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Study of the Prognostic Efficiency of Polymorphism Glu429ala in the Mthfr Gene in Women of the Uzbek Population with Congenital Defects of the Fetal Development

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Annotation: The literature review summarizes modern ideas about the role of cytokines in the pathogenesis of osteoarthritis. Proinflammatory cytokines in joint tissue cause inflammation and damage ofvcartilage, leading to progressive joint degeneration.

Keywords: osteoarthritis; cytokines, pathogenesis, interleukin-1β, interleukin-6.

Relevance. Of particular interest is the question of whether polymorphisms of folate metabolism genes, folate deficiency, and the resulting hyperhomocysteinemia are involved in the development of miscarriage, placental dysfunction, preeclampsia, premature birth, fetal growth retardation, and congenital malformations (2,5,9). In the United States, the prevalence of heterozygous polymorphisms of the MTHFR enzyme gene in the population reaches 60%, and homozygous carriers of these genetic variants constitute about 25% of certain population groups (1,3,7). As a result of genetic polymorphisms, the function of the MTHFR enzyme is reduced by 70% in homozygous individuals and by about 35% in heterozygous individuals (4,6).

Materials and methods. This section presents the results of the analysis of the distribution of alleles and genotypes of the MTHFR gene in patient and control groups. The study voluntarily included 155 women of the Uzbek population with congenital malformations of the fetus and a history of frozen pregnancy (main group), observed in the obstetric and gynecological complex of TMA. The assessment of the deviation of the genotype distributions of the studied genes of the folate cycle MTHFR (Glu429Ala) from the canonical Hardy-Weinberg distribution (HWD) was carried out using the Gene Pop (Genetics of Population) program.

Research results. In the study of polymorphism Glu429Ala in the MTHFR gene in the group with congenital malformations and controls there is no significant decrease in the frequency of the wild allele A compared to healthy women (62.5% versus 79.33%, respectively) and an increase in the frequency of the functionally unfavorable allele C compared to the group of healthy women (32.5% versus 20.67%, respectively)).

Table 1. Distribution frequency of alleles and genotypes of the Glu429Ala polymorphism in the MTHFR gene in patient and control groups

Num	Group	Allele frequency				Genotype frequency distribution					
		A		C		A/A		A/C		C/C	
		n	%	n	%	n	%	n	%	n	%
1	Congenital malformation of the fetus (n = 40)	50	62.5	30	37.5	14	35.0	22	55.0	4	10.0
2	with a frozen pregnancy (n = 40)	65	81.25	15	18.75	27	67.5	11	27.5	2	5.0

3	Control group (n = 75)	119	79.33	31	20.67	47	62,67	25	33,33	3	4.0

However, as a result of the study, statistically significant differences were established in the distribution of genotypes and allele frequencies between the group of women with fetal congenital malformations and women in the control group for the allelic variant of the Glu429Ala polymorphism in the MTHFR gene (62.5% - A, compared with 79.33% in the control) and an increase in the frequency of the functionally unfavorable allele C compared to the control group (37.5%, 20.67% respectively) (table 1).

The most common genotype for the wild-type allele A in the control group, in the group with congenital malformations and in women with non-viable pregnancy is the homozygous genotype A/A, 62.67%, 35.0% and 67.5%, respectively. The homozygous mutant C/C genotype in the group with congenital malformations, in the group with non-viable pregnancy and the control groups occurred with a relatively low frequency of 5.0% in the group with non-viable pregnancy and 4.0% in the control group. However, in the group of women with congenital malformations of the fetus, the mutant homozygous genotype was 2.5 times more common (10.0% compared to 4.0%) than in the control and 1.25 times more common in the group of women with non-viable pregnancy. The highest frequency of the heterozygous genotype A/C was revealed in the group of women with congenital malformations of the fetus (55.0%). The prevalence of the normal A/A genotype in the group of healthy women confirms the protective function of this genotype.

The distribution of genotypes in the analyzed group of patients corresponded to the Hardy-Weiberg equilibrium (HWE), which indicates the representativeness of the sample of the main group and the correctness of the determination of polymorphismGlu429Ala. The detected slight deviation from the RHV may be due to a decrease in heterozygosity, i.e. a lack of heterozygotes in the analyzed group due to an increase in the number of representatives with the wild variant of the genotype (selective effect).

This may indicate that the heterozygous and, especially, homozygous genotypes have a fairly pronounced statistically significant association with development Fetal malformations. These data may indicate a good independent effect of polymorphism. Glu429Ala in the MTHFR gene at risk Fetal malformations in the Uzbek ethnic group (8).

