RESEARCH LETTER

Genetic and clinical characteristics of congenital fibrinogen disorders in 10 Polish patients, with identification of 3 new variants: Fibrinogen Gdańsk II (*FGB* c.749A>G), Fibrinogen Gdańsk III (*FGG* c.246dupA), and Fibrinogen Toruń (*FGB* c.270delT)

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Introduction Congenital fibrinogen disorders (CFDs), caused by pathogenic variants in 1 of the 3 fibrinogen genes: *FGA*, *FGB*, or *FGG*, are classified as quantitative deficiencies—afibrinogenemia and hypofibrinogenemia—typically inherited in an autosomal recessive manner, or qualitative defects—dysfibrinogenemia and hypodysfibrinogenemia—most often showing an autosomal dominant inheritance pattern.[1,2]

Fibrinogen plays a role not only in blood coagulation but also in wound healing, angiogenesis, and inflammation. Consequently, structural or functional abnormalities of fibrinogen may lead to complex and often variable clinical manifestations.[3,4] Patients with afibrinogenemia typically present with umbilical cord or mucocutaneous bleeding during the neonatal period, whereas those with hypofibrinogenemia usually experience mild-to-moderate bleeding, often triggered by trauma or surgery. In contrast, dysfibrinogenemia may result in either bleeding or thrombosis, and a substantial proportion of patients remain asymptomatic.[4-6]

Although genetic testing has improved the confirmation of CFDs, diagnosis is mainly based on functional and antigenic fibrinogen measurement. Nevertheless, CFDs remain underdiagnosed, mainly due to underestimation of mild or asymptomatic decreases in fibrinogen levels and a limited access to molecular testing in routine practice. Next-generation sequencing enables a simultaneous analysis of all 3 fibrinogen genes and has substantially increased the detection of novel variants, contributing to a better understanding of genotype–phenotype correlations.[7]

Recent reviews have emphasized the marked clinical and laboratory heterogeneity of CFDs and the need for an integrated diagnostic approach combining fibrinogen activity, antigen levels, and molecular testing.[8] In Poland, to our knowledge, 49 genetically confirmed patients with CFDs have been reported to date.[4,5] Here, we present clinical and genetic characteristics of 10 unrelated Polish patients with CFDs, with long-term follow-up, including 3 novel variants in the *FGB* and *FGG* genes.

Patients and methods We evaluated 10 unrelated Polish patients with CFDs (5 women) at a mean (SD) age of 25.5 (15.9) years, who had plasma fibrinogen concentration (Clauss method) below 1.8 g/l in at least 2 separate measurements. All patients with thrombotic or bleeding disorders, or those with incidentally determined low fibrinogen

levels, were referred to the Center for Coagulation Disorders at the St. John Paul II Hospital, Kraków, Poland between April 2021 and July 2025. Clinical data were collected at baseline and updated during follow-up visits.

Data on thromboembolic events, obstetric complications, and family history of bleeding or thrombosis were also collected. Bleeding events were classified as major, clinically relevant nonmajor bleeding (CRNMB), or minor bleeding, according to the criteria of the International Society on Thrombosis and Haemostasis.[9] Deep vein thrombosis (DVT) was diagnosed based on duplex Doppler ultrasonography findings along with typical symptoms. Ischemic stroke was defined as an acute episode of focal neurological deficit of vascular etiology documented on brain imaging. The diagnosis of cerebral venous sinus thrombosis (CVST) was established on the basis of characteristic symptoms confirmed on magnetic resonance angiography. Family history was regarded as positive if a thromboembolic event was diagnosed in at least 1 first-degree relative.

Follow-up was conducted through outpatient visits or phone calls. New thromboembolic or bleeding events, along with obstetric complications, were recorded.

Functional fibrinogen concentrations were measured using the Clauss method (Siemens Healthcare Diagnostics, Erlangen, Germany; reference range [RR], 1.8–3.5 g/l), and fibrinogen antigen levels were determined nephelometrically (Siemens Healthcare Diagnostics; RR, 1.9–3.1 g/l).

