CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.1324376

Available online at: http://www.iajps.com Research Article

POLYMORPHISMS OF GENES AND THE RISK OF PREECLAMPSIA

Evgeny A. Reshetnikov, Inna N. Sorokina, Irina V. Batlutskaya, Evgeny N. Krikun, Sergey P. Pahomov, Valery I. Evdokimov

Belgorod State University, Pobedy Street, 85, Belgorod, 308015, Russia

Abstract:

Objectives: they studied the relations of genetic polymorphisms with the risk of preeclampsia occurrence depending on hereditary complication.

Materials and Methods: The study was conducted in two groups of pregnant women: 274 women diagnosed with preeclampsia and 179 women with physiological gestation. They studied seven polymorphisms of folate cycle genes (+677C>T MTHFR (rs1801133), +1298A>C MTHFR (rs1801131), + 66A>G MTRR (rs1801394), + 2756A>G MTR (rs1805087), -1053C>T TYMS (rs699517), IVS 6-68 C>T TYMS (rs1059394), -1122A>G TYMS (rs2790)) by real-time method of polymerase chain reaction (PCR) in DNA synthesis (Real-time-PCR).

Results: The frequencies of alleles +2756G MTR and the genotype +2756GG MTR were higher in the group of pregnant women with preeclampsia without hereditary complication, as compared with the pregnant women of control group (OR = 1.61, p = 0.01, OR = 7.26, p = 0.0007, pbonf = 0.0021, respectively).

Conclusions: Thus, the polymorphism of methionine synthase gene + 2756A>G MTR is associated with the risk of preeclampsia occurrence depending on the presence of a complicated family anamnesis..

Keywords: *preeclampsia, pregnancy, gene, folate cycle genes.*

*** Corresponding author:**

Evgeny A. Reshetnikov,

Belgorod State University,

Pobedy Street, 85,

Belgorod, 308015, Russia

E-mail: Reshetnikov@bsu.edu.ru

QR code

Please cite this article in press Evgeny A. Reshetnikov et al., ***Polymorphisms of Genes and the Risk of Preeclampsia.,*** *Indo Am. J. P. Sci, 2018; 05(07).*

INTRODUCTION:

Preeclampsia (PE) - is a complication of pregnancy, characterizing by the arterial hypertension, proteinuria, oedemata, as well as by deep disorders of the vascular system, hemostasis, immunity, hemodynamics and microcirculation, fetoplacental insufficiency, kidney, hepatic and lungs malfunctions.(Hayashi et al, 2007; Sidorova, Nikitina, 2014).

The prevalence of preeclampsia is 4-18% among all pregnant women (Clark et al, 2008), and the perinatal mortality rate is 23-27% (Trunova et al., 2011).

An important role in the etiology and pathogenesis of preeclampsia belongs to the folate candidate genes (Vorozhinceva, 2014, Xiaoming et al, 2015, Zhou et al, 2016). Mutations in the genes of folate metabolism, causing the decrease in the activity of enzymes of methyltetrahydrofolatereductase and methionine synthase reductase, lead to accumulation of homocysteinein the body of a pregnant woman, and to a deficiency of folic acid (Vorozhinceva, 2014; Xiaoming et al, 2015). Deficiency of folic acid affects the proliferation of chorionic cells and the formation of placenta. This complicates the course of gestation, increasing the risk of placental insufficiency, preeclampsia and other disorders of prenatal development. The role of candidate genes of folate metabolism in the formation of PE is actively studied, but these studies often give conflicting results for different populations (Obolenska et al, 2011; Pavlova et al, 2011; Williams et al, 2011; Valenzuela et al, 2012; Vorozhinceva, 2014; Reilly et al, 2014; Xiaoming et al, 2015).

MATERIALS AND METHODS:

Object of study

The study group included 274 pregnant women, diagnosed with preeclampsia (105 of them with hereditary burden for preeclampsia, 169 pregnant women without genetic predisposition to preeclampsia) and 179 women with normal course of gestation. The average age of women with PE was 27.19 ± 6.4, in the control group - 26.71 ± 6.36. All clinical studies were carried out according to the protocols of ethical committee of the Russian Federation, with the informed consent of patients. The criteria for inclusion in the study were the following: Russian nationality, the absence of kinship, living in the Central Black Earth region of Russia.

