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Coagulation Gene Polymorphisms in Patients with Pediatric-Onset Non-Cirrhotic Portal Vein Thrombosis

Maria Yu. Nadinskaia*, Kseniya A. Gulyaeva, Evelina Trashkun, Diana Daduns, Maxim A. Privalov, Vladimir T. Ivashkin

I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russian Federation

Aim: to investigate the frequency of gene polymorphisms related to coagulation, the folate cycle, platelet receptors, serine protease inhibitor clade E member 1 (*SERPINE1*), selectin P ligand (*SELPLG*), and Janus kinase 2 (*JAK2*) in patients with pediatric-onset portal vein thrombosis (*PVT*).

Materials and methods. A cross-sectional study was conducted, including patients with pediatric-onset non-cirrhotic PVT (n = 31), all of European ancestry. Polymerase chain reaction was used to genotype the following polymorphisms: *F2* (rs1799963), *F5* (rs6025), *FGB* (fibrinogen beta chain) (rs1800790), *ITGA2* (integrin subunit alpha 2) (rs1126643), *ITGB3* (integrin subunit beta 3) (rs5918), *MTHFR* (methylenetetrahydrofolate reductase) (rs1801133), *SERPINE1* (rs1799889), *SELPLG* (rs2228315), and *JAK2* (rs77375493). A history of local risk factors for PVT in the early neonatal period was noted in 12 (39 %) patients, including omphalitis, umbilical sepsis, and umbilical vein catheterization.

Results. Mutations in the *F2* (rs1799963) and *F5* (rs6025) genes were identified in two patients. The A allele of the *FGB* gene (rs1800790) was found with a frequency of 21 %, the T allele of the *ITGA2* gene (rs1126643) with a frequency of 37.1 %, and the T allele of the *MTHFR* gene (rs1801133) with a frequency of 32.3 %. The 4G polymorphism in the *SERPINE1* gene (rs1799889) was the most frequent: it was found in the homozygous form in 18 (58 %) patients and in the heterozygous form in 9 (29 %) patients; the frequency of the 4G allele was 72.6 %. The somatic *JAK2* mutation (rs77375493) was not detected in any of the patients. The presence of either a mutation in the *F2* or *F5* genes, or homozygous variants for the other studied polymorphisms, was identified in 24 (77 %) patients. A single genetic risk factor was present in 15 (48 %) patients, two factors — in 6 (19 %) patients, and three factors — in 3 (10 %) patients. No significant differences in the frequency of individual polymorphisms were found between patients with and without local risk factors. However, the combination of the A allele of the *FGB* gene and the C allele of the *ITGB3* gene was observed significantly more frequently in patients with local risk factors compared to those without (33 % vs. 5 %; p = 0.039).

Conclusion. In a small Russian cohort of patients with pediatric-onset PVT, well-known thrombophilic mutations in the *F2* and *F5* genes were identified. Also, polymorphisms in *SERPINE1*, *MTHFR, FGB*, *ITGA2*, *ITGB3*, and *SELPLG* genes were identified, which potentially contribute to an increased risk of thrombosis.

Keywords: *F2* (rs1799963), *F5* (rs6025), *FGB* (rs1800790), *ITGA2* (rs1126643), *ITGB3* (rs5918), *MTHFR* (rs1801133), *SERPINE1* (rs1799889), *SELPLG* (rs2228315) и *JAK2* (rs77375493)

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Полиморфизмы генов свертывания у пациентов с детским дебютом нецирротического тромбоза воротной вены

М.Ю. Надинская*, К.А. Гуляева, Э. Трашкун, Д. Дадунц, М.А. Привалов, В.Т. Ивашкин

ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет), Москва, Российская Федерация

Цель: изучить частоту полиморфизмов генов коагуляции, фолатного цикла, рецепторов тромбоцитов, ингибитора сериновой протеазы класса E, член 1 (*SERPINE1*, serine protease inhibitor clade E member 1), лиганда P-селектина (*SELPLG*, selectin P ligand) и янус-киназы 2 (*JAK2*, Janus kinase 2) у пациентов с детским дебютом тромбоза воротной вены (ТВВ).