For genotyping, whole blood samples were drawn into tubes containing K_2EDTA as an anticoagulant, and genomic DNA was isolated for subsequent whole exome sequencing performed at the Health 2030 Genome Center Sequencing Platform (Geneva, Switzerland), using Integrated DNA Technologies Research Exome Reagents (IDT, Coralville, Iowa, United States), multiplexing 12 samples during library preparation. Sequencing was performed on the Illumina HiSeq 4000 system (Illumina, San Diego, California, United States), with an estimated mean coverage of 70×. Data analysis focused on variants located in a gene panel of 28 genes involved in the coagulation and fibrinolytic pathways, including *FGA*, *FGB*, and *FGG*.

All patients provided written informed consent to participate. The study design did not require an approval of a Bioethics Committee.

Statistical analysis Continuous variables were presented as mean (SD) or median (interquartile range [IQR]), and categorical variables as numbers and percentages. Statistical analyses were performed using Statistica, version 13.3 (StatSoft, Inc., Tulsa, Oklahoma, United States).

Results and discussion As shown in TABLE 1, among the 10 patients tested, quantitative CFDs were observed in 6 individuals, with mean (SD) functional fibrinogen and antigen levels of 1.27 (0.31) g/l and 1.25 (0.14) g/l, respectively, while qualitative CFDs were identified in 4 patients, with the corresponding mean levels of 1.21 (0.44) g/l and 2.29 (0.19) g/l, respectively. Based on functional and antigenic fibrinogen levels, 4 patients were classified as having dysfibrinogenemia (type 3A according to the functional classification proposed by Casini et al[1]), 5 patients as having mild hypofibrinogenemia (type 2C), and 1 patient as having moderate hypofibrinogenemia (type 2B). In 1 individual (TABLE 1; ID 3) with a Clauss fibrinogen level of 1.43 g/l, fibrinogen antigen measurement was unavailable.

The predominance of mild forms, mainly type 2C hypofibrinogenemia and type 3A dysfibrinogenemia, is consistent with previous Polish and European data showing that most congenital fibrinogen abnormalities identified in adults represent mild quantitative or qualitative deficiencies.[4,5,10]

Thromboembolic events were the most common clinical presentation, observed in 3 women: 1 with ischemic stroke and type 3A dysfibrinogenemia (ID 1), 1 with CVST (ID 3), and 1 with popliteal vein thrombosis (ID 10); the latter 2 diagnosed with hypofibrinogenemia, types 2C and 2B, respectively. Two of these events (IDs 3 and 10) occurred in patients on oral hormonal contraception, underlining the prothrombotic effect of estrogen exposure.[11] Previous studies have shown that approximately 15%–25% of individuals with dysfibrinogenemia may develop thrombosis, particularly when additional risk factors are present.[6,12] Thrombotic complications have also been reported in patients with hypofibrinogenemia, with a prevalence ranging from 10% to as high as 22%, often associated with concomitant thrombotic risk factors.[13]

None of the patients experienced major bleeding or CRNMB. Minor bleeding, such as easy bruising or soft-tissue hematomas, were documented in 3 individuals: 2 patients with type 2C mild hypofibrinogenemia and 1 patient with type 3A dysfibrinogenemia. Impaired wound healing was not observed. One woman with type 3A dysfibrinogenemia (ID 6) experienced 2 first-trimester miscarriages, which agrees with previous reports linking fibrinogen abnormalities to adverse obstetric outcomes, likely due to impaired fibrin–placenta interactions and premature fibrinolysis.[14] Three patients remained asymptomatic and were diagnosed incidentally.

A positive family history of bleeding or thromboembolic disorders was reported in 4 individuals; however, none of the patients reported a known diagnosis of CFDs in their relatives.

Heterozygous pathogenic or likely pathogenic variants were identified in all patients: 1 in the *FGA*, 5 in the *FGB*, and 4 in the *FGG* gene.

Three previously unreported heterozygous variants were detected in the *FGB* and *FGG* genes.

