

Genetic variants associated with D-dimer levels in children born to mothers with recurrent pregnancy loss

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Abstract

Introduction. Theoretically, factors predisposing to miscarriage may influence fetal development during a normal pregnancy, in particular, affect the development of the hemostasis system of the unborn child. However, the factors of hereditary predisposition to thrombophilia in children born to mothers with recurrent miscarriage have not been sufficiently studied.

Objective. To identify the association of a number of hemostasis parameters (the D-dimer level and the level of INR) with the genotypes of genetic variants F5 c.1691G>A, ITGA2 c.807C>T and ITGB3 c.1565 T>C of the hemostasis system genes in pediatric patients born to mothers with recurrent miscarriage.

Methods. We conducted a controlled observational study including 352 children born to mothers with a history of miscarriage, and 261 healthy children. D-dimer and INR were measured monthly for 12 months and averaged. Log-transformed D-dimer was analyzed using multivariable linear regression with interaction terms.

Results. A strong association between F5 genotype and D-dimer levels was observed (both in the group, $p < 0.05$). In the group of children born to mothers with miscarriage, D-dimer levels differed significantly across ITGA2 c.807C>T genotypes ($p = 0.0039$); a genotype-dependent gradient (CC < CT < TT) of D-dimer levels was also identified. In multivariable regression showed the following results: F5 c.1691G>A remained highly significant ($p < 0.001$), ITGA2 c.807C>T remained significant ($p < 0.001$). Group status (Children vs Control) showed the strongest effect ($p < 0.001$). **Conclusion.** Genetic variants in F5 and ITGA2 are independently associated with increased D-dimer levels, with a stronger effect observed in a high-risk pediatric cohort of children born to mothers with recurrent miscarriage.

Introduction

In modern medicine, one of the problems in obstetrics and gynecology is the problem of habitual miscarriage [1]. According to literature, up to 15-25% of pregnancies in women end in spontaneous abortion [2, 3]. One of the factors of such catastrophic events during gestation is the development of thrombophilic conditions [2, 4]. According to modern research, thrombophilia during gestation is associated with a complicated obstetric and gynecological history: recurrent pregnancy loss, spontaneous abortions, disturbances of uteroplacental blood flow and other pathological changes [5, 6]. Theoretically, factors predisposing to habitual miscarriage may influence fetal development during a normal pregnancy, in particular, affect the development of the hemostasis system of the unborn child [5]. However, the factors of hereditary predisposition to thrombophilia in children born to mothers with recurrent miscarriage have not been sufficiently studied. There are only a few studies devoted to the genetics of thrombophilia in children [7]. There are studies that show the role of hereditary predisposition to thrombosis in children with various oncological pathologies [8,9]. They show an association with venous thrombosis in children of genetic variants F2 c.20210G>A, F5 c.1691G>A and the variant MTHFR c.C677T [8]. One study showed that, overall, genetic and acquired factors of venous thrombosis in children are detected in 96.4% of case [10]. According to other authors, genetic predisposition to

thrombophilia in children with venous thrombosis is detected in 7% of cases [11]. A 2008 review showed that the F2 c.20210G>A variant of the prothrombin gene and antithrombin deficiency show the greatest association with thrombosis in children [12]. One study showed that recurrent VTE in children is associated with the Leiden mutation (variant F5 c.1691G>A) [13].

Thus, studies investigating hereditary predisposition to thrombophilia in children are mainly related to the assessment of the combined influence of genetic factors with certain diseases in childhood that can lead to secondary hemostasis disorders, in particular, oncological and cardiovascular diseases [14-18]. However, the influence of hemostatic factors of miscarriage on the development of thrombosis in childhood and their connection with hereditary predisposition to thrombophilia has not been sufficiently studied. There are studies that examine factors predisposing to thrombosis that occur in both the mother and the child [19]. Potentially, risk factors for thrombophilia in the mother, which can lead to miscarriage, may increase the risk of thrombosis in their children.

The purpose of the work is to identify the association of a number of hemostasis parameters (the average D-dimer level and the average level of the international normalized ratio of thromboplastin time (INR)) with the genotypes of genetic variants F5 c.1691G>A (rs6025, 1q24.2), ITGA2 c.807C>T (rs1126643, 5q23-31) and ITGB3 c.1565 T>C (rs5918, 17q21.32) of the hemostasis system genes in pediatric patients born to mothers with recurrent miscarriage.

Materials and Methods

The group of pediatric patients with a history of venous thrombosis episodes included 352 patients selected according to the following criteria for all patients: 1) the patients' age ranged from 7 to 14 years (mean age 9.4 years), 2) the gender distribution was 157 boys and 195 girls, 3) history of episodes of venous thrombosis of various localizations, 4) the mothers of the pediatric patients studied had episodes of miscarriage.