Материалы и методы. Проведено поперечное исследование, в которое включен 31 пациент с детским дебютом нецирротического ТВВ. Все участники исследования были европейского происхождения. Методом полимеразной цепной реакции изучены полиморфизмы генов: *F2* (rs1799963), *F5* (rs6025), *FGB* (fibrinogen beta chain, бета-цепь фибриногена) (rs1800790), *ITGA2* (integrin subunit alpha 2, интегрин альфа-2) (rs1126643), *ITGB3* (integrin subunit beta 3, интегрин бета-3) (rs5918), *MTHFR* (methylenetetrahydrofolate reductase, метилентетрагидрофолатредуктаза) (rs1801133), *SERPINE1* (rs1799889), *SELPLG* (rs2228315) и *JAK2* (rs77375493). У 12 (39 %) пациентов в анамнезе отмечались локальные факторы риска ТВВ в раннем неонатальном периоде: омфалит, пупочный сепсис, катетеризация пупочной вены.
Результаты. Мутация в генах *F2* (rs1799963) и *F5* (rs6025) выявлена у двух пациентов. Аллель А гена *FGB* (rs1800790) встречался с частотой 21 %, аллель Т в гене *ITGA2* (rs1126643) — с частотой 37,1 %, аллель Т в гене *MTHFR* (rs1801133) — 32,3 %. Полиморфизм 4G в гене *SERPINE1* (rs1799889) оказался самым частым: у 18 (58 %) выявлен в гомозиготной форме, у 9 (29 %) — в гетерозиготной форме; частота встречаемости аллеля 4G составила 72,6 %. Соматическая мутация *JAK2* (rs77375493) не выявлена ни у одного из пациентов. Наличие мутации в генах *F2* и *F5* либо гомозиготные варианты полиморфизмов в других изученных генах выявлены у 24 (77 %) пациентов. У 15 (48 %) пациентов имелся один генетический фактор риска, у 6 (19 %) — два и у 3 (10 %) — три. Между пациентами с наличием и отсутствием локальных факторов различий по частоте отдельных полиморфизмов не установлено. Вместе с этим сочетание аллеля А гена *FGB* и аллеля С гена *ITGB3* отмечалось статистически значимо чаще у пациентов при наличии локальных факторов по сравнению с их отсутствием (33 % vs. 5 %; $p = 0,039$).
Выводы. На небольшой выборке российской популяции пациентов с дебютом ТВВ в детском возрасте показано наличие как известных тромбофилических мутаций в генах *F2* и *F5*, так и полиморфизмы генов *SERPINE1, MTHFR, FGB, ITGA2, ITGB3* и *SELPLG*, потенциально повышающих риск тромбоза.
Ключевые слова: *F2* (rs1799963), *F5* (rs6025), *FGB* (rs1800790), *ITGA2* (rs1126643), *ITGB3* (rs5918), *MTHFR* (rs1801133), *SERPINE1* (rs1799889), *SELPLG* (rs2228315) и *JAK2* (rs77375493)
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Introduction

Portal vein thrombosis (PVT) is a rare vascular liver disorder characterized by the occlusion of the main portal vein and/or its branches [1]. A network of tortuous collateral veins may develop around the thrombosed segment in response to obstruction. These veins are known as cavernous transformations of the portal vein [2].

The incidence of PVT in children is unclear. Estimates range from 3.6 to 8.4 per 1000 neonates in intensive care [3, 4], to approximately 1.1 per 100,000 live births [5]. The incidence in the general population is even lower, at 0.72 per 1,000,000 [6], which classifies pediatric PVT as an orphan disease.

Although thrombotic events usually occur in the neonatal period, clinical manifestations typically appear several years later. These manifestations are most often signs of portal hypertension [6–9]. PVT is thought to account for 9–76 % of all cases of portal hypertension in children [10].

Like any venous thrombosis, the pathogenesis of PVT is based on Virchow's triad, encompassing stasis of blood flow, venous injury due to local factors, and an imbalance in the coagulation system. The most common risk factors for PVT in adults are liver cirrhosis, Ph-negative myeloproliferative neoplasms, and local factors [11, 12]. In children, risk factors vary by age group. Among neonates, approximately half of cases are associated with local factors, such as umbilical vein catheterization [13–15], omphalitis, and umbilical sepsis [16]. In older children, PVT may be linked to myeloproliferative neoplasms [17].

In approximately half of all pediatric PVT cases, no identifiable risk factor is found [6, 18]. Only a few studies have suggested an association between cavernous transformations of the portal vein and thrombophilic states, such as antiphospholipid syndrome and deficiencies in proteins C and S [6].

There is strong evidence in adult populations supporting the association between PVT and the most common causes of heritable thrombophilia. These include the factor V Leiden mutation (*F5*, rs6025), the prothrombin G20210A mutation (*F2*, rs1799963) and the C677T polymorphism in the methylenetetrahydrofolate reductase (*MTHFR*) gene (rs1801133) [19]. Several small cohort studies have examined these variants in children with PVT, with highly variable results depending on the geographical region: European studies reported a significant association [5, 20], whereas those from India and Turkey did not [21, 22].

Only a limited number of studies have examined the polymorphism in the promoter region of the serine protease inhibitor clade E member 1 (*SERPINE1*) gene (rs1799889), which encodes plasminogen activator inhibitor-1 (PAI-1), in pediatric PVT, with conflicting findings reported [22, 23].

A literature search revealed no studies investigating polymorphisms in several other hemostasis-related genes in pediatric PVT, including the fibrinogen beta chain (*FGB*), the integrin subunit alpha 2 (*ITGA2*) — the alpha subunit of the platelet collagen receptor, the integrin subunit beta 3 (*ITGB3*) — the beta subunit of the platelet fibrinogen receptor, and the selectin P ligand (*SELPLG*), which encodes P-selectin glycoprotein ligand-1 (PSGL-1) — the primary ligand for the P-selectin receptor. However, the potential contribution of these polymorphisms to thrombotic risk has been discussed in studies of venous thromboembolism in adults.

