Association of common *OGG1* and *SOD2* polymorphisms with Preeclampsia in Russian pregnant women from Rostov region

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Abstract

Background: Preeclampsia (PE) is a pregnancy-specific disorder characterized by high maternal blood pressure and protein in urine, typically occurring after 20 weeks of gestation, making it the most common serious pregnancy medical complication. The aim of this study: This study aimed to investigate the association of *SOD2* (rs4880) and *OGG1* (rs1052133) genetic variants with the risk of developing PE in Russian pregnant women from Rostov region. Materials and methods: A total of 106 samples (60 normotensive pregnant women and 46 preeclamptic pregnant women) were analyzed in this study. Genotyping for (rs1052133) and (rs4880) polymorphisms was done via allele specific RT-PCR. The analysis of Multifactor dimensionality reduction (MDR) was used to assess the gene-gene interaction among selected polymorphisms. Results: The results of *OGG1* (rs1052133) polymorphism did not show any significant association with PE risk in both genotypes and allele models (p>0,05). While, the *SOD2* (rs4880) polymorphism was significantly associated with PE risk (p<0,001). The *SOD2* (rs4880) CC genotype is associated with increased risk of PE (OR=11,36 95 % CI [3,08-41,89]). Both the dominant and recessive models are also associated with increased risk of PE (OR=7,20 95 % CI [2,98-17,40]; OR=12,21 95 % CI [3,32-44,97], respectively). While the TT genotype has a protective effect against PE development (OR=0,14 95 % CI [0,06-0,34]). Moreover, the frequency of minor (C) allele was significantly higher in preeclamptic women and could be considered as a risk factor (p<0,001; OR=5,99 95 % CI [3,24-11,09]). According to the MDR results, the gene-gene interaction was statistically significant (p< 0,0001). Conclusion: Our results provided evidences of a significant association between genotypes of *SOD2* rs564398 polymorphism and susceptibility to develop PE risk in Russian pregnant women from Rostov region. It is worth noting that this study is the first to examine the association of the *OGG1* gene polymorphism and susceptibility to PE.
Keywords: Pre-eclampsia; polymorphisms; OGG1; SOD2.

Ассоциация распространенных полиморфизмов *OGG1* и *SOD2* с преэклампсией у российских беременных женщин из Ростовской области

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Аннотация

Введение: Преэклампсия (ПЭ) - специфическое для беременности заболевание, характеризующееся высоким артериальным давлением и протеинурией, обычно возникающее после 20 недель беременности и являющееся наиболее распространенным серьезным медицинским осложнением беременности. Цель исследования:

Целью данного исследования было изучение ассоциации генетических вариантов *SOD2* (rs4880) и *OGG1* (rs1052133) с риском развития ПЭ у российских беременных женщин из Ростовской области.

Материалы и методы: Всего в исследовании проанализировано 106 образцов (60 беременных с нормотензией и 46 беременных с преэклампсией). Генотипирование полиморфизмов (rs1052133) и (rs4880) проводили методом аллель-специфической RT-PCR. Для оценки ген-генного взаимодействия между выбранными полиморфизмами использовали анализ многофакторного снижения размерности (MDR).

Результаты: Результаты исследования полиморфизма *OGG1* (rs1052133) не выявили значимой ассоциации с риском ПЭ как в генотипах, так и в аллельных моделях ($p>0,05$). В то время как полиморфизм *SOD2* (rs4880) был достоверно ассоциирован с риском ПЭ ($p<0,001$). Генотип *SOD2* (rs4880) CC ассоциирован с повышенным риском ПЭ (OR=11,36 95 % CI [3,08-41,89]). Доминантная и рецессивная модели также связаны с повышенным риском ПЭ (OR=7,20 95 % CI [2,98-17,40]; OR=12,21 95 % CI [3,32-44,97], соответственно). В то время как генотип TT обладает протективным эффектом против развития ПЭ (OR=0,14 95 % CI [0,06-0,34]). Кроме того, частота минорного аллеля (C) была значительно выше у женщин с преэклампсией и может рассматриваться как фактор риска ($p<0,001$; OR=5,99 95 % CI [3,24-11,09]). По результатам MDR анализа взаимодействие генов было статистически значимым ($p<0,0001$).

