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Diagnostic Markers of Placental Insufficiency in Pregnant Women with Thrombophilia

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Abstract The article describes the results of a molecular genetic study of the hemostasis system with the determination of the polymorphism of the folate-dependent gene (MTHFR methylenetetrahydrofolate reductase: MTHFR1298 A>C MTHFR 677 C>T in the examined pregnant women. Genetic polymorphism 2756 A>G of the MTR gene is associated with the pathology under study in the Uzbek population ($\chi 2$=7.25; P=0.004; OR=2.8, CI=1.37–5.70), where the reference allele G has a damaging effect, and the alternative allele A has a protective effect. The presence of the G allele can increase the risk of developing diseases associated with impaired folate metabolism, which makes it an important marker for genetic screening and the development of personalized therapeutic strategies.

Keywords Marker, Placental insufficiency, Pregnant women, Thrombophilia

1. Introduction

Despite advances in medicine, thrombophilia remains a serious problem for many pregnant women, causing undesirable consequences [1,2].

Studies show that thrombophilia and genetic changes in certain genes that regulate blood clotting may be associated with the development of fetoplacental insufficiency. In particular, a link was found between changes in genes responsible for folic acid metabolism and the development of fetoplacental insufficiency in women [3,5,7].

However, such studies have not been conducted among Uzbek women with fetoplacental insufficiency, although it is known that they may have increased MTHFR gene polymorphism due to dietary characteristics [4,8,9,10].

The results of the study demonstrate that genetic changes associated with metabolism involving folic acid play an important role in the development of fetoplacental insufficiency.

The aim of the study: to conduct a molecular genetic study of the hemostasis system with the determination of the polymorphism of the folate-dependent gene (MTHFR methylenetetrahydrofolate reductase: MTHFR1298 A>C MTHFR 677 C>T MTRR 2756 A>G, MTRR 66 A> G in the examined pregnant women.

2. Material and Methods of the Study

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The study included 100 pregnant women who were divided into 2 groups. The main group included 50 pregnant women with placental insufficiency against the background of thrombophilia. The comparison group consisted of 50 pregnant women with placental insufficiency without thrombophilia. The control group consisted of 30 women with a physiological course of pregnancy. All 100 examined women underwent a molecular genetic study revealing hereditary disorders of the hemostasis system: polymorphism of the folate-dependent gene (MTHFR methylenetetrahydrofolate reductase: MTHFR1298 A>C MTHFR 677 C>T MTRR 2756 A>G, MTRR 66 A>G. Genomic DNA was extracted from blood samples using the GeneMATRIX blood DNA purification kit (EURx, Poland). Pre-validated TaqMan real-time PCR methods (Life Technologies, USA) were used to detect the corresponding SNPs in the MTHFR (rs1801131, rs1801133), MTR (rs1805087), and MTRR (rs1801394) genes. Amplification was performed in a 7500 Fast Real-Time PCR System with built-in SDS SNP Genotyping Software (Applied Biosystems, USA) using TaqMan GTXpress Master Mix (Life Technologies, USA).

3. Results of the Study

Analysis of the distribution of allele and genotype frequencies of the polymorphic marker A1298C of the MTHFR gene showed a significant predominance of the heterozygous genotype AC in both groups. The frequency of the reference allele A was 60%, the frequency of the minor allele C - 40% in both study groups. The distribution of allele

frequencies in the Uzbek population was slightly different from the world values, so the frequency of the reference allele A averaged in all populations was 76.66%. The frequencies of genotypes in the two groups we compared differed, so in the case group, the frequency of the AA genotype was 35% in the case group, and 29% in the control group. The frequency of the heterozygous genotype also differed in the two groups: the frequency of the AC genotype was 50% in the case group and 62% in the control group (Fig. 1). The distribution of allele frequencies in both groups corresponded to the Hardy-Weinberg distribution, in the case group the value p=0.79, in the control group p=0.09. The association analysis of the influence of the predictor genotype on the occurrence of pathology did not show a significant association for any of the inheritance models used (p>0.05) (table 1).