The aim of the study was to assess the frequency of polymorphisms in the genes of coagulation, folate cycle, platelet receptors, the fibrinolysis system (*SERPINE1*), as well as the *SELPLG* and *JAK2* (Janus kinase 2) genes, in patients with pediatric-onset PVT.

Materials and methods

A cross-sectional study was conducted [24]. The study protocol was approved by the Local Ethics Committee of Sechenov University (protocol No. 05–13, May 15, 2013). Patients were enrolled through consecutive sampling from among all individuals undergoing examination and treatment at the V.Kh. Vasilenko Clinic of Propaedeutics of Internal Medicine, Gastroenterology and Hepatology at the University Clinical Hospital No. 2 (Sechenov University), between June 1, 2013, and January 31, 2025.

The study included patients with a confirmed diagnosis of prehepatic portal hypertension due to PVT.

Inclusion criteria:

- age ≥ 18 years at the time of enrollment;
- European ancestry;
- onset of PVT-induced prehepatic portal hypertension before 18 years of age;
- radiological confirmation of PVT (thrombosis of the main trunk or branches of the portal vein, or cavernous transformations of the portal vein) by Doppler ultrasonography and/or contrast-enhanced multispiral computed tomography of the portal system at the time of the study;
- provision of written informed consent for participation.

Non-inclusion criteria:

- histologically confirmed liver cirrhosis;
- iver stiffness ≥ 10 kPa on elastography;
- history of liver transplantation or hematopoietic stem cell transplantation.

Liver elastography was performed using a FibroScan® device (Echosens, France), in line with guidelines from the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB). Examinations were conducted after a fast of at least 6 hours and following an abdominal ultrasound. Patients were positioned supine with their right arm abducted behind their head and their torso slightly rotated to the left. The transducer probe was placed between the sixth and eighth intercostal spaces along the right midclavicular line to target the right hepatic lobe, avoiding large vascular structures. The focal zone of the probe was set at a depth of 25–65 mm from the skin surface. Ten valid measurements were obtained in total, and the device software automatically calculated the median liver stiffness value, expressed in kilopascals (kPa). The device's measurement range was 0–75 kPa. An interquartile range to median ratio of ≤ 25 % was considered acceptable for ensuring reliable data [25].

A total of 38 patients were assessed for eligibility. Two patients were excluded due to elevated liver stiffness values (14.2 and 17.8 kPa) and five declined to participate. Consequently, 31 patients (13 men and 18 women) with a median age of 27 years (interquartile range: 24–30 years) were enrolled in the study.

All participants provided written informed consent for the use of their pseudonymized medical data, including health status, examination results, treatment records and other clinical information, for research purposes. This consent explicitly covered the creation of electronic databases containing anonymized medical data, as well as the publication of research findings derived from these data.

Analysis of gene polymorphisms

Gene polymorphisms were analyzed using real-time polymerase chain reaction (PCR) with fluorescent detection in EDTA-anticoagulated venous blood samples. All laboratory analyses were performed at the LITECH laboratory (Russia). Genomic DNA was extracted from the leukocyte fraction using a commercial kit (DNA-Express-Blood, NPO LITECH, Russia), following the manufacturer's instructions. The concentration and purity of the DNA were evaluated spectrophotometrically, with an A260/A280 ratio of 1.7–2.0 being considered acceptable.

Genotyping for point substitutions and insertion-deletion variants was performed using "SNP-express-RV" reagent kits (NPO LITECH, Russia). These kits employ an allele-specific detection method, using the intercalating dye SYBR Green I in parallel reactions to distinguish wild-type and minor alleles.

Amplification reactions were conducted on a CFX96 Touch Real-Time PCR System (Bio-Rad, USA), which is a thermal cycler equipped with an optical fluorescence detection module. Each reaction was performed in a total volume of 25 μL containing 5 μL of Master Mix (buffer, $MgCl_2$, dNTPs, and Taq polymerase), 0.25 μM of each primer, and 50–100 ng of template DNA.

The amplification protocol consisted of an initial denaturation step at 95 °C for 5 min, followed by 40 cycles of denaturation at 95 °C for 15 s and combined annealing/extension at 60 °C for 60 s. Threshold cycle values and amplification curve profiles were automatically analyzed by the instrument software. Genotypes were determined based on the presence or absence of amplification in each allele-specific reaction.

Polymorphisms in genes that regulate hemostasis, folate metabolism and platelet adhesion were analyzed, as were the *SELPLG* gene and the somatic V617F mutation in the *JAK2* gene (Table 1).

For each polymorphism, appropriate positive controls (homozygous and heterozygous genotypes) and negative controls were included. For the *JAK2* V617F mutation, a standard calibration curve for quantification of the mutant allele burden was additionally employed. Reaction conditions and interpretation criteria were in line with the manufacturer's specifications. Any sample exhibiting atypical amplification curves or a threshold cycle difference > 0.5 between replicates was subjected to repeat testing. Genotyping results were reported as allele combinations (e.g. *F2* G20210A: GA), indicating the corresponding nucleotide change and amino acid substitution where applicable. For the *JAK2* V617F mutation, results were reported qualitatively as either "detected" or "not detected".

