Natural Resources for Human Health
eISSN: 2583-1194

Original Research

Received 07 July 2026
Revised 12 Aug 2026
Accepted 31 Aug 2026

Natural Resources for Human Health 2026, Vol. 6 (20s): 216–222

KEYWORDS:
fetal anomalies, pregnancy, genetic polymorphism, PAI1, FGB, fibrinolysis, fibrinogen, genetic markers, fetal abnormality risk.

Molecular Genetic Markers of the Endothelial System in Predicting the Risk of Congenital Fetal Anomalies

Reymova M.K.[1], Mavlyanova N.N.[2]

[1]Republican Specialized Scientific and Practical Medical Center for Mother and Child Health, Ministry of Health of the Republic of Uzbekistan
[2]Karakalpak State Medical Institute

ABSTRACT: Objective. To investigate the distribution of genotypes of the PAI1 (5G/4G) and FGB G(−455)A polymorphisms in pregnant women with fetal anomalies and in a control group, and to assess their potential association with fetal abnormalities.

Materials and Methods. The study included 54 pregnant women with fetal anomalies (study group) and 40 women with uncomplicated pregnancies and no identified fetal anomalies (control group). Genotype distributions were compared using allele and genotype frequencies, odds ratios (ORs), confidence intervals and the chi-square (χ^2) test.

Results. The frequency of the PAI1 5G/5G genotype was 14.8% in the study group and 95.0% in the control group, whereas the 5G/4G genotype was observed in 75.9% and 5.0% of participants, respectively. The 4G/4G genotype was detected in 9.3% of the study group and was absent in the controls. For the FGB G(−455)A polymorphism, the G/G genotype frequencies were 35.2% and 92.5% in the study and control groups, respectively. The G/A genotype occurred in 42.6% and 7.5% of participants, while the A/A genotype was identified in 22.2% of the study group and was not detected in the controls. Neurological abnormalities of the brain were also more frequently observed among carriers of the investigated heterozygous genotypes.

Conclusion. The observed differences suggest a potential association between the PAI1 (5G/4G) and FGB G(−455)A polymorphisms and the presence of fetal anomalies in the population studied. Further research involving larger cohorts and independent validation is necessary to determine the clinical and prognostic significance of these genetic variants.

INTRODUCTION

The investigation of molecular genetic markers potentially associated with congenital fetal anomalies is an important area of contemporary medical genetics and perinatology. Congenital anomalies have a multifactorial etiology involving genetic, chromosomal, and environmental factors, and their specific cause remains unidentified in a substantial proportion of cases [1, 2].

One promising research direction is the investigation of genetic variants involved in the regulation of vascular tone, hemostasis, and fibrinolysis. Disturbances in the interaction of these systems may affect uteroplacental circulation and the course of pregnancy. However, the role of individual genetic polymorphisms in obstetric complications remains uncertain and may depend on population characteristics, combinations of risk factors, and the nature of the condition under investigation [3, 4].

Of particular interest is the SERPINE1 gene, which encodes plasminogen activator inhibitor type 1 (PAI-1). The 4G/5G promoter polymorphism may be associated with regulation of PAI-1 expression and changes in fibrinolytic activity. Several studies have investigated its potential association with pregnancy complications, including preeclampsia and recurrent pregnancy loss. However, systematic reviews indicate heterogeneity in the findings, precluding the use of this polymorphism as a universal marker of obstetric risk [3–5].

Another genetic variant of interest in research on hemostasis is the FGB G(-455)A polymorphism, located in the regulatory region of the gene encoding the fibrinogen beta chain. This variant is investigated in relation to individual differences in fibrinogen levels and thrombotic risk. Findings concerning its associations with thrombotic conditions vary across populations, while a direct association with congenital fetal anomalies requires separate evaluation [6].