Выводы: Полученные нами результаты свидетельствуют о значимой ассоциации между генотипами полиморфизма *SOD2* rs564398 и предрасположенностью к риску

развития ПЭ у российских беременных женщин из Ростовской области. Следует отметить, что данное исследование является первым, в котором изучена ассоциация полиморфизма гена *OGG1* (rs1052133) с предрасположенностью к ПЭ.
Ключевые слова: Преэклампсия; полиморфизмы; OGG1; SOD2.

Introduction

Pre-eclampsia (PE), is one of the most serious and prevalent medical complication that may arise during pregnancy (Martinez-Portilla et al., 2021). The vulnerability of mothers to PE is a complicated and multifaceted process that involves the influence of several key gene variations, which in turn alter hemodynamic and vascular parameters (Ortega et al., 2022; Nadeim, Shkurat, 2022).). The exact cause and mechanisms of PE are not well comprehended, however there is a substantial association between the formation of this condition and oxidative stress (Al-Kuraishy et al., 2018; Tenório et al., 2019). Oxidative stress pathways lead to damage in the endothelial cells and the occurrence of abnormal metabolic and coagulation processes (Incalza et al., 2018). Moreover, oxidative stress is believed to be a significant factor in the development of PE (Tenório et al., 2019). Genetic researches have focused on examining gene polymorphisms associated with oxidative stress to see whether there is an increased risk for PE (N. Zhao et al., 2021).

Manganese superoxide dismutase (MnSOD), also known as superoxide dismutase 2 (*SOD2*), is a protein, which encodes by *SOD2* gene located on chromosome 6q25,3, found in the mitochondria that forms a homotetramer structure. Both subunits of the molecule have an affinity for manganese ions. This enzyme facilitates the transformation of superoxide byproducts generated during oxidative phosphorylation into H2O2 and O2(Zou et al., 2017). There have been reports indicating that a variation in the *SOD2* gene is associated with the heightened production of biomarkers indicating oxidative stress damage (Jerotic et al., 2019). The presence of the *SOD2* variant allele in individuals with PE may indicate an increased vulnerability to the development of PE (Teimoori et al., 2019). Genetic variations in enzymes involved in the process of oxidative stress, such as *SOD2* (Val16Ala; rs4880) polymorphism, might impact it`s antioxidant activity and then contribute to the development of PE. Prior researches have shown a correlation between variations in *SOD2* gene and the likelihood of developing PE (Luo et al., 2018; G. Zhao et al., 2022).

In the other hand, several forms of DNA damage can result from reactive oxygen and nitrogen species (RONS) oxidizing DNA(Rons et al., 2022). These include 7,8-hydroxy-2-deoxyguanosine (8oxodG) lesions, an abasic site (also called an apurinic/apyrimidinic [AP] site), single- and double-strand breaks (DSBs), cross-linking, and alternative base mutations (Koshiji et al., 2005). The primary mechanism for repairing DNA damage caused by RONS is base excision repair (BER). This repair pathway plays a crucial role in preserving the integrity of the genome during chronic inflammation.

Multiple studies have shown a greater degree of oxidative DNA damage in the placentas of women with PE in comparison to placentas obtained from women who had normal pregnancies(Chiarello et al., 2020; Ferreira et al., 2020). It`s known that the BER protein OGG1 is found in the placenta, and it`s level is higher in pregnant women with PE than in normal pregnancy (Tadesse et al., 2016). This can indicate that the ability to withstand DNA damage during the period of increased oxidative stress in the placenta is crucial for successful development of the placenta. The concentration of 8-oxo-dG is notably elevated in pregnancies associated with PE, particularly in cases of early-onset PE, as well as in preterm low-birthweight infants (Aouache et al., 2018).

It is worth noting that several studies have indicated that genetic variations have a role in the pathophysiology and progression of PE (Alpoim et al., 2014; Michita et al., 2018; Sandoval-Carrillo et al., 2014; Serrano et al., 2006; Silva et al., 2015; Telini et al., 2014). Over 50 potential genes and their single nucleotide polymorphisms across several pathophysiological pathways for PE have been proposed by genome-wide association studies (Kessler et al., 2016; Thakoordeen et al., 2018). However, there is still no consensus on which genes are universally associated with susceptibility to the condition of PE. Multiple reported genetic variations in the genes *OGG1* and *SOD2*, specifically *OGG1* (Ser326Cys; rs1052133) and *SOD2* (Val16Ala; rs4880), have been found to impact their enzymatic function. These variations provide an opportunity to investigate the role of these variations in the development of PE, a condition where oxidative stress is believed to play a significant role.

