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Assessment of the Significance of Polymorphism G103T of the F13 Gene in the Development of Preterm Labor

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ABSTRACT

The article presents an analysis of the detectability of the hemostasis gene F13 in pregnant women with premature birth (PB). The results of molecular genetic studies have shown that the mutant T allele and hetero/homozygous genotypes of the F13 polymorphism are one of the markers of an increased risk of thrombophilia in pregnant women with PB with complex subordination, while the functional G allele and the functionally favorable G/G genotype are protective markers for the development of pathology (χ2=2.15; p<0.14; OR=3.81; 95%CI 0.18 – 81.73).

INTRODUCTION

The main objective of obstetrics is to reduce maternal and child morbidity and mortality. Undoubtedly, timely and optimal delivery plays an important role in solving this problem [9, 13]. The most important medical and biological problem of modern obstetrics is premature birth [3, 10, 16]. According to statistics, premature infants account for 58.8-68.5% of early neonatal mortality and 66.1-74.9% of infant mortality. Stillbirth in premature births is observed 8-13 times more often than in timely ones. Perinatal mortality in premature newborns is more than 26 times, and higher than in full-term infants, i.e. its spontaneous interruption at the time from conception to 37 weeks [4, 12, 18].

According to literature data, the F13A1 gene encodes factor XIII, etc. fibrin-stabilizing factor (fibrinase), which is involved in the formation of insoluble fibrin, which is the basis of a blood clot, or thrombus [8, 11, 15]. At the same time, blood clots formed in the presence of fibrinase undergo lysis very slowly. An increase in the activity of factor XIII is accompanied by an increase in the adhesion and aggregation of blood plates. In patients with thromboembolic complications, fibrinase activity is increased [2, 6, 14].

The aim of our research is to assess the detectability of polymorphism of genotypes G103T of the F13 gene in pregnant women with premature birth.

MATERIAL AND METHODS

We examined 90 women aged 21 to 36 years. Among them, patients with PB were 52 persons aged 19 to 42 years and 38 patients with physiological pregnancy without PB, who made up the control group. General clinical, instrumental, functional (ultrasound, Doppler), and ELISA studies were performed in all pregnant women. Pregnant women were consulted by related specialists (therapist, neurologist, infectious disease specialist, dermatologist, endocrinologist, etc.). By informed consent, the molecular genetic study of the G103T gene of the F13A1 gene was performed by polymerase chain reaction in real time. Molecular genetic examination of biomaterials (DNA) was performed on the basis of the clinical laboratory of Genotechnologies LLC. DNA/RNA isolation from all biological blood samples was performed using the Ribot-prep kit (Interlabservice, Russia).

To identify the polymorphism of the genotype consisting of alleles G>A of the F2 gene, allele-specific primers from the manufacturer were selected from DNA samples. 200 DNA samples were examined for genotyping DNA samples by polymerase chain reaction (PCR). To do this, the 96-cell automated amplifier "Applied Biosystems Veriti" was optimized according to the following program: initial denaturation once at 180 seconds 94 ° C, 94 ° C - 10 seconds, 64 ° C - 10 seconds, 72 ° C - 20 seconds in the program, we performed these specified actions 40 times to occur polymerase chain reaction. Statistical analysis of the results was carried out using the statistical software package "OpenEpi 2009, Version 2.3".

THE RESULTS OF THE STUDY

The results of molecular genetic studies are presented in Table 1.

Table 1. Frequency of distribution of allelic variants and polymorphism of the F13A1 gene (G/T) in pregnant women with PR and the control healthy group of pregnant women

№	Group	Frequency of alleles				Frequency of genotype distribution					
		G		T		G/G		G/T		T /T	
		n	%	n	%	n	%	n	%	n	%
1.	**Main group n=52 (104)**	88	84,6	16	15,4	38	73,1	12	23,07*	2	3,8
2	**Control group n=38 (76)**	70	92,1	6	7,8	32	84,2	6	15,7		

n is the number of examined patients; ***** n is the number of alleles studied; * is confidence indicator in relation to the control group (P<0,05)

