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Features of the Distribution of Allelic Polymorphism of Folate Cycle Genes in Women with a Burdened Obstetric History

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Abstract: The study analyzed polymorphisms of folate cycle genes (MTHFR, MTR, MTRR) in women with congenital malformations (CM) of the fetus and non-viable pregnancy. It was found that the homozygous mutant genotype C/C (Glu429Ala, MTHFR) was found 2.5 times more often in the group of women with CM of the fetus than in the control group. The genotype G/G (Ile22Met, MTRR) was found 4.6 times more often in women with CM of the fetus compared to the control. The obtained data confirm the role of mutations in folate cycle genes in the development of reproductive complications, and also indicate the need to take into account endo- and exogenous factors that contribute to their implementation.

Keywords: congenital malformations of the fetus, undeveloped pregnancy, folate exchange.

Introduction

Nowadays, one of the main causes of childhood morbidity, disability, and infant mortality is congenital malformations (CM), and the observed 4-6% of newborns and over 20% of infant mortality occurs because of th Cm [3,5,7]. Most children with CM die in the first months and years of life, and most of those who survive require constant medical and social care [2,6]. There are various causes of congenital malformations, including hereditary, chromosomal and teratogenic. In a significant number of cases, the nature of the defect remains unknown. The different factors, like a higher frequency of chromosomal abnormalities in gametes and embryonic tissues, an increased rate of genetic mutations, with a growing impact of various teratogenic factors create the rising incidence of congenital malformations [1,4]. Due to the severity of the conditions, which in many cases are not amenable to surgical treatment, the medical and social significance of the problem is obvious, and the ways to solve it include, in particular, prenatal diagnosis of congenital and genetic diseases, including developmental defects that can lead to termination of pregnancy.

Aim of the work

The aim of the researchwas to study the characteristics of the distribution of allelic polymorphisms of genes - MTHFR, MTR, MTRR, which determine the synthesis of enzymes responsible for the conversion of folic acid.

Materials and methods

This section presents the results of the analysis of the distribution of alleles and genotypes.Ala222Val, Glu429Ala in MTHFR gene,Asp919Gly in MTR gene, Ile22Met in MTRR genein patient and control groups.The study voluntarily included 80 women of the Uzbek population with congenital malformations of the fetus (40 women) and frozen pregnancy (40 women) in the anamnesis, who formed the main group observed in the obstetric and gynecological complex of TMA. As a control group, DNA of 75 conditionally healthy women with no history of congenital anomalies of the fetus and non-developing pregnancy was studied. In order to analyze the variation in genotype distributions of the examined folate cycle genes from the standard Hardy-Weinberg equilibrium (HWE) was used the GenePop software (Genetics of Population).

Results

During the research were collected 155 women, that women were divided into two group: main group consist of 80 women with the complicated obstetrics anamnesis and control group included 75 women in the control group without the complicated obstetrics anamnesis. We focused on the distribution patterns of allelic polymorphisms in key genes involved in the folate cycle. Specifically, the study examined MTHFR (Ala222Val, Glu429Ala), MTR (Asp919Gly), and MTRR (Ile22Met) polymorphisms, which play a crucial role in methylation processes and homocysteine metabolism. Understanding these genetic variations is essential for assessing potential risks associated with congenital malformations and other metabolic disorders.

TABLE 1. FREQUENCY DISTRIBUTION OF ALLELES AND GENOTYPES FOR THE GLU429ALA POLYMORPHISM IN THE MTHFR GENE

Groups	Allele frequency				Genotype frequency distribution					
	A		C		A/A		A/C		C/C	
	n	%	n	%	n	%	n	%	n	%
Women with malformation of fetus (n = 40)	50	62.5	30	37.5	14	35	22	55	4	10.0
Women with undeveloped pragnancy (n = 40)	65	81.3	15	18.8	27	67.5	11	27.5	2	5.0
Control (n-75)	119	79.4	31	20.7	47	62.6	25	33.4	3	4.0

In the control group and in women with non-viable pregnancies the most observed genotype for the wild-type allele A was the homozygous A/A genotype, observed in 62.67% and 67.5% of cases, respectively. The homozygous mutant C/C genotype was identified at a relatively low frequency across the groups, with 10% in the congenital malformation group, 5.0% in the non-viable pregnancy group, and 4.0% among controls. 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 with 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 found 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.

TABLE 2. ANALYSIS OF THE RESULTS OF THE STUDY OF THE ALA222VA L POLYMORPHISM IN THE MTHFR GENE

Groups	Allele frequency				Genotype frequency distribution					
	C		T		C/C		C/T		T/T	
	n	%	n	%	n	%	n	%	n	%
Women with malformation of fetus	63	78.8	17	21.2	25	62.5	13	32.5	2	5.0

(n = 40)										
Women with undeveloped pragnancy (n = 40)	56	70	24	30	18	45	20	50	2	5.0
Control (n-75)	112	74.7	38	25	40	53.3	32	42.7	3	4.0

The most common genotype for the wild-type C allele in the control group, in women with congenital malformations and with non-viable pregnancy is the homozygous genotype C/C, 53.8%, 62.5% and 45.0%, respectively. The homozygous mutant T/T genotype in all groups was found with a relatively low frequency from 4.0% in the control group to 5.0% in the others. The highest frequency of the heterozygous genotype C/T was found in the group of women with non-viable pregnancy (50.0%). The prevalence of the normal C/C genotype in the group of healthy women confirms the protective function of this genotype (Table 2.).