Thus, investigation of SERPINE1 (PAI1) and FGB polymorphisms in pregnant women of the Karakalpak population is of scientific interest for identifying potential genetic factors associated with hemostatic function and the risk of adverse reproductive outcomes. Any associations identified should be interpreted in the context of the multifactorial nature of congenital anomalies, the clinical characteristics of the women examined, and the characteristics of the study population.

Study Objective

To investigate the distribution of alleles and genotypes of the SERPINE1 (PAI1) 5G/4G and FGB G(-455)A polymorphisms in women with congenital fetal anomalies and in a control group, and to assess the potential association of these genetic variants with the risk of this condition.

We examined 94 pregnant women with fetal developmental anomalies, aged 20 to 43 years. Of these, 54 (57.4%) pregnant patients with fetal developmental anomalies constituted the study group. The control group comprised 40 pregnant women with uncomplicated pregnancies and no congenital malformations.

All patients underwent general clinical, instrumental, functional (ultrasound screening), and genetic real-time PCR examinations. All patients were also evaluated by specialists in related disciplines, including a geneticist, internist, neurologist, infectious disease specialist, dermatologist, endocrinologist, and others.

Molecular genetic analysis of biological material (DNA) was performed at the laboratory of the Republican Specialized Scientific and Practical Medical Center for Mother and Child Health, Ministry of Health of the Republic of Uzbekistan. DNA/RNA was extracted from all blood samples using the Ribo-prep kit (InterLabService, Russia).

Manufacturer-supplied allele-specific primers were selected for DNA samples to identify genotypes comprising alleles of PAI1 (5G/4G) and FGB G(-455)A. A total of 200 DNA samples were analyzed by polymerase chain reaction (PCR) for genotyping. The Applied Biosystems Veriti 96-well automated thermal cycler was optimized using the following program: one initial denaturation step at 94°C for 180 s, followed by 94°C for 10 s, 64°C for 10 s, and 72°C for 20 s. These steps were repeated 40 times to perform PCR. Statistical analysis was conducted using OpenEpi 2009, Version 2.3.

RESULTS

The results of the molecular genetic analyses are presented in Table 1.

Table 1. Genotype frequency distributions of the PAI1 (5G/4G) and FGB G(-455)A polymorphisms in patients with fetal anomalies and in the control group

Polymorphism, genotypes	Fetal anomalies, n=54		Control, n=40		OR (95% CI)	p
PAI1 (5G/4G)						
5G/5G	8	14.8	38	95	0.009 (0.0018-0.0457)	<0.0001
5G/4G	41	75.9	2	5	59.92 (12.68-283.11)	<0.0001
4G/4G	5	9.3	-	-		

Alleles 5G	57	52.7	78	97.5	34.9 (8.16-149.29)	0.0001
4G	51	47.2	2	2.5		
FGB G(-455)A						
G/G	19	35.2	37	92.5	0.044(0.012–0.162)	0.0002
G/A	23	42.6	3	7.5	9.15 (2.51–33.39)	0.0002
A/A	12	22.2	0	0		
Alleles G	61	56.5	77	96.3	19.78 (5.87–66.62)	0.0001
A	47	43.5	3	3.75		

As shown in the table, analysis of the PAI1 (5G/4G) polymorphism in patients with fetal developmental anomalies revealed that the functional 5G/5G genotype was present in 95% of the control group (38/40) and 14.8% of the study group (8/54), representing a 6.4-fold lower frequency in the study group (χ^2=59.12; P<0.0001; OR=0.009; 95% CI=0.0018–0.0457). In contrast, the heterozygous PAI1 5G/4G variant was identified in 5% of the control group (2/40) and 75.9% of the study group (41/54), a 15.2-fold higher frequency than among healthy patients (χ^2=46.58; P<0.0001; OR=59.92; 95% CI=12.68–283.11).

The homozygous mutant PAI1 4G/4G variant was identified in 5 (9.3%) of the 54 patients with fetal anomalies, whereas this genotype was not detected in the healthy group.

