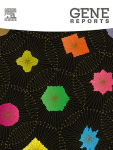
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**MTHFR and ERVFRD-1 polymorphisms and preeclampsia risk in Iran population: A case-control study**

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**Abstract**

**Background and aims**

Preeclampsia (PE) is a complicated disease during pregnancy that could be a risk factor for the mother's health and fetus. The mechanisms of PE pathogenesis might associate with some candidate [gene polymorphisms](https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/gene-polymorphism). This study is aimed to evaluate the relation between [MTHFR](https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/methylenetetrahydrofolate-reductase) (C677T) [MTHFR](https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/methylenetetrahydrofolate-reductase) (A1298C) and ERVFRD-1 (rs9393931) [single nucleotide polymorphisms](https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/single-nucleotide-polymorphism) (SNPs) and PE in our patients.

**Material and methods**

The present study was a case-control study carried out between January 2019 and January 2021, in the Kamali hospital, Karaj, Iran. A total of 104 pregnant women who were diagnosed with Preeclampsia clinically as a case, and 100 healthy pregnant women as a control group were compared for the study.

**Results**

There was not a 39 T allele of the ERVFRD-1 gene was observed in this studied population. There was a significant difference in frequency of 677CT genotype in PE pregnant women compared to controls (*P* = 0.002). Also, our result indicated that the frequency of the MTHFR 1298C allele was found to be significantly higher in the control group than in the case group (*P* = 0.021).

**Conclusion**

Our results suggested that C677T polymorphism in MTHFR might be related to an increased risk of Preeclampsia in pregnancy.

**Introduction**

Preeclampsia (PE) is one of the complications of pregnancy that cause perinatal and maternal morbidity and mortality, particularly when early onset. The prevalence of this disease varies from 3 % to 7 % and causes over 50,000 maternal deaths, and >500,000 fetal deaths around the world (Mol et al., 2016; Ghulmiyyah and Sibai, 2012; Zhang et al., 2003); this rate is reported in Iran as about 4–7 % (Andarge et al., 2020). It causes 16 % of maternal mortality in high-income countries, compared to 9 % to 26 % in low-income nations (Karrar and Hong, 2022). Risk factors for PE include those with previous early onset preeclampsia, diabetes type one, chronic kidney disease, and women with preexisting hypertension (English et al., 2015). Short-term maternal complications of PE include HELLP syndrome, retinal detachment, cerebrovascular bleeding, and eclampsia. Also, it is related to an increased risk of ischemic heart disease stroke, chronic hypertension, and death from cardiovascular events (Turbeville and Sasser, 2020).

Single-nucleotide polymorphisms (SNPs) and genetic linkage have been studied until now, and various genes have been identified with an increased risk of PE. For example, SNP rs479200 in the EGLN1 gene and SNP rs4759314 in the HOTAIR gene are associated with increased susceptibility to PE (Steinthorsdottir et al., 2020; Mohammadpour-Gharehbagh et al., 2019). Due to the multifactorial nature of PE and the low odds ratio of identified genes, more genetic traits and pathways remain to be identified.

The enzyme tetrahydrofolate reductase is encoded by the methylenetetrahydrofolate reductase (MTHFR) gene, which catalyzes the irreversible conversion of 10-,5-methylene tetrahydrofolate to 5-methyltetrahydrofolate. Subsequently, 5-methyltetrahydrofolate is used as a substrate to convert homocysteine to methionine (Ho et al., 2013). Methionine is used to synthesize s-adenosyl methionine (SAM), and it is the most important donor of methyl groups for the methylation of DNA, lipids, and proteins. The gene encoded by this enzyme is located on chromosomal region 1p36.3. The presence of two single nucleotide polymorphisms, rs1801133, and rs1801131, in this gene, influences its enzymatic activity (Ghaffari et al., 2015). The rs1801133 mononucleotide polymorphism replaces the amino acid valine with alanine at point 222. In rs1801131, the amino acid valine replaces glutamic acid (Val429Ala). These mononucleotide polymorphisms lead to a 70 % reduction in MTHFR activity compared to the standard type (Weisberg et al., 1998). A decrease in the activity of the MTHFR enzyme has been identified in association with several developmental and reproductive disorders. The presence of rs1801133 and rs1801131 variants in parents has been associated with abortion and neural tube defects in the fetus (Soleimani-Jadidi et al., 2022). Previous studies reported that MTHFR rs1801133 and rs1801131 SNPs were implicated in several pregnancy-related complications such as placental abruption or infarction, and PE (Mtiraoui et al., 2006; Gaiday et al., 2018; Hague, 2003).