The aim of this study of this study was to examine the correlation between *SOD2* (rs4880) and *OGG1* (rs1052133) genetic polymorphisms and the susceptibility of PE in Russian pregnant women from Rostov region. Understanding the impact of different SNPs in increasing the risk of preeclampsia and its associated traits is of paramount importance, as it can set the stage for identifying potential diagnostic markers to combat and manage the PE.

Materials and Methods

1. Participants

A total of 106 pregnant women participated in our study. Of them 60 normotensive pregnant women and 46 preeclamptic pregnant women. This study being conducted at Southern Federal University in cooperation with the “Nauka” medical center (Rostov-on-Don, Russian Federation) in the period between 2019 and 2022. The genetic analysis was performed using blood samples of 106 pregnant women aged between 25-43 years old, from Rostov-on-Don region, Russia. The women were divided into two groups to study *OGG1* (rs1052133) and *SOD2* (rs4880) genetic polymorphisms: the first group consist of

pregnant women with PE (n=46), and the second group consist of pregnant women with normal pregnancy (n=60). All participants' ages, parities, and gestational ages were carefully matched in the study. Definition of PE based on the American College of Obstetricians and Gynecologist (ACOG) standards. Conditions including hypertension, chronic liver, kidney, or endocrine diseases, abnormalities in the amount of amniotic fluid, disorders of metabolism or bleeding, Rh incompatibility, systemic lupus erythematosus, or any other systemic disease were not eligible for inclusion in the study. This study was approved by Southern Federal University's Academy of Biology and Biotechnology's Local Ethics Committee. All participants gave informed permission for the study.

2. DNA extraction and genotyping

Samples of blood from veins were collected and preserved at a temperature of -20◦C. Genomic DNA was extracted from peripheral blood leukocytes using the "PROBA-NK" extraction kit ("DNA-Technology", Russia) following the manufacturer's instructions. The DNA that was separated from other substances was measured accurately using NanoDrop, a device manufactured by (Thermo Fisher Scientific-United States). The genotyping of *OGG1* (rs1052133) and *SOD2* (rs4880) genetic polymorphisms was performed using SNPexpress kits and a SYBR green qPCR reagent from Lytech. Co. Ltd., Russian Federation. The genotyping was conducted using the QuantStudio™5 Real-Time PCR apparatus manufactured by (Thermo Fisher-United States). The PCR procedure consisted of an initial denaturation at 95 ◦C for 1 minute, followed by 35 cycles of denaturation at 93 ◦C for 10 seconds, annealing at 60 ◦C for 10 seconds, and a final extension step at 72 ◦C for 20 seconds. Fluorescent labels were used to target certain groups of polymorphisms. The findings were automatically recorded using the DT-96 detecting amplifier from "DNA Technology" in Russia, following the instructions provided by the manufacturer. Amplification plots and melt curve analysis were conducted to verify the specificity and correctness of the used kit after the execution of qPCR.

3. Statistical analysis

The statistical analysis was conducted using the free online platform "Medical Statistics" (https://www.medstatistic.ru). The qualitative characteristics of PE pregnancies were compared to those of the control group using an independent t-test. The findings were reported as the mean value ± the standard deviation. The disparity in those parameters between the study groups was assessed by computing the P value (where a value of <0,05 was deemed statistically significant). The genotypes were assessed for Hardy-Weinberg equilibrium using a Chi-square test using an internet calculator found at https://gene-calc.pl/hardy-weinberg-page. Chi-squared tests were used to analyze the

disparities in allele frequency and genotype distribution of each examined polymorphisms in both PE and control pregnancies. The association with PE risk in both groups was measured by calculating odds ratios (OR) with 95 % confidence intervals (CI). A positive association (risk effect) was regarded when odds ratios (OR) were more than 1, whereas a negative association (protective effect) was indicated by OR values less than 1. A P value of less than 0,05 was used as the threshold for statistical significance. In order to examine the relationships between our genetic variations, we used the multifactor dimensionality reduction (MDR) method v3.0.2 software (https://sourceforge.net/projects/mdr/). Furthermore, to address the issue of a limited number of samples, the Fisher's exact test was chosen to be used in MDR.

Results

1. Association between SOD2 (rs4880) and OGG1 (rs1052133) polymorphisms and risk of PE

Table 1 summarizes the genotyping distribution of *SOD2* (rs4880) and *OGG1* (rs1052133) polymorphisms in all groups. The genotype distributions of the two polymorphisms rs4880 and rs1052133 follows the Hardy-Weinberg equilibrium (HWE) (Chi-square test, P>0,05) in both *OGG1* (rs1052133) p=0,33 and *SOD2* (rs4880) p=0,43.