These findings indicate that the heterozygous PAI1 5G/4G and homozygous mutant 4G/4G genotypes are genetic determinants involved in impaired reproductive function, increasing the odds of fetal anomalies and raising their risk 59.9-fold (OR=12.7–283.1).

Analysis of the FGB G(-455)A genotypes identified the functional G/G genotype in 92.5% of the control group (37/40) and 35.2% of the study group (19/54) (χ^2=31.3; p<0.0002; OR=0.044 (0.012–0.162)). The heterozygous G/A genotype occurred in 42.6% of the study group (23/54) and 7.5% of the control group (3/40), respectively (χ^2=14.14; p<0.0002; OR=9.15 (2.51–33.39)). The homozygous mutant FGB A/A genotype was detected in 22.2% of the study group (12/54) and was absent in the controls (χ^2=10.19; p<0.001; OR=0.00141).

Under the multiplicative inheritance model, the association between the FGB G(-455)A polymorphism and the risk of fetal anomalies was considered highly significant (χ^2=37.23; df=1; p<0.0001), with the presence of the G allele increasing the odds of the condition 19.78-fold.

We analyzed the occurrence of PAI1 (5G/4G) and FGB G(-455)A genotypes according to the diagnostic categories of fetal anomalies (Figures 1 and 2).

Natural Resources for Human Health
eISSN: 2583-1194

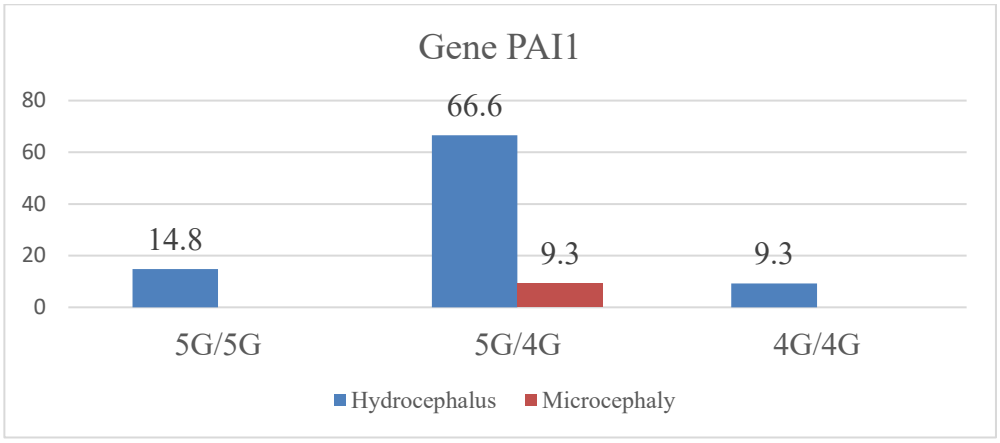


Figure 1. Frequency of PAI1 genotypes by diagnostic category of neurological abnormalities of the brain (%)

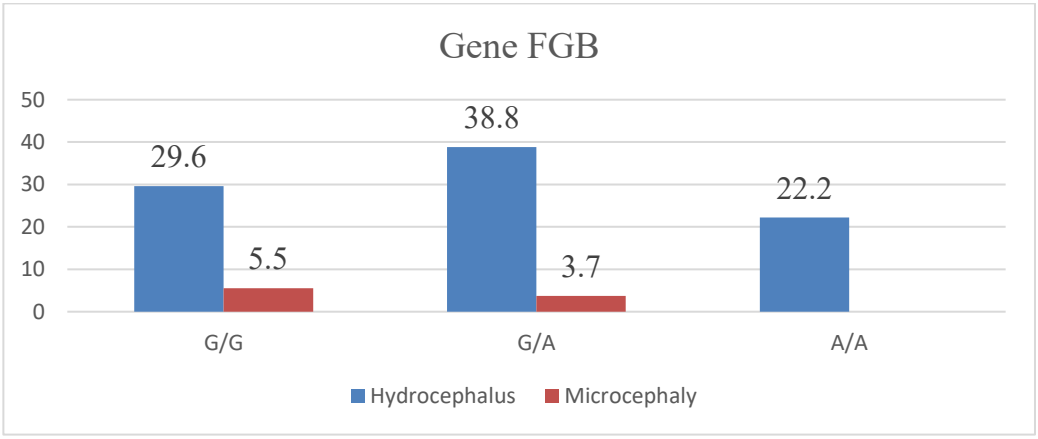


Figure 2. Frequency of FGB G(-455)A genotypes by diagnostic category of neurological abnormalities of the brain (%)