Table 1. Associative analysis of the influence of the A1298C polymorphism of the MTHFR gene on the occurrence of pathology

Multiplicative model of inheritance						
	Happening	Control				
	n = 40	n = 34	χ2	p	OR	95% CI
Allele A	0.600	0.603	0.00	0.97	0.99	0.51 – 1.91
Allele C	0.400	0.397			1.01	0.52 – 1.96
General model of inheritance						
	Happening	Control				
	n = 40	n = 34	χ2	p	OR	95% CI
Genotip A/A	0.350	0.294	1.21	0.55	1.29	0.48 – 3.45
Genotip A/C	0.500	0.618			0.62	0.24 – 1.57
Genotip C/C	0.150	0.088			1.82	0.42 – 7.92
Additive model of inheritance						
	Happening	Control				
	n = 40	n = 34	χ2	p	OR	95% CI
Genotip A/A	0.350	0.294	0.00	0.97	1.29	0.48 – 3.45
Genotip A/C	0.500	0.618			0.62	0.24 – 1.57
Genotip C/C	0.150	0.088			1.82	0.42 – 7.92
Dominant inheritance model						
	Happening	Control				
	n = 40	n = 34	χ2	p	OR	95% CI
Genotip A/A	0.350	0.294	0.26	0.61	1.29	0.48 – 3.45
Genotip A/C+C/C	0.650	0.706			0.77	0.29 – 2.07
Recessive inheritance model						
	Happening	Control				
	n = 40	n = 34	χ2	p	OR	95% CI
Genotip A/A+A/C	0.850	0.912	0.66	0.42	0.55	0.13 – 2.38
Genotip C/C	0.150	0.088			1.82	0.42 – 7.92
Hardy-Weinberg test for controls						
	Control	HWE	χ2	p		
n = 34						
Genotip A/A	0.294	0.364	2.86	0.09		
Genotip A/C	0.618	0.479				
Genotip C/C	0.088	0.158				
Hardy-Weinberg test for cases						
	Happening	HWE	χ2	p		
n = 40						
Genotip A/A	0.350	0.360	0.07	0.79		
Genotip A/C	0.500	0.480				
Genotip C/C	0.150	0.160				

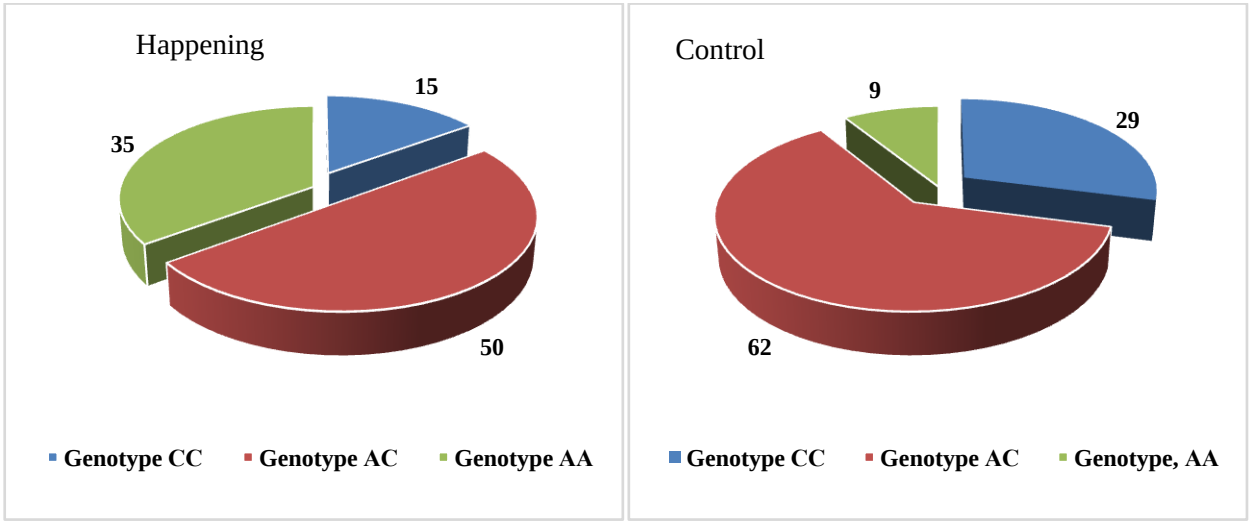

Figure 1. Distribution of genotype frequencies of the polymorphic marker A1298C of the MTHFR gene in the case and control groups