The exclusion criteria for the sample formation were the following: uterine pathology, pathology of pregnancy, fetal pathology, multifetal pregnancy. Preeclampsia was diagnosed by the presence of arterial hypertension, proteinuria and generalized oedemata (Turner, 2010).

Molecular and genetic methods

Typing of the following polymorphic variants of folate cycle genes was carried out for all pregnant women with preeclampsia and pregnant women from the control group: methylenetetrahydrofolatereductase (+677C>T *MTHFR* (rs1801133), +1298A>*CMTHFR* (rs1801131)), methionine synthase reductase (+ 66A>G *MTRR* (rs1801394)), methionine synthase (+2756A>G *MTR* (rs1805087)), thymidylatesynthetase (-1053C>T *TYMS* (rs699517), IVS 6-68 *C>TTYMS* (rs1059394), -1122A>G *TYMS* (rs2790)). All polymorphic variants of folate cycle enzymes were analyzed using the method of polymerase chain reaction (PCR) of DNA synthesis in real-time (Real-time-PCR).

Statistical methods

Gene and phenotypic frequencies were calculated using the standard methods. The conformity of the observed distribution of genotypes to the expected one, according to the Hardy-Weinberg equilibrium, was performed using the $\chi 2$ criterion. The Bonferroni correction was used when carrying out multiple comparisons.

The associations of alleles and genotypes of the studied polymorphic variants with the formation of preeclampsia were assessed using 2×2 conjugation tables, with calculation of $\chi 2$ criterion, with the Yates correction for continuity and odds ratio (OR), with 95% confidence interval (Schlesselman J., 1982).

RESULTS:

Significant differences were not revealed in the process of comparative analysis of the frequency distribution of alleles and genotypes of polymorphic markers of folate cycle genes in the group of pregnant women with PE, having hereditary burden, and in the group of healthy pregnant women (taking into account the Bonferroni correction).

In the group of pregnant women with preeclampsia, without hereditary burden, high frequencies of alleles + 2756G *MTR* (33.73%), IVS6-68T *TYMS* (29.01%) and the genotype + 2756GG *MTR* (15.53%) were found, in comparison with the pregnant women from the control group (21.30%, OR=1.61; 95%CI 1.12-2.31; χ^2=6.87; p=0.01; 21.50%, OR=1.49; 95%CI 1.02-2.18; χ^2=4.31; p=0.04; 2.47%, OR=7.26; 95%CI 2.32-25.29; χ^2=15.29; p=0.0007, p_{bonf}=0.0021).

When using Bonferronicorrection, the differences

between pregnant women with PE, without a burdened familial history, and pregnant women from the control group were statistically not significant for the genotype IVS6-68TT *TYMS*.

DISCUSSION:

The results of this study show, that polymorphism of the methionine synthase gene +2756A>G *MTR* has significant pathogeneticimportance for the occurrence of preeclampsia. The allele +2756G *MTR* and the genotype +2756GG *MTR* are associated with a risk of preeclampsia in pregnant women without a burdened familial history.

Methionine synthase (MTR) is one of the most important enzymes of folate metabolism. This cytoplasmic enzyme catalyzes the reaction of homocysteine methylation, with its conversion to methionine, using 5-methyltetrahydrofolate as a donor of the methyl group, thereby reducing the concentration of homocysteinein blood. The polymorphism of the gene +2756A>G *MTR* is associated with the replacement of asparagine to glycine at the 919 position of the protein, that may affect its secondary structure, and therefore has a functional significance (Furness et al, 2008).

In other studies on the search for associations of folate cycle genes with the risk of preeclampsia, opposite results were obtained. Thus, in the studies on the Polish, Spanish and South American populations, there was no association of polymorphism of gene +2756A>G *MTR* with the risk of preeclampsia development (Also-Rallo et al, 2005, Pérez-Sepúlveda et al, 2013, Seremak-Mrozikiewicz et al, 2017).