As shown in Figures 1 and 2, neurological abnormalities of the brain were most frequently identified among carriers of heterozygous variants of PAI1 and FGB, accounting for 66.6% and 38.8% of cases, respectively.

Thus, investigation of the vascular system genes PAI1 and FGB indicates that the mutant 4G allele and heterozygous PAI1 5G/4G genotype, together with the mutant A allele and heterozygous FGB G/A genotype, are genetic determinants involved in the development of neurological abnormalities of the brain, thereby increasing the risk of fetal anomalies 80.2-fold (OR=34.9; OR=19.78).

Table 2. Expected and observed genotype frequency distributions under Hardy–Weinberg equilibrium for the PAI 5G/4G polymorphism in the healthy control group

Control group				
Genotypes	Genotype frequency		χ^2	p
	Observed	Expected		
5G/5G	95.0	60.58		
5G/4G	5.0	34.51		
4G/4G	0	4.91		
Total	100.00	100.00	0.026	0.8

Study group				
5G/5G	14.81	55.02		
5G/4G	75.93	38.31		
4G/4G	9.26	6.67		
Total	100.00	100.00	14.783	0.0003

As shown in the table, analysis of the genotype frequency distribution under Hardy–Weinberg equilibrium for the PAI polymorphism in the study group revealed that the expected frequency of the functional homozygous 5G/5G genotype was 55.02%, compared with 60.6% in the control group, a 1.1-fold higher frequency in the controls. The expected frequency of the heterozygous 5G/4G genotype was 1.1-fold higher than in the control group (38.3% versus 34.5%). The expected frequency of the unfavorable homozygous PAI 4G/4G genotype was 6.67% in the study group and 4.91% in the control group. These findings are important indicators for use as criteria for predicting disease risk.

Table 3. Expected and observed genotype frequency distributions under Hardy–Weinberg equilibrium for the FGB G(-455)A polymorphism in the healthy control and study groups

Control group				
Genotypes	Genotype frequency		χ^2	p
	Observed	Expected		
G/G	92.5	60.58		
G/A	7.5	34.5		
A/A	0	4.9		0.8
Total	100.00	100.00	0.061	
Study group				
G/G	14.81	55.02		
G/A	75.93	38.31	0.9	**0.3**
A/A	9.26	6.67		
G/G	14.81	55.02		

A similar trend was observed for the FGB G(-455)A polymorphism in patients with fetal anomalies compared with the healthy control group. The frequency of heterozygous FGB G(-455)A G/A variants was 1.1-fold higher than in the control group (38.31% versus 34.5%), and that of homozygous FGB G(-455)A A/A variants was 1.4-fold higher than among healthy individuals.

The analysis revealed statistically significant differences in the genotype distributions of the PAI1 (5G/4G) and FGB G(−455)A polymorphisms between pregnant women with fetal anomalies and the control group. The study group had higher frequencies of the PAI1 5G/4G and 4G/4G genotypes and the FGB G/A and A/A genotypes. Analysis of allele frequencies revealed marked differences between groups for both polymorphisms.

Comparison of the expected and observed genotype frequencies of the PAI 5G/4G and FGB G(-455)A polymorphisms showed statistically significant deviations (P>0.05) in all groups and subgroups studied, indicating that the observed genotype proportions in the study samples were consistent with Hardy–Weinberg equilibrium.
Plasminogen activator inhibitor-1 (PAI1) is the principal antagonist of tissue plasminogen activator (tPA) and urokinase (uPA), which promote fibrinolysis (clot dissolution). It belongs to the serine protease inhibitor (serpin) family and is also referred to as Serpin-1.