Our study found that the *OGG1* (rs1052133) polymorphisms was not associated with an increased risk of developing PE in all genotype and allele models (p>0,05). While, we found a significant association between *SOD2* (rs4880) and risk of developing PE risk. According to our results, we found a significant frequency differences between the controls and cases groups (p<0,05). The frequency of the minor homozygote CC was significantly higher in preeclamptic group (39,1 %) compared to control group (5,0 %) and this means that pregnant women with the CC genotype are at higher risk of developing PE (OR=11,36 95 % CI [3,08-41,89]; p<0,001). Moreover, both of the dominant (TC + CC) and recessive (TT + TC) models were also significantly different between the two groups (p<0,0001). The OR of both models (dominant and recessive) revealed that both models are associated with increased risk of developing PE (OR=7,20 95 % CI [2,98-17,40]; OR=12,21 95 % CI [3,32-44,97], respectively). In the other hand, the frequency of TT genotype was higher in control group compared to preeclamptic cases group (66,7 % vs 21,7 %) showing a protective effect against PE developing (OR=0,14 95 % CI [0,06-0,34]). In addition, the studying of allele frequency of the *SOD2* (rs4880) polymorphisms showed that the minor alleles C was more frequent in preeclamptic groups (58,7 %) compared to control groups (19,2 %), which means that carriers of the minor allele C are more likely to develop PE (OR=5,99 95 % CI [3,24-11,09]; p<0,001).

Table 1 - Genotype and Allele frequencies of SOD2 (rs4880) and OGG1 (rs1052133) polymorphisms.

Genotype/allele	Control n (%) (n = 60)	PE n (%) (n = 46)	*P* value	OR (95 % CI)
***OGG1* (rs1052133)**				
CC	42 (70,0 %)	31 (67,4 %)	p=0,514	0,89 (0,39-2,03)
CG	18 (30,0 %)	14 (30,4 %)		1,02 (0,44-2,36)
GG	0 (0,0 %)	1 (2,2 %)		-
CG+GG	18 (30,0 %)	15 (32,6 %)	p=0,770	1,13 (0,49-2,58)
CC+CG	0 (0,0 %)	1 (2,2 %)	p=0,191	-
C	102 (85,0 %)	76 (82,6 %)	p=0,639	0,84 (0,40-1,75)
G	18 (15,0 %)	16 (17,4 %)		1,19 (0,57-2,49)
HWE	0,33			
***SOD2* (rs4880)**				
TT	40 (66,7 %)	10 (21,7 %)	**p<0,001**	**0,14 (0,06-0,34)**
TC	17 (28,3 %)	18 (39,1 %)		1,63 (0,72-3,68)
CC	3 (5,0 %)	18 (39,1 %)		**11,36 (3,08-41,89)**
TC+CC	20 (33,3 %)	36 (78,3 %)	**p<0,0001**	**7,20 (2,98-17,40)**
TT+TC	3 (5,0 %)	18 (39,1 %)	**p<0,0001**	**12,21 (3,32-44,97)**
T	97 (80,8 %)	38 (41,3 %)	**p<0,001**	**0,17 (0,09-0,31)**
C	23 (19,2 %)	54 (58,7 %)		**5,99 (3,24-11,09)**
HWE	0,43			

HWE: Hardy-Weinberg equilibrium; OR: odds ratio; CI: confidence interval; *p < 0,05 is considered statistically significant.

2. Multiple-locus interactions for SOD2 (rs4880) and OGG1 (rs1052133) polymorphisms

The MDR analysis was used in our study to determine the combined effect of these two polymorphisms (rs4880) and (rs1052133) on the susceptibility to developing PE in pregnant women from the Rostov area of Russia. The resulted interaction model is statistically significant (p< 0,0001, OR = 39,60 CI 95 % (12,50-125,42)), with accuracy of 85,8 % and cross-validation consistency of 10/10 (Table 2). The interactive model had the highest accuracy, surpassing the single-locus model (85 % vs 72,5 %), suggesting an epistatic effect between the two loci. Fig. 1A presents high-risk and low-risk interactive genotypes rs4880 and rs1052133, indicating their individual contribution to PE. The combinations of CC/TT and CG/TC between *OGG1* (rs1052133) and *SOD2* (rs4880) polymorphisms showed a low-risk of developing PE, while CC/TC and CG/CC showed a high-risk of developing PE. Furthermore, data-analysis indicated that individuals with

CC/TC genotype have a significant 9-fold higher risk of developing PE and 4,6-fold for CG/CC genotype. According to the Fruchterman-Rheingold graph results, as shown in Fig. 1C, *SOD2* (rs4880) has the strongest predictive potential (19,96 %), supporting our prior findings in Table 1. Furthermore, the interaction between these two polymorphisms is considered effective intergenic interaction, representing a synergistic effect of these two polymorphisms in PE pathogenesis.