The inconsistency of the results, obtained in various studies, may be related to the differences in the ethnic and, respectively, genetic background of the studied populations (Churnosov et al., 2005; Sorokina et al., 2007; Xiaoming et al, 2015). Even the population of certain regional groups of Russians (Belgorod region, the south of Central Russia, the center of Central Russia) is so genetically diverse, as some of the nations of Western Europe (Germans, Norwegians, etc.) and is significantly higher, than the variability of most ethnic Slavic groups (Bulgarians, Czechs, Poles) (Churnosov et al., 2005; Sorokina et al., 2007). This feature of the Russian gene pool determines the need to take into account the population sample, for which the results are obtained.

SUMMARY:

Thus, as a result of this study, significant associations of polymorphism of the gene +2756A>G *MTR* with the risk of preeclampsia were established, depending on the burdened familial history.

CONCLUSION:

The data, obtained in the process of the research, will make it possible to form risk groups of preeclampsia at the preclinical stage, and to carry out effective preventive measures in these groups. On the other hand, it will allow to predict the nature of the clinical course of disease among patients, that will optimize the therapeutic-diagnostic process for each patient.

Conflicts of interest

The authors confirm that there are no conflicts of interest.

REFERENCES:

1. Ajlamazyan, E.K., Mozgovaya, E.V., 2008. Gestational toxicosis: theory and practice. M.: Publishing house MEDpress-inform.
2. Bailey, L., Gregory, J., 1999. Polymorphisms of methylenetetrahydrofolate reductase and other enzymes: metabolic significance, risks and impact on folate requirement. J Nutr, 129:919-922.
3. Baranov, V.S., 2009. Genetic passport is the basis of individual and predictive medicine. SPb.: Publishing House N-L.
4. Baranova, E.I., Bolshakova, O.O., 2004. Clinical relevance of homocysteinemia (literature review). Arterial hypertension, 1: 12-15.
5. Churnosov, M.I., Pesik, V.Yu.,Rudyh, N.A., 2005. Materials on the study of gene pool structure of the Russian population in Central Russia. Medical Genetics, 6 (4): 289a-289.
6. Clark, S.L., Belfort, M.A., Dildy, G.A., Herbst, M.A., Meyers, J.A., Hankins, G.D., 2008. Maternal death in the 21st century: causes, prevention, and relationship to cesarean delivery. Am J ObstetGynecol, 199(1): 36.e1–36.e5.
7. Friedman, G., Goldschmidt, N., Friedlander, Y., Ben-Yehuda, A., Selhub, J., Babaey, S., Mendel, M., Kidron, M., Bar-On, H., 1999. A common mutation A1298C in human methylenetetrahydrofolate reductase gene: association with plasma total homocysteineand folate concentrations. J Nutr, 129: 1656-1661.
8. Furness, D.L., Fenech, M.F., Khong, Y.T., Romero, R., Dekker, G.A., 2008. One-carbon metabolism enzyme polymorphisms and uteroplacental insufficiency. Am J ObstetGynecol, 199(3): 276.e1-8.
9. Halford-Knyazeva, I.P., 2013. Genetic markers for the prediction of preeclampsia: extended abstract of Cand. Sci. (Medicine) Dissertation. M., 16p.