Statistical analysis

Quantitative data are presented as the median and the interquartile range (25th–75th percentiles). The Mann — Whitney U test was used to compare them. Qualitative characteristics are presented as absolute numbers and percentages. Genotype and allele frequencies were compared using either Pearson's chi-square test or Fisher's exact test. Differences were considered statistically significant at $p < 0.05$.

Statistical analysis was performed using IBM SPSS v. 23.0 (SPSS: an IBM company, USA).

Results

Characteristics of the cohort with pediatric-onset portal vein thrombosis

The median age at presentation of portal hypertension due to PVT was 5 (3; 11) years, with a median duration of 19 (14.5; 25) years at the time of the study. At the initial diagnosis of PVT, all patients underwent hematological evaluation to rule out primary hematological disorders. However, the medical documentation of none of the patients contained any records of prior genetic testing for the mutations and polymorphisms analyzed in the present study.

All patients had cavernous transformations of the portal vein confirmed by Doppler ultrasonography and contrast-enhanced multispiral computed tomography. Liver stiffness, as evaluated by elastography, was 6 (5; 8) kPa.

The most common symptoms of prehepatic portal hypertension were bleeding from esophageal varices in 16 (52 %) patients and hypersplenism (splenomegaly with thrombocytopenia and leukopenia) in 15 (48 %) patients.

The majority of patients (n = 22; 71 %) underwent portosystemic shunt surgery (mesocaval or distal splenorenal) during childhood. Nine patients (29 %) underwent splenectomy for cytopenias.

Analysis of local risk factors, based on medical history and available records, revealed a history of

Table 1. Studied gene polymorphisms

Gene	Polymorphism	
	Nucleotide substitution	ID in the dbSNP database
F2 (factor II, prothrombin)	G20210A	rs1799963
F5 (factor V, Leiden mutation)	G1691A	rs6025
FGB	G-455A	rs1800790
ITGA2	C807T	rs1126643
ITGB3	T1565C	rs5918
MTHFR	C677T	rs1801133
SERPINE1	5G(-675)4G	rs1799889
SELPLG	G62A	rs2228315
JAK2	V617F	rs77375493

Note: *FGB — fibrinogen beta chain; ITGA2 — integrin subunit alpha 2; ITGB3 — integrin subunit beta 3; MTHFR — methylenetetrahydrofolate reductase; SELPLG — selectin P ligand; SERPINE1 — serine protease inhibitor clade E member 1; JAK2 — Janus kinase 2.*

omphalitis in the early neonatal period in nine patients (29 %), seven of whom developed umbilical sepsis. Umbilical vein catheterization had been performed in three other patients (10 %).

Genotype and allele frequencies

The genotype frequency distributions were in Hardy — Weinberg equilibrium for all loci except *JAK2* V617F (rs77375493). Calculation of the chi-squared statistics was not possible for this locus due to the absence of the mutation in all study participants.

The genotype and allele frequencies are presented in Table 2.

Two patients were found to have mutations in the *F2* (rs1799963) and *F5* (rs6025) genes. The *FGB* polymorphism (rs1800790) was detected in 9 (29 %) patients in a heterozygous state and in 2 (6 %) patients in a homozygous state. The *ITGA2* platelet receptor gene variant (rs1126643) was found in 15 (48 %) patients in the heterozygous state and in 4 (13 %) patients in the homozygous state. The *ITGB3* polymorphism (rs5918) was present in 8 (26 %) patients in the heterozygous state and in 3 (10 %) patients in the homozygous state. More than half of the patients (n = 18; 58 %) were homozygous for the *SERPINE1* polymorphism (rs1799889), while 9 (29 %) patients were heterozygous carriers. The *MTHFR* variant (rs1801133) was present in 10 (32 %) patients in the heterozygous state and in 5 (16 %) patients in the homozygous state. The *SELPLG* polymorphism (rs2228315) was the least frequent, being observed in 4 (13 %) patients in the heterozygous state and in 1 (3 %) patient in the homozygous state. The somatic *JAK2* mutation (rs77375493) was not detected in any patients.

At least one mutation (in the *F2* or *F5* genes) or a homozygous polymorphism in the other genes under study was observed in 24 (77 %) patients. Of these patients, 15 (48 %) had one genetic risk factor, 6 (19 %) had two, and 3 (10 %) had three.

Of the study group, 12 (39 %) patients had a history of local PVT risk factors during the early neonatal period. Comparative analysis revealed no statistically significant differences in sex, age, or the total number of inherited thrombophilic factors between patients with and without these risk factors (Table 3). The proportion of males among patients with local risk factors was 58 %, compared to 32 % among those without ($p > 0.05$). The median age at diagnosis of PVT was 5 (3; 5.5) years in the subgroup with local factors and 7 (3.5; 13.5) years in the subgroup without local factors; no significant differences were found.