As can be seen from the table, a comparative analysis of the distribution frequencies of alleles and genotypes of the F13 (G/T) polymorphism of the fibrinase gene among 104 DNA samples in 52 pregnant women with PB, the presence of a functional G allele was 84.6% (88/104) cases, and in the control group this allele was detected in 92.1% (70/76), which it was 1.1 times higher compared to the indicators of the main group (χ^2=2.30; p<0.13; OR=0.47; 95%CI 0.18 – 1.27). Whereas the mutant T allele in the control group was determined in 7.8% of cases (6/76), and in the main group – 15.4% (16/104), respectively, which was 1.9 times more than in the control group (χ^2=2.30; p<0.13; OR=2.12; 95%CI 0.79 – 5.71). General inheritance model (xi-square test, df=2) is presented in the following table (Table 2).

The analysis of the detectability of genotypes of the F13 gene showed that the homozygous variant of functional genotypes G/G in the control group of pregnant women without PB was detected in 84.2% of cases (32/38), and in the main group – 73.1% (38/52), which was 1.2 times lower than the control group (χ^2=2.15; p<0.14; OR=0.51; 95%CI 0.18 – 1.48). Whereas the heterozygous variant of the G/T F2 gene in the control group was determined in 15.7% of cases (6/38). And in the main group of patients with PB, the heterozygous variant of the G/T gene F13 was determined in 23.07% of cases (12/52), respectively, which was 1.5 times higher than the indicators of control individuals (χ^2=2.15; p<0.14; OR=1.60; 95%CI 0.54 – 4.73).

Table 2. Differences in the frequency of occurrence of alleles and genotypes of G/T polymorphism of the F13A1 gene in the group of pregnant women with PB and without

Alleles and genotypes	Frequency of occurrence of alleles and genotypes		Statistical difference
	Main group	***Control group***	
Allele G	88	70	χ^2=2.30; p<0.13; OR=2.12; 95%CI 0.79 – 5.71
Allele T	16	6	
Genotype G/G	38	32	χ^2=2.15; p<0.14; OR=0.51; 95%CI 0.18 – 1.48
Genotype G/T	12	6	χ^2=2.15; p<0.14; OR=1.60; 95%CI 0.54 – 4.73
Genotype T/T	2	-	χ^2=2.15; p<0.14; OR=3.81; 95%CI 0.18 – 81.73

The mutant genotype T/T of the F13 gene in our cases was determined in 3.8% of cases (2/52) in the main group (χ^2=2.15; p<0.14; OR=3.81; 95%CI 0.18 – 81.73). In the control group of patients, this genotype was not determined.

In the studies of Malyshkin A.I., Fetisova I.N., Zholobov Y.N. et al. (2018) found that an increased risk of bleeding in patients with threatening preterm birth compared to women with a physiological course of pregnancy was evidenced by the results of an analysis of the distribution of gene and genotypic frequencies at the F13A1 0103T locus [1, 5, 17]. At the same time, the frequency of occurrence of the mutant allele T of the F13A1 gene in the control group was significantly higher than in patients with threatening PB (38,36% и 25,24%, respectively; p=0,015; OR=0,54 [0,34-0,86]) and in patients with realized PB (38,36% и 23,00%, respectively; p=0,015, OR=0,48 [0,27-0,85]).

It is noteworthy that the heterozygous carriage of the F13A1 T variant in the examined groups was similar, however, the homozygous carriage of the F13A1 T allele in women of the control group was almost 4 times higher than that in patients with threatening PB. The F13A1 gene encodes a fibrin-stabilizing factor protein responsible for the final step in the blood coagulation cascade.

In our cases, unfavorable allele variants were most often detected in women with PB, which was 1.9 times higher than in control women with a physiological course of pregnancy (P <0,05). According to A.D. Makatsaria (2011) with the F13A1 T/T genotype, the ability of the protein to “crosslink” fibrin monomers changes, as a result of which fibrin clots become thinner and more unstable, which increases the risk of bleeding [7, 19]. It should be noted that the reliable determinability of carriage of T/T mutant genotypes in the F13A1 gene in pregnant women with the threat of preterm birth allows us to regard this fact as a genetic component of an increased risk of placental circulation disorders, bleeding and early termination of pregnancy.