10. Hayashi, M., Inoue, T., Hoshimoto, K., Negishi, H., Ohkura, T., Inaba, N., 2007.Characterization of five marker levels of the hemostatic system and endothelial status in normotensive pregnancy and preeclampsia. Eur J Haematol, 69(5-6); 297-302.
11. Obolenska, M.I., Rodrihes, R.R., Martseniuk, O.P., 2011.Folate-relatedprocesses in humanplacenta: gene expression, aminothiols, proliferationandapoptosis. Ukr.Biokhim.Zh., 83(1):5-17.
12. Pavlova, K.K., Trifonova, E.A., Gotovceva, L.V., Maksimova, N.R., Nogovicyna, A.N., Stepanov, V.A., 2010. The role of polymorphisms of genes eNOS, ACE and MTHFR in the development of gestational toxicosis in the Yakut population. Yakut Medical Journal, 3 (31): 28-31.
13. Pérez-Sepúlveda, A., España-Perrot, P.P., Fernández, X.B., Ahumada, V., Bustos, V., Arraztoa, J.A., Dobierzewska A., Figueroa-Diesel, H., Rice, G.E., Illanes, S.E., 2013. Levels of key enzymes of methionine-homocysteine metabolism in preeclampsia. Biomed Res Int, 2013:731962.
14. Rebrova, O.Yu., 2006. Statistical analysis of medical data. Application of program package STATISTISA. Moscow: Publishing House Media Sfera.
15. Reilly, R., McNulty, H., Pentieva, K., Strain, J.J., Ward, M., 2014. MTHFR 677TT genotypeanddisease risk: is there a modulating role for B-vitamins? Proc. Nutr. Soc., 73(1):47-56.
16. Seremak-Mrozikiewicz, A., Bogacz, A., Deka-Pawlik, D., Klejewski, A., Wolski, H., Drews, K., Karasiewicz, M., Czerny, B., 2017. The polymorphisms of methionine synthase (MTR) and methionine synthase reductase (MTRR) genes in pathogenesis of preeclampsia. J Matern Fetal Neonatal Med, 30(20):2498-2504.
17. Sidorova, I.S., Nikitina, N.A., 2014. Preeclampsia in the spotlight of a practitioner. Obstetrics and Gynecology, 6; 4-9.
18. Sidorova, I.S., 2016. Preeclampsia. M.: Publishing house "Meditsinskoe informatsionnoe agenstvo".
19. Sorokina, I.N., Churnosov, M.I., Balanovskaya, E.V., 2007. Genetic resources of the population of Belgorod region II."Familial portraits" in groups of regions with different levels of division, and the role of migrations in their formation. Genetics, 8 (43): 1120-1128.
20. Strizhakov, A.N., Makacariya, A.D., Timohina, E.V., Bajmuradova, S.M., Kozlova U.A., 2009. Clinical significance of acquired and hereditary forms of thrombophilia in the pathogenesis of intrauterine growth restriction syndrome. Questions of gynecology, obstetrics and perinatology, 8 (2): 16-21.
21. Suhih, G.T., Murashko, L.E., 2010. Preeclampsia.M.: Publishing house GEOTAR-media.
22. Trunova, L.A., Pekarev, O.G., Avdiyuk, G.A., Obuhova, O.O., Gorbenko, O.M., Shwayuk, A.P., Trunov, A.N., 2011. Chronic infectious and inflammatory diseases of the pelvic organs as the factor of formation of gestation processes malfunction. Allergology and Immunology, 12 (4): 347-349.
23. Turner, J.A., 2010. Diagnosis and management of preeclampsia: an update. Int. J. Womens Health, 2: 327-337.
24. Valenzuela, F.J., Pérez-Sepúlveda, A., Torres, M.J., Correa, P., Repetto, G.M., Illanes, S.E., 2012. Pathogenesis of preeclampsia: the genetic component. J Pregnancy, 2012:632732.
25. Vorozhishcheva, A.Yu., 2014. Genetic factors for development of preeclampsia in populations of different ethnic origins: extended abstract of Cand. Sci. (Medicine) Dissertation.Tomsk; 24p.
26. Williams, P.J., Broughton Pipkin F., 2011. The genetics of preeclampsia and other hypertensive disorders of pregnancy. Best Pract Res ClinObstetGynaecol, 25(4):405-417.
27. Xiaoming Wu, Kunxian Yang, Xiaodan Tang, Yalian Sa, Ruoyu Zhou, Jing Liu, Ying Luo, andWenru Tang, 2015. Folate metabolism gene polymorphisms MTHFR C677T and A1298C and risk for preeclampsia: a meta-analysis. J Assist Reprod Genet, 32(5): 797-805.
28. Zhou, L., Cheng, L., He, Y., Gu, Y., Wang, Y., Wang, C., 2016. Association of gene polymorphisms of FV, FII, MTHFR, SERPINE1, CTLA4, IL10, and TNFalpha with preeclampsia in Chinese women. Inflamm Res, 65(9): 717-724.