Analysis of the distribution of allele and genotype frequencies of the polymorphic marker C677T of the MTHFR gene showed the prevalence of the homozygous genotype CC in the case group and was 53%, while in the control group it was 62%. The frequency of the reference allele C was 73% in the case group and 79% in the control group. The frequency of the CC genotype in the case group was 53%, while in the controls it was 10 percent higher (62%).

The frequency of occurrence of the heterozygous genotype CT was practically the same in the two groups and was 37% in the case group, and 35% in the control group. The allele frequency indices slightly differ from the world ones (A allele 34%; G allele 66%) (Fig. 2). The distribution of allele frequencies in both groups corresponded to the Hardy-Weinberg distribution, in the case group the value p=0.59, in the control group P=0.64. The association analysis of the influence of the predictor genotype on the occurrence of pathology did not show a significant association for any of the inheritance models used (P>0.05) (Table 2).

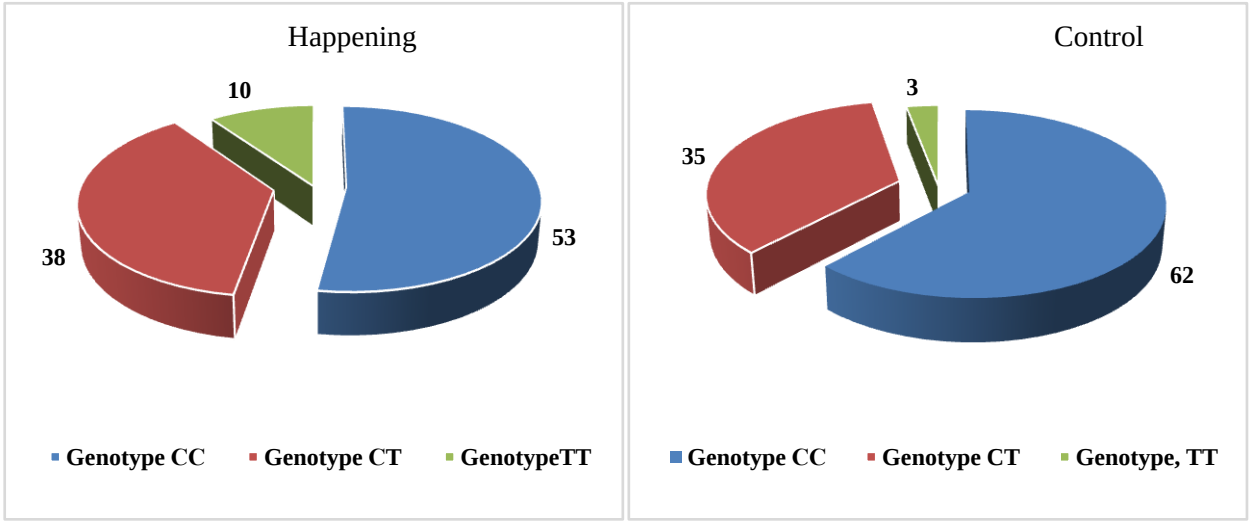

Figure 2. Distribution of genotype frequencies of the polymorphic marker C677T of the MTHFR gene in the case and control groups

Table 2. Associative analysis of the influence of the C677T polymorphism of the MTHFR gene on the occurrence of pathology