The first novel variant, Fibrinogen Gdańsk II (*FGB* c.749A>G; p.Glu250Gly), located in exon 5, was detected in a 12-year-old girl with

TABLE 1 Characteristics of patients with quantitative and qualitative congenital fibrinogen disorders

Patient ID	Sex/age, y	Fibrinogen (Clauss/antigen), g/l	Classification of congenital fibrinogen disorders	Type of mutation (all heterozygous)	Gene/exon	New/reported	Presentation on admission	Duration of follow-up, mo	Major bleeding/ CRNMB/ minor bleeding	Thromboembolic events	Family history of bleeding or thromboembolism
1	F/12	1.62; 1.55/2.42	3A Dysfibrinogenemia	c.749A>G (p.Glu250Gly)	*FGB*/5	New; Fibrinogen Gdańsk II	Ischemic stroke of the left hemisphere at the age of 11 y	15	0/0/0	0	0
2	F/1	1.1/1.08	2C Mild hypofibrinogenemia	c.246dupA (p.Val83Serfs13)	*FGG*/3	New; Fibrinogen Gdańsk III	Easy bruising, soft--tissue hematoma	15	0/0/1	0	1
3	F/29	1.43/nd	2C Mild hypofibrinogenemia?	c.270delT (p.Asp91Metfs40)	*FGB*/2	New; Fibrinogen Toruń	CVST at the age of 28 y (on oral contraceptives)	14	0/0/0	0	0
4	M/34	0.82/2.23	3A Dysfibrinogenemia	c.1168G>C (p.Asp390His)	*FGG*/9	Reported	Easy bruising, soft--tissue hematoma	20	0/0/0	0	0
5	M/14	1.63/2.05	3A Dysfibrinogenemia	c.901 C>T (p.Arg301Cys)	*FGG*/8	Reported	Nosebleeds once a week	7	0/0/1	0	0
6	F/30	1.26/2.48	3A Dysfibrinogenemia	c.104G>A (p.Arg35His)	*FGA*/2	Reported	2 miscarriages	12	0/0/0	0	1
7	M/22	1.15/1.2	2C Mild hypofibrinogenemia	c.1330 G>A (p.Gly444Ser)	*FGB*/8	Reported	Asymptomatic; detected accidentally	38	0/0/0	0	1
8	M/28	1.37/1.4	2C Mild hypofibrinogenemia	c.1330G>A (p.Gly444Ser)	*FGB*/8	Reported	Asymptomatic; detected accidentally	14	0/0/0	0	1
9	M/61	1.71/1.32	2C Mild hypofibrinogenemia	c.331A>T (p.Lys111X)	*FGG*/4	Reported	Asymptomatic; detected accidentally	27	0/0/0	0	0
10	F/24	0.78/nd	2B Moderate hypofibrinogenemia	c.1330G>A (p.Gly444Ser)	*FGB*/8	Reported	Popliteal vein thrombosis (on oral contraceptives)	18	0/0/0	0	0

Abbreviations: CRNMB, clinically relevant nonmajor bleeding; CVST, cerebral venous sinus thrombosis; F, female; M, male; nd, not determined

dysfibrinogenemia (type 3A) who experienced an ischemic stroke at the age of 11 years. The patient was treated with enoxaparin, followed by acetylsalicylic acid (ASA; 150 mg daily). Screening for inherited and acquired thrombophilia was negative and no thromboembolic events were reported in the proband's family. Although missense mutations in the *FGB* gene causing dysfibrinogenemia are relatively uncommon, pathogenic variants affecting this region have been reported.[15]