According to published studies, an imbalance in uteroplacental fibrinolytic regulation in gestosis resulting from increased PAI-1 production is responsible for increased fibrin deposition in uterine vessels and reduced uteroplacental blood flow. It also plays an important role in reducing trophoblast invasion in early pregnancy, thereby creating conditions for the subsequent development of gestosis.

According to the literature, FGB G(-455)A polymorphisms play an important role in indirect mechanisms underlying pregnancy complications. Carriage of the unfavorable A allele leads to increased gene expression and higher maternal blood fibrinogen concentrations, promoting microthrombus formation. This subsequently contributes to nutrient and oxygen deficiency, fetal growth restriction, fetal developmental anomalies (microcephaly and hydrocephalus), and the risk of premature placental abruption or pregnancy loss.

CONCLUSION

The findings indicate associations between the hemostasis-related PAI1 (5G/4G) and FGB G(−455)A polymorphisms and fetal developmental anomalies among the pregnant women of the Karakalpak population examined. The PAI1 5G/5G genotype was significantly less frequent in the study group than in the control group (14.8% versus 95.0%; p<0.0001). In contrast, the heterozygous 5G/4G genotype was substantially more frequent (75.9% versus 5.0%; p<0.0001). The 4G/4G genotype was detected in 9.3% of the study group and was absent in the controls.

Investigation of the FGB G(−455)A polymorphism also revealed differences in genotype distributions between groups. The G/G genotype frequency was 35.2% in the study group and 92.5% in the control group. The heterozygous G/A variant was detected in 42.6% and 7.5% of cases, respectively, while the A/A genotype was present in 22.2% of patients with fetal anomalies and was absent in the controls.

Analysis of the diagnostic categories of fetal anomalies showed that neurological abnormalities of the brain were more frequent among carriers of heterozygous variants of the investigated genes. These findings suggest that genetic factors associated with the regulation of fibrinolysis and fibrinogen metabolism may contribute to certain disturbances of intrauterine development.

Thus, the PAI1 (5G/4G) and FGB G(−455)A polymorphisms are of interest as potential genetic markers for further investigation of the risk of fetal anomalies.

REFERENCES

[1] World Health Organization. Congenital disorders. 27 February 2023. URL: https://www.who.int/news-room/fact-sheets/detail/birth-defects.

[2] World Health Organization, Centers for Disease Control and Prevention, International Clearinghouse for Birth Defects Surveillance and Research. Birth defects surveillance: quick reference handbook of selected congenital anomalies and infections. Geneva: WHO; 2020. URL: https://www.who.int/publications/i/item/9789240015418.

[3] Mavlyanova N.N. Fetal Loss Syndrome (Molecular Genetic Aspects). Monograph. Tashkent; 2020. 144 pp.

[4] Association of plasminogen activator inhibitor-type 1 (-675 4G/5G) polymorphism with pre-eclampsia: systematic review. PLOS ONE. 2013. DOI: 10.1371/journal.pone.0056907.

[5] The Role of Plasminogen Activator Inhibitor Type 1 (PAI-1) in Placenta-Mediated Pregnancy Complications: A Systematic Review. A systematic review of genetic variants and PAI-1 levels in placenta-mediated pregnancy complications. 2022. URL: PubMed — PMID: 35021249.

[6] Systematic review and meta-analysis of association between plasminogen activator inhibitor-1 4G/5G polymorphism

and recurrent pregnancy loss: an update. Thrombosis Journal. 2024. DOI: 10.1186/s12959-024-00612-9.

[7] Association of β-fibrinogen polymorphisms and venous thromboembolism risk: A PRISMA-compliant meta-analysis. A meta-analysis of FGB polymorphisms, including G(-455)A, and the risk of venous thromboembolism. 2019. URL: Full text in PubMed Central.