Multiplicative model of inheritance						
	Happening	Control				
	n = 40	n = 34	$\chi 2$	p	OR	95% CI
Allele C	0.713	0.794	1.31	0.25	0.64	0.30 – 1.38
Allele T	0.288	0.206			1.56	0.73 – 3.33
General model of inheritance						
	Happening	Control				
	n = 40	n = 34	$\chi 2$	p	OR	95% CI
Genotip C/C	0.525	0.618	1.66	0.44	0.68	0.27 – 1.73
Genotip C/T	0.375	0.353			1.10	0.42 – 2.85
Genotip T/T	0.100	0.029			3.67	0.39 – 34.50
Additive model of inheritance						
Genotip	Happening	Control				
	n = 40	n = 34	$\chi 2$	p	OR	95% CI
Genotip C/C	0.525	0.618	1.27	0.26	0.68	0.27 – 1.73
Genotip C/T	0.375	0.353			1.10	0.42 – 2.85
Genotip T/T	0.100	0.029			3.67	0.39 – 34.50
Dominant inheritance model						
	Happening	Control				
	n = 40	n = 34	$\chi 2$	p	OR	95% CI
Genotip C/C	0.525	0.618	0.64	0.42	0.68	0.27 – 1.73
Genotip C/T+T/T	0.475	0.382			1.46	0.58 – 3.70
Recessive inheritance model						
	Happening	Control				
	n = 40	n = 34	$\chi 2$	p	OR	95% CI
Genotip C/C+C/T	0.900	0.971	1.45	0.23	0.27	0.03 – 2.57
Genotip T/T	0.100	0.029			3.67	0.39 – 34.50
Hardy-Weinberg test for control						
	Control	HWE	$\chi 2$	p		
n = 34						
Genotip C/C	0.618	0.631	0.21	0.64		
Genotip C/T	0.353	0.327				
Genotip T/T	0.029	0.042				
Hardy-Weinberg test for cases for Happening						
	Happening	HWE	$\chi 2$	p		
	n = 40					
Genotip C/C	0.525	0.508	0.29	0.59		
Genotip C/T	0.375	0.410				
Genotip T/T	0.100	0.083				

Analysis of the distribution of allele and genotype frequencies of the polymorphic marker A2756G of the MTR gene showed a significant predominance of the homozygous genotype AA in the control group (62%) compared to the case group (35%). The frequency of the reference allele A was 76% in the control group and 53% in the case group. The frequency of the AA genotype in the case group was 35%, and in the controls 62%. The distribution was similar to world indicators (A allele - 81%; G allele - 19%). The frequency of the heterozygous genotype AG was slightly more common than in the control group (Fig. 3). The distribution of allele frequencies in both groups corresponded to the Hardy-Weinberg distribution, in the case group the p value = 0.12, in the control group p = 0.29. The association analysis of the influence of the predictor genotype on the occurrence of pathology showed the presence of a significant association for several inheritance models at once: according to the multiplicative model $\chi 2$=7.25; p=0.004; OR=2.8; 95% CI 1.37-5.70, where the G allele has a damaging effect, and the A allele has a protective effect. According to other inheritance models, a statistically significant correlation of the genotype with pathology was also revealed with a significance level of $p<0.05$. (Table 3).