The second novel variant, Fibrinogen Gdańsk III (*FGG* c.246dupA; p.Val83Serfs13), located in exon 3, was identified in a 1-year-old girl with mild hypofibrinogenemia (type 2C), easy bruising, and soft-tissue hematoma. Frameshift and nonsense variants affecting the N-terminal region of the fibrinogen γ-chain, including mutations located in exon 2 of the *FGG* gene, have been previously reported in patients with CFDs.[5] These variants are known to impair fibrinogen assembly and secretion,[7] supporting the pathogenic relevance of the c.246dupA (p.Val83Serfs13) variant identified in our study. Interestingly, this patient also carried a rare heterozygous variant in exon 28 of the *VWF* gene (c.4196G>A; p.Arg1399His). The clinical significance of this variant remains unclear, as it has been inconsistently classified in genetic databases (ranging from benign to pathogenic). The von Willebrand factor antigen level was within the normal range (81%; RR, 50%–160%). Therefore, the bleeding phenotype was most likely related to an inherited fibrinogen disorder. Her family history was positive: her father was diagnosed with hypofibrinogenemia (Clauss fibrinogen level, 1.45 g/l) without bleeding. Recently, the patient has been complaining of increased bruising and subcutaneous hematomas, but not of severe bleeding.

The third variant, designated Fibrinogen Toruń (*FGB* c.270delT; p.Asp91Metfs40), located in exon 2, was identified in a 28-year-old woman. In this patient, fibrinogen antigen measurement was unavailable and definitive classification was therefore not possible. However, the presence of a frameshift mutation (c.270delT; p.Asp91Metfs40) in the *FGB* gene suggested a quantitative fibrinogen defect consistent with mild hypofibrinogenemia (type 2C). The patient developed CVST while receiving oral hormonal contraception. She was treated with heparins and then rivaroxaban (20 mg daily); however, she later decided to discontinue anticoagulation. To date, she has remained free of recurrent thromboembolic events and obstetric complications, and no such events have been reported in her family. Mutations in the N-terminal region of the *FGB* gene, including early loss-of-function variants, such as p.Arg17X, have previously been associated with hypofibrinogenemia, supporting the pathogenic plausibility of the c.270delT (p.Asp91Metfs40) variant.[16]

Two probands with dysfibrinogenemia were heterozygous carriers of known "hot spot" mutations (*FGA* p.Arg35His and *FGG* p.Arg301Cys).[4,5] Among the remaining patients, the *FGB* p.Gly444Ser variant was found in 3 individuals with mild or moderate hypofibrinogenemia (2 asymptomatic and 1 with DVT), while the *FGG* p.Lys111X variant was identified in an asymptomatic patient. All of these variants have been previously reported in Slavic populations and associated with CFDs,[4,5] In contrast, the *FGG* c.1168G>C (p.Asp390His) variant identified in the current cohort has been described in a Japanese pediatric patient with Down syndrome[17]; however, to our knowledge, this is the first report of this variant in a Polish patient.

During follow-up (median [IQR], 17 [14–34] months), no new thrombotic or major bleeding events were reported. Impaired wound healing was not observed. Two patients received antithrombotic therapy: an 11 year-old girl (ID 1) with a history of ischemic stroke was treated with ASA, and a 24-year-old woman (ID 10) with a history of provoked DVT received ASA 100 mg daily and prophylactic-dose enoxaparin during periods of increased thrombotic risk. None of the patients received oral anticoagulants. Two individuals reported mild, self-limiting bleeding episodes, mainly epistaxis and easy bruising; neither required specific treatment.

Our findings confirm the considerable genetic and clinical heterogeneity of CFDs and expand the mutational spectrum of the *FGB* and *FGG* genes. The coexistence of bleeding and thrombotic manifestations within this small cohort highlights the dual biological effects of fibrinogen abnormalities and the complexity of genotype–phenotype relationships.[3,6,10,12] The marked phenotypic variability observed among affected families, often with incomplete segregation of variants, underscores the importance of comprehensive molecular characterization in selected cases.[18] Although functional fibrinogen levels are crucial for clinical management, genetic testing can provide additional information on inheritance, the influence of variants, and the possible risk of thrombosis or bleeding, helping refine the diagnosis and assess risk, especially in clinically complex cases.

In conclusion, we reported 3 novel fibrinogen variants: Fibrinogen Gdańsk II, Fibrinogen Gdańsk III, and Fibrinogen Toruń, identified in Polish patients. Since clinical manifestations were predominantly mild, the presence of thrombotic and obstetric complications, along with bleeding tendency, underscores the need for specialized clinical follow-up.

ARTICLE INFORMATION

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