Table 2. Expected and observed frequencies of genotype distribution of the locus for RHB (Glu429Ala polymorphism in the MTHFR gene)

Main group					
Alleles	Allele frequency				
A	0.72				
C	0.28				
Genotypes	Genotype frequency		χ2	p	df
	observable	expected			
A/A	0.51	0.52	0		
A/C	0.41	0.4	0.01		
C/C	0.08	0.08	0.02		
Total	1	1	0.03	0.821	1

Control group					
Alleles	Allele frequency				
A	0.79				
C	0.21				
Genotypes	Genotype frequency		χ2	p	df
	observable	expected			
A/A	0.63	0.63	0		

A/C	0.33	0.33	0.01		
C/C	0.04	0.04	0.01		
Total	1	1	0.02	0.846	1

Groups	Ho	He	D*
Main group	0.41	0.4	0.02
Control group	0.33	0.33	0.02

Note: D = (Ho - He)/He

Thus, for women from the group with fetal congenital malformations, the prognostic value as an independent marker of the Glu429Ala polymorphism in the MTHFR gene is high (table 2). Heterozygotes for the Glu429Ala polymorphism in the MTHFR gene (AC) had an increased risk of developing pathology in the group with VPR compared with the control (OR 2.0). There was also a significant increase in risk for homozygotes for polymorphism Glu429Ala in the MTHFR gene (CC) compared with controls (OR 2). We found a significant association between the Glu429Ala polymorphism in the MTHFR gene and an increased risk of fetal congenital malformations. The most common genotype for the wild-type allele C in the control group, in women with congenital malformations and with non-viable pregnancies, is the homozygous genotype C/C, 53.3%, 62.5% and 45.0%, respectively. The highest frequency of the heterozygous genotype C/T was found in the group of women with non-viable pregnancies (50.0%).

Conclusion. In the group of women studied A direct, strong connection was found between the polymorphism of the studied genes and an increased risk of developing fetal congenital malformations: thus, the homozygous mutant genotype C/C of the Glu429Ala polymorphism in the MTHFR gene was found 2.5 times more often ($\chi2$=1.6; P=0.2; RR=2.5; OR=2.7) than in the control and 2 times more often ($\chi2$=0.7; P=0.4; RR=2.0; OR=2.1) than in the group of women with non-viable pregnancies (10.0 vs. 4.0 and 5%, respectively), as well as a high frequency (55.0%) of the heterozygous genotype A/C ($\chi2$=5.1; P=0.025; RR=1.7; OR=2.4).

Bibliography

1. Achiron R, Adamo L, Kassif E. From screening chromosomal anomalies to early diagnosis of fetal malformations. // Curr Opin Obstet Gynecol. 2020 Apr;32(2):128-133.
2. Chitayat D, Matsui D, Amitai Y, Kennedy D, Vohra S, Rieder M, Koren G. Folic acid supplementation for pregnant women and those planning pregnancy: 2015 update. J Clin Pharmacol. 2016 Feb;56(2):170-5.
3. Irwin R.E., Pentieva K., Cassidy T., Lees-Murdock D.J., McLaughlin M., Prasad G. et al. The interplay between DNA methylation, folate and neurocognitive development. Epigenomics. 2016; 8(6): 863–79. DOI: 10.2217/epi-2016-0003.
4. Ledowsky CJ, Schloss J, Steel A. Variations in folate prescriptions for patients with the MTHFR genetic polymorphisms: A case series study. Explor Res Clin Soc Pharm. 2023 May 8;10:100277.
5. Palacios AM, Feiner RA, Cabrera RM. Characterization of folic acid, 5-methyltetrahydrofolate and synthetic folinic acid in the high-affinity folate transporters: impact on pregnancy and development. Reprod Dev Med. 2023 Jun;7(2):102-107.
6. Puri, M., Kaur, L., Walia, G.K., et al. “MTHFR C677T polymorphism, folate, vitamin B12 and homocysteine in recurrent pregnancy losses: a case control study among North Indian women.” J Perinat Med 41.5 (2013): 549–54
7. Yangibayeva D. T. et al. The Role of Folate Cycle Genes in the Developing of Fetal Disorders //Central Asian Journal of Medical and Natural Science. – 2022. – Т. 3. – №. 6. – С. 388-391.
8. Yangibayeva D.T., Yuldasheva D.Yu., Sadikova D.R., Choriyeva G.Z., Sadullayeva U.A. Influence of folate cycle MTHFR gene polymorphism on the process of fetus development in residens of the republic Uzbekistan. World Bulletin of public Health Volume 22, May 2023. P 43.

9. Yoshizato T, Kozuma Y, Horinouchi T, Shinagawa T, Yokomine M, Ushijima K. Diagnosis of Fetal Abnormalities during the First Trimester. // Kurume Med J. 2021 Jul 21;66(2):85-92. doi: 10.2739/kurumemedj.MS662002