The frequency of a single genetic risk factor was similar in both subgroups, ranging from 74 to 83 %. The presence of two or more risk factors was observed in 25 % of patients in the subgroup with local risk factors, compared to 32 % of patients without those ($p > 0.05$).

No significant differences were found between the subgroups for individual hemostatic gene polymorphisms. Mutations in the *F2* (rs1799963) and *F5* (rs6025) genes, as well as the *FGB* (rs1800790) AA genotype, were only identified in patients without local risk factors (one case each). The frequencies of the *ITGA2* (rs1126643) TT, *ITGB3* (rs5918) CC, *SERPINE1* (rs1799889) 4G/4G, and *MTHFR* (rs1801133) TT genotypes did not differ between subgroups. The presence of at least one A allele in the *SELPLG* gene (rs2228315) was observed in 2 (17 %) patients in the subgroup with local risk factors.

A combination of at least one A allele in the fibrinogen gene (*FGB*) and one C allele in the platelet receptor gene (*ITGB3*) was significantly more prevalent in the subgroup with local risk factors, occurring in 4 (33 %) patients vs. 1 (5 %) patient in the subgroup without local factors ($p = 0.039$).

Discussion

Our study describes a cohort of patients with an orphan disease. The size of our cohort is comparable to that in international studies, where European cohorts range from 12 to 31 participants [20, 23]. No analogous studies published in the Russian Federation were identified.

Two patients had gene mutations involved in coagulation: *F5* (rs6025) and *F2* (rs1799963). The former confers resistance to Factor V being inactivated by activated protein C, while the latter leads to increased prothrombin synthesis, both of which contribute to a hypercoagulable state. These variants are the two most extensively studied and prevalent inherited causes of thrombophilia in Europe. Studies from Germany [5], Italy [20], Bulgaria [23], and Egypt [18] have demonstrated an association between these mutations and pediatric PVT, whereas a report from India found no such relationship [21]. Findings from Turkey are inconsistent: one study identified an association between PVT and the Factor V Leiden mutation [26], while another found no correlation with either *F5* or *F2* mutations [22].

These discrepancies in findings may be attributed to ethnic differences between Caucasians and individuals of South Asian (Indian) descent. Specifically, Factor II (rs1799963) and Factor V (rs6025) mutations are significantly less prevalent in Indian patients with venous thromboembolism than in Caucasians. Deficiencies of antithrombin, protein C and protein S are also more common in the Indian population [27].

The *MTHFR* gene polymorphism (rs1801133) reduces the activity of the enzyme, which can lead

Table 2. Genotype and allele frequencies in patients with childhood-onset portal vein thrombosis

Gene, polymorphism	Genotype, allele	Portal vein thrombosis (n = 31)
F2 (rs1799963)	GG	30 (97 %)
	GA	1 (3 %)
	G	0.984
	A	0.016
F5 (rs6025)	GG	30 (97 %)
	GA	1 (3 %)
	G	0.984
	A	0.016
FGB (rs1800790)	GG	20 (65 %)
	GA	9 (29 %)
	AA	2 (6 %)
	G	0.790
	A	0.210
ITGA2 (rs1126643)	CC	12 (39 %)
	CT	15 (48 %)
	TT	4 (13 %)
	C	0.629
	T	0.371
ITGB3 (rs5918)	TT	20 (64 %)
	TC	8 (26 %)
	CC	3 (10 %)
	T	0.774
	C	0.226
SERPINE1 (rs1799889)	5G/5G	4 (13 %)
	5G/4G	9 (29 %)
	4G/4G	18 (58 %)
	5G	0.274
	4G	0.726
MTHFR (rs1801133)	CC	16 (52 %)
	CT	10 (32 %)
	TT	5 (16 %)
	C	0.677
	T	0.323
SELPLG (rs2228315)	GG	26 (84 %)
	GA	4 (13 %)
	AA	1 (3 %)
	G	0.903
	A	0.097
JAK2 (rs77375493)	GG	31 (100 %)
	G	1
	T	0

Note: *data are presented as the absolute number of patients and the proportion of the total number, n (%), for genotypes or as frequencies for alleles; FGB — fibrinogen beta chain; ITGA2 — integrin subunit alpha 2; ITGB3 — integrin subunit beta 3; MTHFR — methylenetetrahydrofolate reductase; SELPLG — selectin P ligand; SERPINE1 — serine protease inhibitor clade E member 1; JAK2 — Janus kinase 2.*

Table 3. Risk factors in patients with childhood-onset portal vein thrombosis in subgroups depending on the presence of local factors in the early neonatal period

Variable	Local factors in the early neonatal period		*p*
	Yes (*n* = 12)	No (*n* = 19)	
Males	7 (58 %)	6 (32 %)	n.s.
Females	5 (42 %)	14 (68 %)	
Age, years	5 (3; 5.5)	7 (3.5; 13.5)	n.s.
≥1 risk factor	10 (83 %)	14 (74 %)	n.s.
≥2 risk factors	3 (25 %)	6 (32 %)	n.s.
F2 (rs1799963) GA	0	1 (5 %)	n.s.
F5 (rs6025) GA	0	1 (5 %)	n.s.
FGB (rs1800790) AA	0	2 (11 %)	n.s.
ITGA2 (rs1126643) TT	2 (17 %)	2 (11 %)	n.s.
ITGB3 (rs5918) CC	2 (17 %)	1 (5 %)	n.s.
FGB A + ITGB3 C	4 (33 %)	1 (5 %)	0,039
SERPINE1 (rs1799889) 4G/4G	8 (67 %)	10 (53 %)	n.s.
MTHFR (rs1801133) TT	1 (8 %)	4 (21 %)	n.s.
SELPLG (rs2228315) AA	1 (8 %)	0 (0 %)	n.s.