The data obtained on the frequency of occurrence of genotypic variants may indicate that the polymorphism of the F13A1 gene is of pathogenetic significance in the mechanism of development of preterm labor with a complex sentence.

Considering the fact that both the mutant allele and the mutant genotype carrying one "T" allele were significantly less frequently detected in patients with PB against the background of complex suggestions that the T/T genotype may also have a protective effect. However, the proof of this hypothesis requires a significant increase in the sample of patients due to

the rare frequency of occurrence of a polymorphic genotype with two mutant alleles.

Thus, the data of our study showed the connection of the "T" allele and the heterozygous genotype of the polymorphism of the F13A1 gene with the development of premature birth in women of the Uzbek population. At the same time, the risk of pathology formation with the carrier of the "T" allele and the G/T genotype increases by 2.1 (OR=2.12) and 1.5 (OR=3.8) times, respectively. The presence of wild allele and genotype of polymorphism of the F13A1 gene in patients plays a protective role in relation to the formation of premature birth. The obtained result also indicates that the variant allele and heterozygous genotype of the polymorphism of the F13A1 gene predicts the risk of premature birth on a complex sentence.

To assess the frequency of occurrence of various genotypes of the polymorphic gene F13 and the potential influence of a number of dynamic factors determining the genetic structure of the population, as well as to assess the population risk of the development of PB, we analyzed the expected and observed frequency of the genotypes of the polymorphism under study and the correspondence of the frequency distribution to the Hardy-Weinberg equilibrium.

Table 3. The expected and observed frequency of distribution of genotypes by Hardy-Weinberg equilibrium of polymorphism F13A1 in the main group of pregnant preterm births

Genotypes	Frequency of genotypes		χ^2	P
	Observed	Expected		
G/G	73,08	58,26	0.716	**0,48**
G/T	23,08	36,14	0.260	
T/T	3,85	5,6	0.024	
Total	**100,00**	**100,00**	**0.50**	

Calculated by the Hardy-Weinberg equation, in the main group, the frequency of observed favorable genotypes G/G was 1.3 times higher than the expected frequencies – 73.08% and 58.3%, respectively. The heterozygous G/T variant of the observed frequency of the F13A1 gene was 23.08%, and the theoretically expected frequency was 36.14%, respectively, which indicates an increase in this indicator by 1.6 times (P <0,05). The frequency of the mutant homozygous variant of the T/T gene F13A1 was 3.8%, and the expected one was 5.6%, which was 1.5 times higher than the indicators observed (P<0,05).

Table 3. Expected and observed frequency of genotype distribution according to the Hardy-Weinberg equilibrium of F13A1 polymorphism in the control group of pregnant women without PB

Genotypes	Frequency of genotypes		χ^2	P
	Observed	Expected		
G/G	84,21	60,6	0.848	**1**
G/T	15,7	34,51	0.145	
T/T	0	13,3	0.006	
Total	**100,00**	**100,00**	0	

Analysis of the expected frequencies of genotypes of the F13A1 gene in the control group showed that the observed frequency of genotypes of functional genotypes G/G was 84.2%, then the expected frequency was 60.6%, which was 1.4 times lower than the observed indicators. While the observed frequency of the heterozygous variant of G/T was – 15.7, the expected increased 2.2 times and was - 34.5%. The study showed mutant genotypes of the F13A1 gene in the control group. Therefore, at the observed frequency – 0, the expected frequency was – 13.3, which indicates an increase in the definiteness of the carrier polymorphism of the association of mutant genotypes.

The analysis of the obtained results indicates that the distribution of all F13A1 polymorphism genotypes in the main and control groups corresponds to the Hardy-Weinberg equilibrium, indicating that there is no influence of systematic or random factors that can change the genetic structure of populations. The study of the genetic structure of this marker revealed a relatively high level of expected heterozygosity and homozygous variants of mutant alleles in the main and control groups of pregnant women (36,14% and 34,5%; 5,6% and 13,3% accordingly). In both groups, the indicator D is to the left of 0, that is, it is negative (D<0). The revealed fact indicates higher frequencies of expected heterozygotes and homozygotes, rather than actually calculated frequencies of genotypes.