The exclusion criteria were the absence of a history of miscarriage in the mother of a child with episodes of venous thrombosis, the child was from the first pregnancy (since, in this case, it is impossible to clearly trace the features of this anamnesis). Also excluded were patients with rare cases of monogenic hereditary diseases associated with hemostasis disorders and children born in case of prematurity, children with congenital heart and vascular defects and with manifestations of perinatal CNS damage of ischemic genesis as risk factors for the development of secondary venous thrombosis.

The control group included 261 healthy children, selected according to the following criteria: 1) age from 7 to 14 years (average age 9.7 years), 2) no history of venous thrombosis episodes, 3) The children were born to mothers with no history of miscarriage.

All patients and individuals in the control group were selected at Regional Consultative and Diagnostic Center, Rostov-on-Don, Russia, from March 2021 to January 2026. Ethnically, all patients belonged to the southern Russian population. D-dimer and INR levels were measured every month for all patients and

comparison group members during the year. Genotyping of genetic variants F5 c.1691G>A, ITGA2 c.807C>T and ITGB3 c.1565 T>C was also performed.

Ethical approval: the study was approved by the Local Ethics Committee of Rostov State Medical University, all legal representatives of pediatric patients gave informed consent to the study in accordance with the Declaration of Helsinki. All legal representatives of the pediatric patients signed voluntary informed consent for the study.

Molecular genetic analysis. DNA was extracted from blood using the Proba-Rapid-Genetics reagent kit (DNA Technology, Russia). Research of genetic variants (F5 c.1691G>A, ITGA2 c.807C>T and ITGB3 c.1565 T>C) was performed using real-time PCR with melting curve analysis using the Cardiogenetics Thrombophilia kit (DNA Technology, Russia) on a 4-channel DTprime (DNA Technology, Russia) detection amplifier. Registration and accounting of PCR results genotyping) were performed automatically by the amplifier software. In questionable cases, the genotype was confirmed by Sanger sequencing using an automatic nucleic acid analyzer ABI PRISM 3500 (Applied Biosystems, USA).

Coagulographic analysis. D-dimer and INR levels were measured using an automatic coagulometer Sysmex CA-600 (Sysmex, Japan). Measurements were taken on a monthly basis throughout the year, and the average value of these parameters was calculated.

Statistical analysis. Data are presented as median and interquartile range (Me [IQR]). For intragroup analysis, the nonparametric Kpaskell Willis method was used. Mann–Whitney test with Benjamini–Hochberg correction was used for intergroup comparisons. For multivariate analysis, we used analysis of variance (ANOVA). The program Statistics 10.0 was used for calculations.

Results

Genetic variant F5 c.1691G>A.

For the genetic variant F5 c.1691G>A, the analysis was carried out in a dominant model (GA+AA vs GG). In group of children born to mothers with recurrent miscarriage the GA+AA genotype is associated with the highest D-dimer levels (Table 1). This difference was statistically significant ($p<0.001$). In the group of patients with genotypes GA+AA, the percentage of children with D-dimer levels above reference values >550 ng/ml was approximately twice as high as with genotype (82.8% versus 48.3%) (Table 1). In the control group, higher levels of D-dimer were also observed in individuals with genotypes GA+AA, but the percentage of children with D-dimer levels above reference values was lower (Table I).

Table I.

D-dimer levels depending on the genotype of the genetic variant F5 c.1691G>A in control group and group of children born to mothers with recurrent miscarriage (RM).

Group	Genotype	n	Median [IQR] of D-dimer, ng/mL	Min-max	D-dimer>550	p (Kruskal-Wallis)
Children born to mothers with RM	F5 c.1691G>A GA	323	534 [417.5–664]	122–1011	48.3%	<0.001
	F5 c.1691G>A GA+AA	29	679 [577–844]	344–1055	82.8%	
Contol	F5 c.1691G>A GG	181	375 [248–457]	122–1011	15.5%	<0.05
	F5 c.1691G>A GA+AA	80	437 [342–563]	134–911	26.3%	

No significant relationship between INR and F5 c.1691G>A genotype was found ($p>0.05$). There was no between-group interaction.

Genetic variant ITGA2 c.807C>T

The **ITGA2** genetic variant **c.807C>T** was analyzed according to a three-genotype model (CC, CT, TT) (Table II).

Table II.

D-dimer levels depending on the genotype of the genetic variant ITGA2 c.807C>T in control group and group of children born to mothers with RM.

