indian women did not demonstrate an association between rs662 and PCOS development [32,33]. A meta-analysis revealed a significant association between rs662 in PON1 in both the allelic and recessive models [34]. According to the 1000 Genomes Browsers, the C allele frequency of rs662 varies among populations, ranging from 29% in Europeans to 75% in Africans and 67% in Eastern and 42% in Southern Asians. Rs662 has a significant impact on lipid profiles, disease severity, and mortality in COVID-19 patients [35]. It also affects PON1 activity and HDL-cholesterol levels in individuals with metabolic syndrome [36]. A meta-analysis has revealed a significant association of rs662 with recurrent pregnancy loss risk [37]. Therefore, PON1 is crucial for averting oxidative stress and managing inflammation. A deficiency in its activity may contribute to PCOS development.

OS significantly impacts key aspects of PCOS. It plays a role in the development of insulin resistance (IR) in PCOS patients. OS disrupts glucose uptake in muscle and adipose tissue and diminishes insulin secretion from

pancreatic β-cells [38]. IR can be triggered by intracellular signaling in response to OS, both in vitro and in vivo [39]. Although the precise mechanism is not fully understood, exposure to OS inhibits insulin-stimulated glucose uptake, glycogen, and protein synthesis [40]. The elevated OS activates various protein kinases, leading to abnormal phosphorylation of insulin receptor substrate (IRS) and reducing its ability to bind with the insulin receptor, thereby suppressing downstream phosphatidylinositol 3-kinase activation. Moreover, OS influences steroidogenesis in the ovaries, disrupting follicular development, resulting in infertility and heightened androgen production [40]. Oocyte maturation relies on a complex process involving proliferation and differentiation of various cell types during follicle development, which directly impacts gamete quality. Studies, both systemic and localized, examining follicular maturation, oocyte quality, and overall fertility efficiency in relation to OS levels establish a direct association between fundamental processes and OS in the ovary. These processes encompass atresia of primordial and primary follicles, oxidative damage to lipids leading to suboptimal oocyte quality, oocyte fertilization, early embryonic development, and reduced female fertility [2].

PCOS is a multifaceted condition influenced by a complex interplay of genetic, epigenetic, and environmental factors. The intricate network of genetic elements, including polymorphic loci in genes such as *GPX4*, *PON1*, *CYP17A1*, *SOD2* [41], and more, exerts an influence on various fundamental processes central to PCOS, including steroidogenesis and oxidative stress.

This study has several limitations. Firstly, the modest number of PCOS patients who could be included in the trial after meeting crucial diagnosis criteria was its main limiting factor. Secondly, potential selection bias could have been introduced by recruiting primarily from specialized clinics, possibly excluding individuals with milder or undiagnosed forms of the condition. To comprehensively understand the effects of genetic polymorphic loci on various aspects of PCOS, large multicentric research involving diverse ethnic groups is necessary.

Conclusion

Our investigation highlights that genetic variations in *GPX4* (rs713041) and *PON1* (rs662) may play a significant role in predisposing individuals to PCOS, whereas *GSTP1* (rs1695) does not appear to have a significant association with the condition. These findings underscore the crucial role of the oxidative stress defense system in the pathogenesis of PCOS.

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