The ERVFRD-1 gene, located on chromosomal position 6p24.2, encodes a functional protein called syncytin-2. This gene is part of the human endogenous retrovirus (HERV) family, which is expressed at high levels in placental tissue and plays a functional role in reproduction (Poursadegh Zonouzi et al., 2012; Harris, 1998). The syncytin-2 protein is involved in the placenta's growth and development, the integration of cytotrophoblast mononuclear cells, and the formation of the syncytium, the last differentiated step in the trophoblast line. Histological placental abnormalities in pregnancy with decreased perfusion and oxidative stress are associated with PE (Blaise et al., 2003; Mi et al., 2000). Previous studies show a decrease in syncytin gene expression levels in pregnant women with PE compared with healthy women (Frendo et al., 2003; Blond et al., 2000). Ying Hua et.al in a newly published research reported that ERVFRD-1 (rs9393931) polymorphism was significantly associated with an increased risk of preeclampsia development (Hua et al., 2018).

In this study, we examined the association of rs1801133 and rs1801131 variants in the MTHFR gene and the rs9393931 variant in the ERVFRD-1 gene with PE in a population of Iranian women. We chose the rs9393931 variant in the ERVFRD-1 gene because it was a newly discussed polymorphism in association with PE in China population. Then to prove the result of this study we try to add polymorphisms related to PE like MTHFR (rs1801133) and MTHFR (rs1801131) which were previously discussed in many research.

**Section snippets**

**Study design**

The Ethical Committee at the Alborz University of medical sciences approved this project, and all participants provided written informed consent. (Ethical number: IR.ABZUMS.REC.1397.132, IR.ABZUMS.REC.1397.159).

We used a 95 % confidence interval and power of 90 %, to estimate sample size. It is estimated that at least 200 participants are required. In this case-control study, 104 pregnant women with PE based on clinical and laboratory evidence and 100 healthy pregnant women with blood pressure

**Results**

A hundred healthy individuals were included in the control group, whereas 104 patients with PE applied to the case group. The mean age of the control group and cases were 30.7 years and 28.8 years, respectively. Maternal age was significantly different between the two groups (*p* = 0.037). The history of hypertension in the case group was significantly higher (*p* < 0.001) than in the control group. The two groups also differentiated significantly in terms of multiple gestations (*p* = 0.002) and

**Discussion**

This study revealed that rs1801133 polymorphism in the MTHFR gene is associated with a risk of PE; however, there was no association of rs1801131 variants in the MTHFR gene. Which was reported in the previous studies in Iran and in meta-analyses.

Increased homocysteine levels are caused by a decrease in MTHFR protein levels or activity caused by distinct gene variations. The rs1801133 variant in the MTHFR gene converts an alanine to valine at aminoacid in the enzyme regulatory domain, causing a

**Conclusion**

The results of this study demonstrate that the MTHFR rs1801133 polymorphism may be involved in the development of PE. Additional genetic research should be performed to determine other genes or polymorphisms involved in the pathogenesis of the disease. It could be helpful in the earlier recognition of PE in pregnant women, hence reducing the disease's consequences.

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**CRediT authorship contribution statement**

**Masoumeh Farahani:** Conceptualization, Investigation, Resources, Visualization, Supervision, Project administration, Funding acquisition. **Danoosh Zargar:** Conceptualization, Investigation, Visualization. **Sahar Ameri:** Conceptualization, Investigation, Validation. **Mahnaz Seifi Alan:** Conceptualization, Methodology, Validation, Writing – original draft, Supervision. **Hadith Rastad:** Methodology, Software, Formal analysis, Data curation. **Matineh Nirouei:** Conceptualization, Investigation, Writing –

**Declaration of competing interest**

None.

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