Group	Genotype	n	Median [IQR] of D-dimer, ng/mL	Min-max	D-dimer>550	p (Kruskal-Wallis)
Children born to mothers with RM	ITGA2 c.807C>T CC	156	475 [377.75–577]	123–1055	42.9%	<0.01
	ITGA2 c.807C>T CT	128	566 [433.75–681.25]	122–1011	54.7%	
	ITGA2 c.807C>T TT	68	577 [474–738.75]	248–1011	63.2%	
Contol	ITGA2 c.807C>T CC	120	377.5 [248–473]	122–911	17.5%	=0.681
	ITGA2 c.807C>T CT	95	377 [235.5–476]	122–911	20.0%	
	ITGA2 c.807C>T TT	46	434 [341.25–476.5]	122–1011	19.6%	

Table II shows that a clear dose-dependent gradient was identified: CC < CT < TT. Differences between genotype groups are statistically highly significant ($p < 0.001$). The TT genotype is associated with the highest D-dimer values and the highest proportion of patients with levels >550 ng/mL (63.2 %). In the control group, no statistical differences in the D-dimer level were found in children with different genotypes of this genetic variant ($p > 0.05$) (Table II).

No significant association between INR and ITGA2 c.807C>T genotype was observed in either group ($p > 0.05$). No interaction effect was detected. The F2 genotype is not associated with INR.

Genetic variant ITGB3 c.1565T>C

The **ITGB3** genetic variant **c.1565T>C** was analyzed according to a three-genotype model (TT, TC, CC) (Table III). This genetic variant did not show statistically significant differences in D-dimer levels either among children born to mothers with miscarriage or in the control group ($p > 0.05$).

Table III.

D-dimer levels depending on the genotype of the genetic variant **ITGB3 c.1565T>C** in control group and group of children born to mothers with RM.

Group	Genotype	n	Median [IQR] of D-dimer, ng/mL	Min–max	D-dimer>550	p (Kruskal-Wallis)
Children born to mothers with RM	ITGB3 c.1565T>C TT	213	566 [433–677]	122–1055	51.6%	=0.349
	ITGB3 c.1565T>C TC	116	521.5 [433.75–657.25]	122–1011	49.1%	
	ITGB3 c.1565T>C CC	23	566 [455.5–777.5]	344–977	56.5%	
Contol	ITGB3 c.1565T>C TT	164	377 [236.25–473]	122–1011	164	=0.188
	ITGB3 c.1565T>C TC	72	383 [309–477]	122–911	72	
	ITGB3 c.1565T>C CC	25	444 [346–566]	123–788	25	

No significant association between INR and ITGB3 c.1565T>C genotype was observed in either group ($p > 0.05$). No interaction effect was detected. The F2 genotype is not associated with INR.

Multivariate model.

We also applied a multivariate model to assess the influence of several genotypes on the hemostatic parameters we examined. D-dimer (ln-transformed) was used as the primary endpoint, as a secondary – INR. The following reference categories are included in the multifactor model: group of children born to mothers with RM: D-dimer, F5 genotype c.1691G>A: GA, ITGA2 genotypes c.807C>T: CT and TT and their interaction, ITGB3 genotypes c.1565T>C: TC+CC; control: F5 c.1691G>A: GG, ITGA2 c.807C>T: CC, ITGB3 c.1565T>C: TT. The main effects (excluding interactions) are shown in Table IV.

Table IV.

Multivariable linear regression (log D-dimer).

Variable	β	p-value
Group (Children)	↑	<0.001
F5 (GA+AA)	↑	<0.001
ITGA2	↑	0.0105
ITGB3	—	0.0919

In multivariable linear regression, both F5 c.1691G>A and ITGA2 c.807C>T remained independently associated with log-transformed D-dimer levels, where as ITGB3 c.1565T>C did not retain statistical significance. Group status (Children vs Control) was the strongest determinant of D-dimer levels (p <0.001).

Binary model for clinical threshold

We also constructed a binary model for the clinical threshold using logistic regression. D-dimer levels above the upper reference value (>550 ng/ml) were chosen as the main parameter for the clinical significance of thrombosis development in children. The second parameter chosen was: belonging to a group of children born to mothers with miscarriage, genetic variants F5 c.1691G>A, ITGA2 c.807C>T, ITGB3 c.1565T>C. Using a clinically relevant threshold of D-dimer>550 ng/mL, logistic regression demonstrated that (Table V):

- belonging to the children group, born to mothers with RM, increased the risk by more than six fold (OR = 6.25),
- carriage of the A allele in F5 increased risk approximately 2.7-fold,
- the TT genotype of ITGA2 showed a moderate effect,
- ITGB3 was not associated with elevated D-dimer.