TABLE 3. DISTRIBUTION OF ALLELE AND GENOTYPE FREQUENCIES FOR THE ASP919GLY POLYMORPHISM IN THE MTR GENE

Groups	Allele frequency				Genotype frequency distribution					
	A		G		A/A		A/G		G/G	
	n	%	n	%	n	%	n	%	n	%
Women with malformation of fetus (n = 40)	60	75	20	25	22	55	16	40	2	5.0
Women with undeveloped pragnancy (n = 40)	63	78.8	17	21.3	26	65	11	27.5	3	7.5
Control (n-75)	122	81.3	28	18.67	49	65.33	24	32	2	2.7

The most common genotype for the wild-type allele A in the control group, in women with congenital malformations and with non-viable pregnancy is the homozygous genotype A/A, 65.0%, 55.0% and 65.0%, respectively. The homozygous mutant G/G genotype was observed at 6.25% of women with fetal congenital malformations and 7.5% in those with non-viable pregnancies, however it was a significantly higher frequency in all study groups compared to the control group. In control group it was 2.67%. The highest level of the heterozygous A/G genotype was recorded in the main group who are with fetal congenital malformations, reaching at 40.0%. The prevalence of the normal homozygous A/A genotype in the group of healthy women confirms the protective function of this genotype.(table 3.).

TABLE 4. ANALYSIS OF THE RESULTS OF THE STUDY OF THE ALA222VA L POLYMORPHISM IN THE MTHFR GENE

Groups	Allele frequency				Genotype frequency distribution					
	A		G		A/A		A/G		G/G	
	n	%	n	%	n	%	n	%	n	%
Women with malformation of fetus (n = 40)	49	61.3	31	38.7	14	35	21	52.55	5	12.5
Women with undeveloped pragnancy (n = 40)	62	77.5	18	22.5	22	55	18	45	0	0
Control (n-75)	115	76.7	35	23.3	42	56	31	41.3	2	2.6

The most common genotype for the wild-type allele A was the homozygous genotype A/A and observed at 55.0% in the control group and 56.0% women with non-viable pregnancy in groups. The frequency of homozygous mutant G/G genotype in the main group with a congenital malformation of the fetus was 12.5%. Moreover, homozygous mutant G/G genotype was not determined in women with non-viable pregnancy. In the group of women with congenital malformations of the fetus the frequency of the heterozygous genotype A/G was also detected and it was 52.5%. When the prevalence of the normal A/A genotype (56.0%) in the group of

healthy women confirms the protective function of this genotype, the lowest frequency of the normal homozygous genotype was found in women with congenital malformations of the fetus (Table4).

Discussion

The analysis of the MTHFR gene Glu429Ala polymorphism in the group with congenital malformations and the control group revealed no significant reduction in the frequency of the wild-type allele A compared to healthy women (62.5% vs. 79.33%). However, there was an observed increase in the prevalence of the functionally unfavorable allele C in the congenital malformation group compared to healthy women (32.5% vs. 20.67%).

The distribution of genotypes in the analyzed group of patients corresponded to the Hardy-Weiberg equilibrium (HWE), which indicates the representativeness of the main group sample and the correctness of the Glu429Ala polymorphism determination. The revealed slight deviation from the HWE 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-type genotype (selective effect).

These results suggest that heterozygous and, particularly, homozygous genotypes have a significant statistical association with the development of fetal malformations. This may indicate that the Uzbek ethnic group in increasing the risk of fetal malformations within. the MTHFR gene Glu429Ala polymorphism plays an independent role.

Thus, for women, who have fetal malformations in the anamnesis, the prognostic value of the Glu429Ala polymorphism in the MTHFR gene as an independent marker is high.

Heterozygotes forAla222Val polymorphism in the MTHFR gene (CT) did not have an increased risk of developing pathology. We did not find a connection between the Ala222Val polymorphism in the MTHFR gene and an increased risk of developing different pathologies.

The study revealed non-significant yet noticeable trends in genotype distribution and allele frequencies between women with fetal congenital malformations and those in the control group for the Asp919Gly polymorphism in the MTR gene. Specifically, the frequency of the A allele was slightly lower in the affected group (75.0%) compared to the control group (81.33%). Additionally, there was an increase in the prevalence of the functionally unfavorable G allele in the congenital malformation group (25.0% vs. 18.67% in the control group).

The analysis showed that the distribution of genotype and allele frequencies for the Asp919Gly polymorphism in the MTR gene across all groups was consistent with the expected Hardy-Weinberg equilibrium ($p>0.05$). This confirms the representativeness of the study sample and the accuracy of polymorphism determination.

The most common genotype for the wild-type allele A in the control group, in women with non-viable pregnancy, is the homozygous genotype A/A, 56.0% and 56.0%, respectively. The homozygous mutant G/G genotype in the group with fetal congenital malformations was found with the highest frequency (12.5% compared to 2.67% in the control). This genotype was not detected in women with non-viable pregnancy. The highest frequency of the heterozygous genotype A/G was also detected in the group of women with fetal congenital malformations (52.5%). The prevalence of the normal A/A genotype (56.0%) in the group of healthy women confirms the protective function of this genotype. While the lowest frequency of the normal homozygous genotype was found in women with fetal congenital malformations. The study found that the distribution of genotype and allele frequencies for the Ile22Met polymorphism in the MTRR gene across all groups aligned with the expected Hardy-Weinberg equilibrium ($p>0.05$). This confirms the sample's representativeness and the accuracy of polymorphism assessment.

Conclusion.

When studying the ratios of polymorphism of folate cycle genes among the women studied, the genotypeThe A/C marker Glu429Ala in the MTHFR gene was found 1.5 times more often, and the C/C genotype 2.5 times more often than in the control group.In the markerIle22Met in the MTRR genegenotype G/Goccurred 4.6 times more often than in the control group. Although mutations in folate cycle genes in the general population can occur in every third woman, which confirms the need for triggers in the form of endo and exogenous factors to activate these genes.

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