Note: *data are presented as the absolute number of patients and proportion of the total number, n (%), or as the median and interquartile range Me (25th, 75th percentiles); n.s. — not significant; FGB — fibrinogen beta chain; ITGA2 — integrin subunit alpha 2; ITGB3 — integrin subunit beta 3; MTHFR — methylenetetrahydrofolate reductase; SELPLG — selectin P ligand; SERPINE1 — serine protease inhibitor clade E member 1; JAK2 — Janus kinase 2.*

to hyperhomocysteinemia and endothelial dysfunction, and possibly increase the risk of blood clots. This polymorphism was identified in 15 (48 %) patients in our study: 10 (32 %) were heterozygous and 5 (16 %) were homozygous; the T allele frequency was 32.3 %. These results are consistent with an Italian study in which the *MTHFR* gene polymorphism was found in 16 out of 31 PVT patients (68 %), four of whom were homozygous. The odds ratio for carrying at least one C677T allele was found to be 7.00 (95 % confidence interval: 2.15–22.85) [20]. In contrast, studies on PVT in Israel and Turkey identified the *MTHFR* (rs1801133) polymorphism in only one patient each [6, 22]. The rs1801133 polymorphism exhibits significant differences between populations: in Caucasian populations, the average T allele frequency is 36.5 % [28], which aligns with the frequency observed in our PVT patients.

In our cohort, the frequency of the 4G allele of the *SERPINE1* polymorphism (rs1799889) was 72.6 %, which is higher than the 54.2 % (95 % confidence interval: 51.9–56.6 %) reported in the European population [29]. PAI-1 is the primary physiological inhibitor of fibrinolysis, binding to and irreversibly inactivating both t-PA (tissue-type plasminogen activator) and u-PA (urokinase-type plasminogen activator). This blocks the conversion of plasminogen to plasmin, reduces fibrin degradation and ultimately prevents thrombus dissolution [30, 31]. The 4G allele is associated with higher gene expression and increased plasma levels of PAI-1.

In placental tissue, *SERPINE1* is predominantly expressed in fetal cells, such as extravillous trophoblasts and endothelial cells of the chorionic villi, with minimal expression observed in maternal decidual cells [32, 33]. Consequently, newborns with the 4G/4G genotype are presumed to have higher concentrations of PAI-1. Furthermore, PAI-1 is synthesized by endothelial cells and adipose tissue and stored in platelet alpha-granules. Newborns may exhibit heightened PAI-1 levels due to endothelial activation in various conditions, including sepsis, hypoxia, intrauterine infections, and umbilical vein catheterisation [34].

The 4G/4G polymorphism was present in eight patients (67 %) who had local risk factors during the early neonatal period, such as omphalitis, umbilical sepsis and umbilical vein catheterisation. This genotype likely resulted in the highest PAI-1 concentrations, serving as a risk factor for PVT. This finding is consistent with several studies that have demonstrated the role of impaired fibrinolysis in the pathogenesis of pediatric PVT [35, 36]. Specifically, studies from Bulgaria and Turkey have also reported an increased frequency of the *SERPINE1* polymorphism in children with catheter-associated PVT [22, 23].

The frequencies of polymorphisms in the following genes are reported here for the first time in

patients with pediatric-onset PVT: *FGB* (rs1800790), *ITGA2* (rs1126643) and *ITGB3* (rs5918), and the *SELPLG* (rs2228315).

The transcriptional activity of the *FGB* gene and the concentration of plasma fibrinogen are both elevated in individuals with the *FGB* (rs1800790) polymorphism, which promotes hypercoagulability. A recently published study [37] established an association between *FGB* (rs1800790) and deep vein thrombosis of the lower extremities, particularly in combination with other inherited thrombophilias: the frequency of the A allele was 14 % in the control group vs. 14.6 % in the thrombosis group. Another study identified an association between *FGB* (rs1800790) and pulmonary thromboembolism, with an A allele frequency of 17 % [38]. In our study cohort, the frequency of the A allele was even higher, at 21 %.

The *ITGA2* gene polymorphism (rs1126643) causes a conformational change in the α2 subunit of the platelet collagen receptor, integrin α2β1 (glycoprotein Ia/IIa). This results in increased receptor expression on the platelet surface, enhancing platelet adhesion to collagen. In our PVT cohort, the frequency of the T allele of *ITGA2* (rs1126643) was 37.1 %, which is comparable to its frequency in the European population (27.6–44.4 %) [39].