Table 2 - Best predictive gene–gene interaction models identified by MDR analysis.

Locus model	Accuracy	CVC consistency	Sensitivity	Specificity	χ2 (P value)	OR (95% CI)
SOD2 (rs4880) and *OGG1* (rs1052133)	% 85,8	10/10	% 78,3	% 91,7	53,68 **(p< 0,0001)**	39,60 (12,50-125,42)

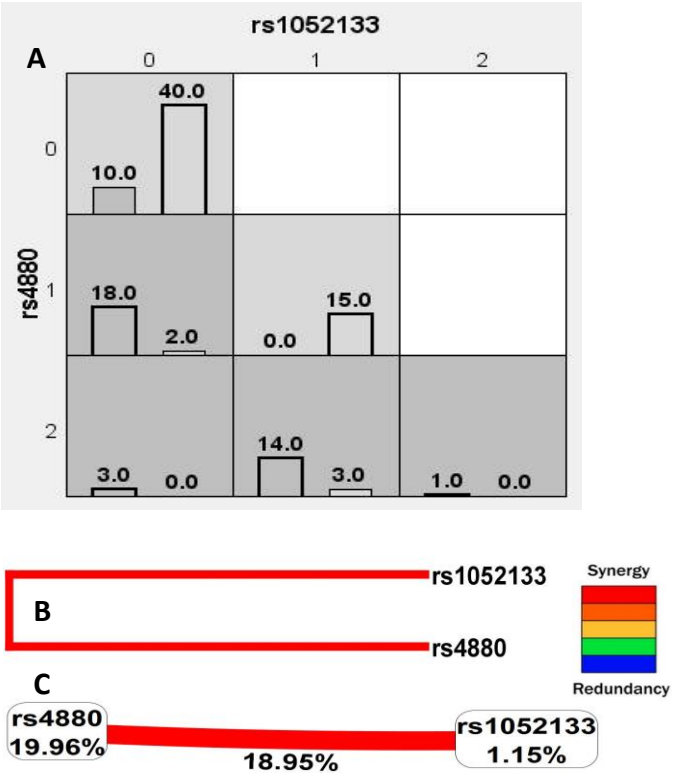

Fig. 1 - SOD2 (rs4880) and OGG1 (rs1052133) MDR interaction model. For each multilocus genotype combination, the distributions of cases (shown by the left bars) and controls (shown by the right bars) were shown. Unknown information is represented by white cells, while light gray cells indicate "low-risk" and dark gray cells indicate "high-risk". (B) interaction dendrogram. (C) Fruchterman–Rheingold scheme. Graph of interaction with nodes that are connected to one another in a pairwise connection. The main effect of each polymorphism is represented by values in nodes. On the other hand, the value between nodes shows the interaction effects. Red color represents the positive entropy (epistasis), whereas blue color (negative entropy) indicates redundancy. Yellow color represents independence.