When analyzing the frequency distribution of alleles and genotypes of this polymorphism in the group of pregnant women with fetal growth restriction syndrome, significant differences were found

compared with the control group. The functionally unfavorable allele of the T gene F13A1 was 1.9 times statistically not significantly predominant in the studied alleles in pregnant women with PB compared with pregnant women without PB (χ^2=2.30; p<0.13; OR=2.12; 95%CI 0.79 – 5.71).

The distribution of genotype frequencies of this polymorphism also revealed significant differences between the pregnant group and the comparison group in the general sample (P<0.05). Associations of "functionally unfavorable" genotypes of G/T (χ2=2.15; p<0.14; OR=1.60; 95% CI 0.54 – 4.73) and T/T (χ2=2.15; p<0.14; OR=3.81; 95%CI 0.18 – 81.73) with the development of preterm labor were revealed.

Analyzing the results of molecular genetic studies, we can say that the T allele and the heterozygous genotypes of the F13A1 polymorphism are one of the markers of an increased risk of thrombophilia in pregnant women with a complex sentence, and the functional G allele and the functionally favorable G/G genotype are functional markers for the development of pathology (χ^2=2.15; p<0.14; OR=3.81; 95%CI 0.18 – 81.73).

The connection with the development of the studied problems of the functionally unfavorable T/T genotype requires additional research.

Thus, the results of our own studies published in the literature and conducted by us indicate that the F13A1 hemostasis gene plays an important role in the development of an increased risk of placental circulatory disorders, the development of bleeding and early termination of pregnancy.

CONCLUSIONS:

1. The analysis of the detectability of the genotypes of the F13A1 gene showed that the homozygous variant of the functional genotypes G/G in the control group of pregnant women without PB was detected in 84.2% of cases (32/38), and in the main group – 73.1% (38/52), which was 1.5times lower than the control group (χ2=2.15; p<0.14; OR=0.51; 95%CI 0.18 – 1.48). Whereas the heterozygous variant of the G/T gene F13 in the control group was determined in 15.7% of cases (6/38). And in the main group of patients with PB, the heterozygous variant of the G/T gene F13A1 was determined in 23.07% of cases (12/52), respectively, which was 1.5 times higher than the indicators of control individuals (χ2=2.15; p<0.14; OR=1.60; 95% CI 0.54 – 4.73).

2. The mutant genotype of the T/T gene F13A1 in our cases was determined in 3.8% of cases (2/52) in the main group. (χ2=2.15; p<0.14; OR=3.81; 95%CI 0.18 – 81.73). In the control group of patients, this genotype was not determined.

3. Based on the Hardy-Weinberg equation, in the main group, the heterozygous variant G/T of the observed frequency of the F13A1 gene was 23.08%, and the theoretically expected frequency was 36.14%, respectively, which indicates an increase in this indicator by 1.6 times (P <0.05). the frequency of the mutant homozygous variant of the T/T gene F13 was 3.8%, and the expected one was 5.6%, which was 1.5 times higher than the indicators observed (P<0,05).

4. Analyzing the results of molecular genetic studies, it can be said that the T allele and heterozygous genotypes of F13A1 polymorphism are one of the markers of increased risk of thrombophilia in pregnant women with PB (χ^2=2.15; p<0.14; OR=3.81; 95%CI 0.18 – 81.73).

REFERENCES:

1. Afanasyeva N.V., Strizhakov A.N. Outcomes of pregnancy and childbirth with fetoplacental insufficiency of varying severity // Journal "Issues of gynecology, obstetrics and perinatology". – 2004. – №3 (2). – P. 7-13.
2. Ahmadzade V.A. Pregnancy and childbirth with antiphospholipid syndrome: course, perinatal outcomes // Medical news. - 2011. – No. 5. – pp. 81-85.
3. Bitsadze V.O., Makatsaria A.D., Khizroeva D.H., Makatsaria N.A., Yashenina E.V. Thrombophilia as the most important link in the pathogenesis of pregnancy complications. Practical medicine. 2012; 5 (60): 22-29.
4. Bushtyreva I.O., Kuznetsova N.B., Kovaleva A.V., Barinova B.B., Sundeeva A.G. Prevalence of thrombophilic polymorphisms in women with a history of habitual miscarriage. Obstetrics, gynecology and reproduction. 2015; 9 (2): 13-8.
5. Carbone J.F., Rampersad R. Prenatal screening for thrombophilias: indications and controversies. Clin Lab Med. 2010; 30 (3): 747-60. https://doi.org/10.1016/j.cll.2010.05.003
6. Gargano J.W., Holzman C.B., Senagore P.K., Reuss M.L., Pathak D.R., Friderici K.H., Jernigan K., Fisher R. Polymorphisms in thrombophilia and renin-angiotensin system pathways, preterm delivery, and evidence of placental hemorrhage. Am J Obstet Gynecol. 2009; 201 (3): 317. e1-9. https://doi.org/10.1016/j.ajog.2009.05.060.
7. Khruslov M.V., Boeva M.I., Zhabin S.N., Ukhanova I.Yu., Avagova S.A. The frequency of occurrence of thrombophilic polymorphisms in women with fetal loss syndrome living in the Kursk region. Thrombosis, hemostasis and rheology. 2014; 3: 35-8.
8. Kosar A., Kasapoglu B., Kalyoncu S., Turan H., Balcik O.S., Gumus E.I. Treatment of adverse perinatal outcome in inherited thrombophilias: a clinical study. Blood Coagul Fibrinolysis. 2011; 22

(1): 14-8. https://doi.org/10.1097/MBC.0b013e32834013f2.
9. Kramer M.S., Kahn S.R., Rozen R., Evans R., Platt R.W., Chen M.F. et al. Vasculopathic and thrombophilic risk factors for spontaneous preterm birth. Int J Epidemiol. 2009; 38 (3): 715-23. https://doi.org/10.1093/ije/dyp167.
10. Maltseva L.I., Pavlova T.V. Genetic risk factors for the development of gestosis in primiparous women. Practical medicine. 2011; 5: 111-3.
11. Mavlyanova N.N. Molecular genetic and autoimmune mechanisms of fetal growth restriction syndrome development // Doc. Dissertation for the DSc. – 2022 – 206 p.
12. Medyannikova I.V., Gudinov Zh.V. Prevalence of genetic polymorphisms associated with thrombohemorrhagic and vascular complications of the gestational period in a cohort of pregnant women of the Russian population. Obstetrics and gynecology. 2012; 4 (1): 10-5.
13. Obstetrics: National Guidelines [Edited by E.K. Aylamazyan, V.I. Kulakov, B.E. Radzinsky, G.M. Savelyeva]. Moscow: GEOTAR-Media. 2013: P. 1200.
14. Shifman E.M., Barinov S.V., Dolgikh V.T., Medyannikova I.V., Blauman S.I. Prevention of obstetric complications associated with polymorphism of thrombophilia genes. Hematology and transfusiology. 2015; 1: 24-8.
15. Thrombohemorrhagic complications in obstetric and gynecological practice: a guide for doctors [Edited by A.D. Makatsaria]. Moscow: MIA. 2011: 1056 p.
16. Tretyakova T.B., Bashmakova N.V., Demchenko N.S. Genetic predictors of obstetric complications: intergenic associations. Russian Bulletin of the obstetrician-gynecologist. 2012; 12 (6): 18-20.
17. Uvuz F., Kilic S., Yilmaz N., Tuncay G., Cakar E., Yuksel B., Bilge U. Relationship between preterm labor and thrombophilic gene polymorphism: A prospective sequential cohort study. Gynecol Obstet Invest. 2009; 68 (4): 234-8. https://doi.org/10.1159/000237743.
18. Volkova A.S., Kruglova E.A., Kuzmin A.A., Sokolova T.M., Kuzmina V.V. Thrombophilia in clinical practice of an obstetrician-gynecologist. Medicine and education in Siberia. 2014; 3:79.
19. Vorozhishcheva A.Y. Genetic factors of preeclampsia development in populations of different ethnic origin: Abstract. diss. candidate of medical sciences. Tomsk. 2014: 23 p.

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