We also investigated the rs5918 polymorphism in the *ITGB3* gene, which encodes the β subunit of the platelet fibrinogen receptor, integrin αIIbβ3 (glycoprotein IIb/IIIa). This polymorphism alters the conformation of the receptor, thereby increasing its affinity for fibrinogen and promoting enhanced platelet aggregation. In our study, the frequency of the C allele of *ITGB3* (rs5918) was 22.6 %, which is higher than the figures reported for European populations (approximately 15 %) [40] and inhabitants of Siberia (14.7–15.0 %) [41].

Unlike mutations in the *F2* and *F5* genes, polymorphisms in the *FGB* (rs1800790), *ITGA2* (rs1126643), and *ITGB3* (rs5918) genes are not recognized as independent risk factors for thrombosis. However, they may contribute to an increased thrombotic risk when combined with other prothrombotic factors. For example, next-generation sequencing has revealed rare and combined prothrombotic variants, including the *ITGB3* (rs5918) polymorphism, in patients with cerebral venous thrombosis who lack classical Factor V and Factor II mutations, suggesting their potential role in genetic predisposition to thrombosis [42]. Similar findings were reported in a study of four children with retinal central vein thrombosis which found an association between thrombosis and the *ITGA2* (rs1126643) and *ITGB3* (rs5918) polymorphisms [43].

The rs2228315 genetic polymorphism in the *SELPLG* gene, which encodes PSGL-1, enhances the adhesion of leukocytes and platelets to the endothelium. In our study, the frequency of the A allele of rs2228315 was 9.7 %, which is higher than the 6.7 % reported in the European population [44]. Neonates exhibit reduced neutrophil adhesion to P-selectin, which is associated with decreased PSGL-1 ligand expression and functional activity, as well as altered sialylation of its glycoprotein structure. These characteristics lead to diminished inflammatory and thrombotic responses [45]. In the subgroup of patients with local risk factors, one patient was homozygous and two were heterozygous for the *SELPLG* polymorphism. This could potentially have modified the inflammatory response and served as a risk factor for PVT. However, this remains a cautious hypothesis as no direct studies on the rs2228315 polymorphism in newborns with infectious complications or portal vein catheterization were found. Furthermore, our study did not reveal any differences in the frequency of this polymorphism between subgroups with and without local risk factors.

Overall, the subgroup with local risk factors in the early neonatal period did not exhibit a higher prevalence of the examined polymorphisms or a greater combined genetic risk for PVT compared to those without such factors. However, an exception was the combination of polymorphisms in the fibrinogen gene and its platelet receptor (*FGB*: rs1800790 and *ITGB3*: rs5918), which was observed more frequently in the subgroup with local risk factors. A similar combination has been reported in studies of women with recurrent pregnancy loss [46].

The most common marker of myeloproliferative neoplasms — the *JAK2* mutation (rs77375493) — was not detected in any of the patients examined. Although this mutation is frequently identified in adult PVT patients with myeloproliferative neoplasms [47], PVT has also been associated with essential thrombocythemia or polycythemia vera in pediatric cases. Notably, some of these pediatric patients were found to harbor a mutation in exon 14 of the *JAK2* gene [17].

The study's limitations stem from the small patient group, which is due to the rarity of the condition; the cross-sectional study design; and the inability to develop a comprehensive model of PVT development accounting for all factors, including local ones, given the potential for recall bias regarding neonatal events and loss of medical records. However, as the genotype for the studied polymorphisms was present at birth and remained unchanged throughout life (patients who had undergone liver or hematopoietic stem cell transplantation were excluded from the study), the results can be extrapolated to the time of PVT onset.

Future research directions

Further prospective studies should focus on analyzing hemostatic gene polymorphisms in larger

cohorts, as well as evaluating gene-gene interactions in combination with local factors that may increase the risk of PVT in children.

Conclusion

This study presents the first data from the Russian Federation on genetic polymorphisms in patients with pediatric-onset PVT. Both known mutations in the *F5* (rs6025) and *F2* G20210A (rs1799963) genes were identified, as well as polymorphisms in the *MTHFR* (rs1801133), *SERPINE1* (rs1799889), *FGB* (rs1800790), *ITGA2* (rs1126643), *ITGB3* (rs5918), and *SELPLG* (rs2228315) genes that may affect blood coagulation and the inflammatory response. The frequency of the *F5* (rs6025) and *F2* G20210A (rs1799963) mutations was comparable to that observed in Europeans, whereas the 4G *SERPINE1* (rs1799889) polymorphism allele was more prevalent. This could potentially result in elevated PAI-1 levels and reduced fibrinolysis capacity in newborns, particularly in cases of omphalitis, umbilical sepsis, or umbilical vein catheterisation. Polymorphisms in the *FGB*, *ITGA2*, *ITGB3*, and *SELPLG* genes may enhance the risk of PVT when combined with other inherited and external factors.