Table V.

Logistic regression (D-dimer>550 ng/mL).

Variable	OR	Interpretation
Children vs Control	6.25	Strong effect
F5 (GA+AA)	2.68	Independent risk
ITGA2 TT	~1.88	Moderate effect
ITGB3	ns	No effect

Discussion

The present study demonstrates that genetic variability in coagulation-related pathways contributes to inter-individual differences in D-dimer levels, particularly in a high-risk pediatric cohort (children born to mothers with miscarriages).

The most robust and consistent finding was observed for F5 c.1691G>A, which showed a significant association with both continuous and dichotomized D-dimer levels across groups. This is biologically plausible, as Factor V Leiden is a well-established prothrombotic variant leading to resistance to activated protein C and increased thrombin generation [20-23]. This genetic variant is one of the key factors in hereditary thrombophilia [24]. As mentioned above, the relationship between this genetic variant and thrombosis in childhood has been clearly demonstrated in children with certain pathologies that may increase the risk of secondary coagulation disorders. In particular, these may be childhood oncological diseases that affect the hemostasis system [25]. Our study shows that this genetic variant may increase the risk of thrombotic readiness in children born to mothers with miscarriage. It is known that pregnant women with habitual miscarriage, even in the case of a normal pregnancy, have an increased risk of disturbances in fetoplacental blood flow [26-28]. The development of antiphospholipid syndrome in the pregnant mother can also affect the state of the hemostasis system of the unborn child [29]. It has been shown that mothers with recurrent miscarriages may be more likely to have the Leiden mutation, which increases the likelihood of its transmission (in a heterozygous or homozygous state) to the unborn child [30]. Thus, belonging to a group of children born to mothers with miscarriage and a genetic variant F5 c.1691G>A may jointly potentiate the development of thrombotic readiness.

The effect of ITGA2 c.807C>T appeared to be context-dependent, being significant only in the group of children born to mothers with RM. This may reflect gene–environment interaction mechanisms, where platelet adhesion pathways become more relevant under prothrombotic or inflammatory conditions. It is known that platelet receptors belonging to the integrin group can influence their adhesive properties [31, 32]. Inactivation of integrin genes may even lead to a decrease in platelet volume and a reduction in their ability to adhere [33]. We have shown that the genotype of the genetic variant manifests itself only in the group of children born to mothers with a history of miscarriage, but not in the control group. In the

literature, the association of this genetic variant is shown only in children with ischemic stroke [34]. It can be assumed that in women with miscarriage, even in cases of normal pregnancy, platelet reactivity changes, which can affect the platelet reactivity of the unborn child, and risky genotypes of the genetic variant potentiate platelet reactivity in childhood towards increased thrombotic readiness [35].

In contrast, ITGB3 c.1565T>C did not demonstrate a stable or independent association, suggesting a limited role in modulating fibrin turn over in this setting.

Importantly, the absence of statistically significant interaction terms in regression models indicates that genetic effects are largely additive rather than strongly modified by group status. However, the magnitude of effect appears amplified in the group, suggesting underlying biological susceptibility.

Why did INR not show any association with the genotypes of the genetic variants studied? INR reflects the activity of the extrinsic coagulation pathway and primarily the level of factors VII and prothrombin under standard conditions [36, 37]. In the case of INR, this parameter provides a poor reflection of thrombotic capacity because it assesses only the initial thrombin generation [37]. D-dimer reflects the actual intravascular generation and degradation of fibrin [38, 39]. Therefore, D-dimer assessment can be used as a screening assessment of thrombotic readiness.

A limitation of this study is the narrow ethnicity of the sample, as all children born to mothers with miscarriages were selected from the Rostov Region and belong to the Russian cohort. To establish a more precise relationship between genetic variants of hemostasis genes and laboratory coagulation parameters, studies in other ethnic cohorts, including a comprehensive meta-analysis, are needed.

In conclusion, it is worth noting that genetic testing of variants that have shown an association with thrombotic readiness in children born to mothers with miscarriage cannot be used for screening. In our work, the association of the Leiden mutation and the gene variant ITGA2 c.807C>T is shown only for a certain group of children, many of whom have a burdened history of miscarriage. Therefore, genetic testing of these variants can only be used as an assessment of thrombotic readiness in this cohort in conjunction with D-dimer assessment.

Declarations

Author Contribution

O.P.: article topic idea, molecular genetic analysis, writing the text. I.M.: statistical data processing, literature review. D.B.: text editing, general guidance. All authors reviewed the manuscript

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