Discussion

On a global scale, PE is associated with maternal morbidity and death; it is a hypertensive pregnancy condition that impacts 8 % of all pregnancies every year (N. Zhang et al., 2020; Bordaeva, et al., 2023). In spite of the extensive research conducted on potential genes, there have been conflicting findings. Pregnancy induces significant physiological alterations in organs, resulting in elevated basal oxygen and energy use, as well as heightened generation of reactive oxygen species (ROS). The creation of antioxidant enzymes counteracts the harmful effects of these poisonous compounds. Oxidative stress indicators show an elevation, whereas anti-oxidants experience a decline in preeclamptic women (Kirbas et al., 2016) Lipid peroxidation and endothelial cell injury, which are often seen in pregnancy complications such as PE, occur as a result of the interaction between ROS and polyunsaturated fatty acids(Sánchez-Aranguren et al., 2014). Superoxide anion and H2O2 are very potent free radicals, and cell membranes are safeguarded against their harmful effects by superoxide dismutase and glutathione peroxidase (Carmo de Carvalho e Martins et al., 2022). In our study, *SOD2* (rs4880) polymorphism was notable more frequent in cases group compared to the control group. The rs4880 homozygote CC was more frequent in PE group compered to control group. The same were notable in both dominant and recessive models, they were more frequent in preeclamptic pregnancies compared to controls. In addition, the minor allele C was also associated with increased risk of developing PE. While the TT genotype is associated with low-risk of developing PE, which means that it has a protective effect against PE risk. These findings confirms the fact that replacement of Alanine with Valine has an impact on the activity of *SOD2* by modifying the β-sheet structure (Val allele) to an α-helix structure (Ala-allele) in the mitochondrial targeting domain. This alteration reduces the antioxidant function of *SOD2* and hinders its transportation into the mitochondrial matrix, resulting in a 30-40 % decrease in *SOD2's* antioxidant activity(Broz et al., 2022).

In comparison with previous studies, Teimoori and colleagues reported that TC and CC genotypes of *SOD2* rs4880 polymorphism are associated with increased risk of PE in Iranian pregnant women (Teimoori et al., 2019). While, in the other hand, there were no significant difference in the rs4880 polymorphism of *SOD2* genotypes between PE and those in the control group in other studies (Kim et al., 2005; J. Zhang et al., 2008).

On the other hand, the DNA damage caused by free radicals may be especially harmful since it can lead to the formation of mutations and genotoxic base excision intermediates(Slupphaug et al., 2003). Base excision repair is a well organized and tightly regulated technique. The OGG1 enzyme is responsible for the first removal of 8-oxoG lesions, followed by the action of many BER proteins to repair the integrity of DNA (Whitaker et al., 2017). A previous study by Tadesse et al. demonstrated a significant elevation of OGG1 in the placenta of women with PE compared to control group (Tadesse et al., 2016). They concluded that obtained results indicated that the expression of the

OGG1 gene is increased when oxidative stress is present. Moreover, other studies have shown a greater degree of oxidative DNA damage in the placentas of women with PE in comparison to placentas obtained from women who had normal pregnancies (Fujimaki et al., 2011; Kimura et al., 2013). According to our results, the *OGG1* (rs1052133) was not associated with the risk of PE among Russian pregnant women in all genetic models, which means that the rs1052133 polymorphism of *OGG1* gene has no affect on the protein`s function. It`s known that the BER protein OGG1 is found in the placenta and this protein is likely to identify and handle 8-oxoG DNA abnormalities or OGG1-8-oxoG complexes caused by oxidative stress (Storr et al., 2013). This, in turn, triggers an inflammatory reaction that leads to the release of more RONS and causes further DNA damage. Ultimately, this results in placental dysfunction and the development of PE.

MDR analysis was also investigated in our study and showed that the carriers of *OGG1* (rs1052133) CC * *SOD2* (rs4880) TT and *OGG1* (rs1052133) CG * *SOD2* (rs4880) TC had a significantly lower risk of developing PE. Furthermore, *OGG1* (rs1052133) CC * *SOD2* (rs4880) TC and *OGG1* (rs1052133) CG * *SOD2* (rs4880) CC interactions were associated with a higher risk of developing PE, in accordance with genotyping data presented in Table 2.

One limitation of our study is its relatively small sample size, which may limit the generalizability of our findings. Additionally, our study was conducted on a single population, which may limit the ability to generalize these results to other populations. Other factors, such as environmental and lifestyle factors, could also have influenced the results. Future studies with larger sample sizes and more diverse populations are necessary to confirm our findings and further explore the relationship between *OGG1* and *SOD2* polymorphisms and PE risk.

Conclusion

In conclusion, we identified that *OGG1* (rs1052133) polymorphism was not associated with PE risk. While, the *SOD2* (rs4880) polymorphism was significantly associated with increased risk of developing PE in Russian pregnant women from Rostov region. These results may serve as a basis for future studies in other ethnic groups to confirm the potential involvement of this genetic variation in PE risk. Furthermore, larger sample size and functional investigations to detect more polymorphisms are needed to corroborate these results.

Ethical approval: The research received approval from the Ethics Committee of Southern Federal University, Academy of Biology and Biotechnology. Consent was acquired from all subjects participating in the research.

Declaration of competing interest: The authors declare no conflict of interests.

Data availability: The research presented in the article did not make use of any data.

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