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Information about the authors

Maria Yu. Nadinskaia* — Cand. Sci. (Med.), Associate Professor at the Department of Propaedeutics of Internal Diseases, Gastroenterology and Hepatology, I.M. Sechenov First Moscow State Medical University (Sechenov University).
Contact information: nadinskaya_m_yu@staff.sechenov.ru;
119048, Moscow, Trubetskaya str., 8, build. 2.
ORCID: https://orcid.org/0000-0002-1210-2528

Kseniya A. Gulyaeva — Teaching Assistant at the Department of Propaedeutics of Internal Diseases, Gastroenterology and Hepatology, I.M. Sechenov First Moscow State Medical University (Sechenov University).
Contact information: gulyaeva_k_a@staff.sechenov.ru;
119048, Moscow, Trubetskaya str., 8, build. 2.
ORCID: https://orcid.org/0000-0002-3462-0123

Evelina Trashkun — Student, Institute of International Education, I.M. Sechenov First Moscow State Medical University (Sechenov University).
Contact information: trashkun02@mail.ru;
119048, Moscow, Trubetskaya str., 8, build. 2.
ORCID: https://orcid.org/0009-0006-4570-592X

Diana Daduns — Student, Institute of International Education, I.M. Sechenov First Moscow State Medical University (Sechenov University).
Contact information: dadunsdiana2002@mail.ru;
119048, Moscow, Trubetskaya str., 8, build. 2.
ORCID: https://orcid.org/0009-0006-0156-7668

Maxim A. Privalov — Resident, Postgraduate at the Department of Oncology, Radiotherapy and Reconstructive Surgery, I.M. Sechenov First Moscow State Medical University (Sechenov University).
Contact information: makspr24@gmail.com;
119048, Moscow, Trubetskaya str., 8, build. 2.
ORCID: https://orcid.org/0000-0002-6836-4228

Vladimir T. Ivashkin — Dr. Sci. (Med.), Professor, Academician of the Russian Academy of Sciences, Head of the Department of Propaedeutics of Internal Diseases, Gastroenterology and Hepatology; Director of the V.Kh. Vasilenko Clinic of Internal Disease Propaedeutics, Gastroenterology and Hepatology, I.M. Sechenov First Moscow State Medical University (Sechenov University).
Contact information: ivashkin_v_t@staff.sechenov.ru;
119048, Moscow, Trubetskaya str., 8, build. 2.
ORCID: https://orcid.org/0000-0002-6815-6015

Сведения об авторах

Надинская Мария Юрьевна* — кандидат медицинских наук, доцент кафедры пропедевтики внутренних болезней, гастроэнтерологии и гепатологии, ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет).
Контактная информация: nadinskaya_m_yu@staff.sechenov.ru;
119048, г. Москва, ул. Трубецкая, 8, стр. 2.
ORCID: https://orcid.org/0000-0002-1210-2528

Гуляева Ксения Александровна — ассистент кафедры пропедевтики внутренних болезней, гастроэнтерологии и гепатологии, ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет).
Контактная информация: gulyaeva_k_a@staff.sechenov.ru;
119048, г. Москва, ул. Трубецкая, 8, стр. 2.
ORCID: https://orcid.org/0000-0002-3462-0123

Трашкун Эвелина — студентка Института международного образования, ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет).
Контактная информация: trashkun02@mail.ru;
119048, г. Москва, ул. Трубецкая, 8, стр. 2.
ORCID: https://orcid.org/0009-0006-4570-592X

Дадунц Диана — студентка Института международного образования, ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет).
Контактная информация: dadunsdiana2002@mail.ru;
119048, г. Москва, ул. Трубецкая, 8, стр. 2.
ORCID: https://orcid.org/0009-0006-0156-7668

Привалов Максим Александрович — ординатор, аспирант кафедры онкологии, радиотерапии и реконструктивной хирургии, ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет).
Контактная информация: makspr24@gmail.com;
119048, г. Москва, ул. Трубецкая, 8, стр. 2.
ORCID: https://orcid.org/0000-0002-6836-4228

Ивашкин Владимир Трофимович — доктор медицинских наук, профессор, академик РАН, заведующий кафедрой пропедевтики внутренних болезней, гастроэнтерологии и гепатологии; директор Клиники пропедевтики внутренних болезней, гастроэнтерологии и гепатологии им. В.Х. Василенко, ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения
Российской Федерации (Сеченовский Университет).
Контактная информация: ivashkin_v_t@staff.sechenov.ru;
119048, г. Москва, ул. Трубецкая, 8, стр. 2.
ORCID: https://orcid.org/0000-0002-6815-6015

* Corresponding author / Автор, ответственный за переписку

Authors' contributions

Concept and design of the study: Nadinskaia M.Yu., Ivashkin V.T.
Collection and processing of the material: Nadinskaia M.Yu., Gulyaeva K.A.
Statistical processing: Trashkun E., Daduns D., Privalov M.A., Nadinskaia M.Yu.
Writing of the text: Trashkun E., Daduns D., Privalov M.A.
Editing: Nadinskaia M.Yu., Gulyaeva K.A.
Proof checking and approval with authors: Nadinskaia M.Yu.

Вклад авторов

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