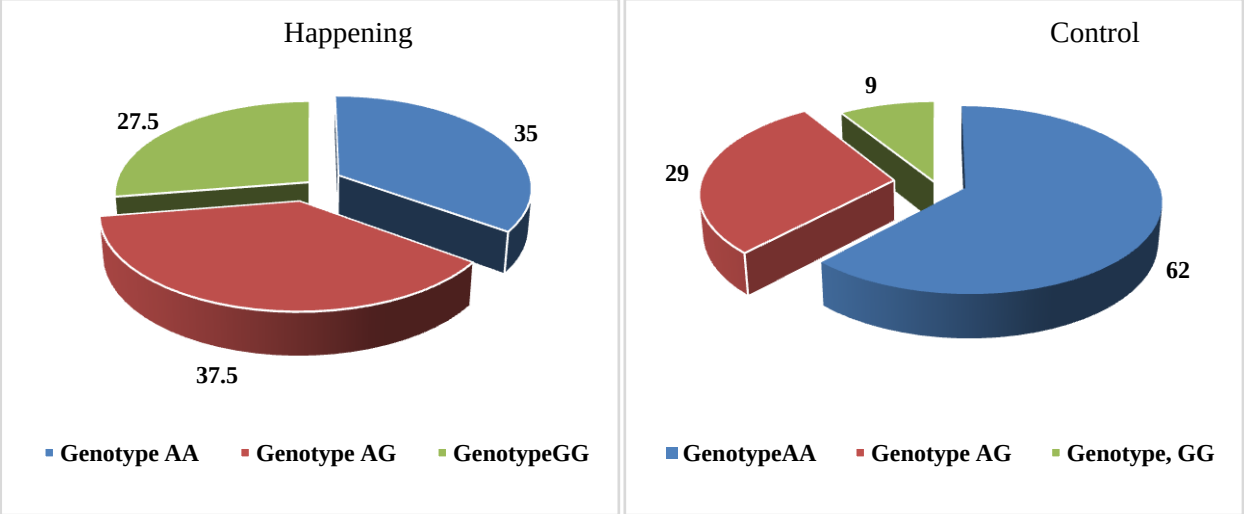

Figure 3. Distribution of genotype frequencies of the polymorphic marker A2756G of the MTR gene in the case and control groups

Table 3. Association analysis of the influence of the polymorphic marker A2756G of the MTR gene in the case and control groups

Multiplicative model of inheritance						
	Happening	Control				
	n = 40	n = 34	χ2	P	OR	95% CI
Allele A	0.538	0.765	7,25	0,004	0,36	0.18 – 0.73
Allele G	0.463	0.235			2,8	1.37 – 5.70
General model of inheritance						
	Happening	Control				
	n = 40	n = 34	χ2	P	OR	95% CI
Genotip A/A	0.350	0.618	6,53	0,04	0,33	0.13 – 0.86
Genotip A/G	0.375	0.294			1,44	0.54 – 3.82
Genotip G/G	0.275	0.088			3,92	0.99 – 15.48
	Happening	Control				
	n = 40	n = 34	χ2	P	OR	95% CI
Genotip A/A+A/G	0.350	0.618	5,28	0,02	0,33	0.13 – 0.86
Genotip G/G	0.650	0.382			3,0	1.16 – 7.75
Recessive inheritance model						
	Happening	Control				
	n = 40	n = 34	χ2	P	OR	95% CI
Genotip A/A	0.725	0.912	4,18	0,04	0,26	0.06 – 1.01
Genotip A/G+G/G	0.275	0.088			3,92	0.99 – 15.48
Hardy-Weinberg test for controls						
	Control	HWE	χ2	P		
n = 34						
Genotip A/A	0.618	0.585	1,13	0,29		
Genotip A/G	0.294	0.360				
Genotip G/G	0.088	0.055				
Hardy-Weinberg test for cases						
	Happening	HWE	χ2	P		
n = 40						
Genotip A/A	0.350	0.289	2,42	0,12		
Genotip A/G	0.375	0.497				
Genotip G/G	0.275	0.214				

4. Conclusions

Genetic polymorphisms 1298 A>C and 677 C>T of the MTHFR gene, 66 A>G of the MTRR gene, 20210 G>A of the F2 gene, 807 C>T of the α2 ITGA2 gene did not show an association with pathology among the studied women of the Uzbek population according to any of the inheritance models used ($p > 0.05$).

Genetic polymorphism 2756 A>G of the MTR gene is associated with the studied pathology in the Uzbek population ($\chi 2 = 7.25$; $P = 0.004$; $OR = 2.8$, $CI = 1.37–5.70$), where the reference allele G has a damaging effect, and the alternative allele A has a protective effect. The presence of the G allele may increase the risk of developing diseases associated with impaired folate metabolism, making it an important marker for genetic screening and the development of personalized therapeutic strategies.

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