

ARTICLE

Factor XI gene variants in factor XI-deficient patients of Southern Italy: identification of a novel mutation and genotype–phenotype relationship

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Congenital Factor XI (FXI) deficiency shows a high variability in clinical phenotype. To date, many allele variants have been shown to cause this bleeding disorder. However, the genotype–phenotype relationship is difficult to establish. This report provides insights into this bleeding disorder. Sixteen unrelated Italian index cases with congenital FXI deficiency and their relatives were investigated. After the identification of the deficiency, we obtained DNA from each subject and analyzed the FXI gene using direct sequencing. We identified 5 and 11 individuals with severe and moderate deficiency of FXI activity, respectively. Most patients (8/16) carried mutations in the Apple 2 domain and 4 patients showed c.403G>T (p.Glu135*; type II mutation). Four novel compound heterozygosities were identified. Bleeding symptoms were present in two severely deficient subjects carrying the combinations c.901T>C (p.Phe301Leu)/c.1556G>A (p.Trp519*) and c.943G>A (p.Glu315)/c.1556G>A (p.Trp519*), respectively. Bleeding episodes were also observed in the presence of a moderate deficiency in two individuals heterozygous for c.449C>T (p.Thr150Met) and c.1253G>T (p.Gly418Val), respectively. One novel mutation, c.1682C>A (p.Ala561Asp), was identified as potentially deleterious in an asymptomatic individual. We confirm an unclear prediction of phenotype from mutational data. The FXI levels should be coupled with FXI analysis for a more comprehensive prediction of the bleeding phenotype in FXI deficiency.

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INTRODUCTION

Congenital Factor XI (FXI) deficiency, which is inherited as an autosomal recessive trait,¹ is a mild bleeding disorder that often goes undiagnosed.² Severe deficiency is defined as FXI < 15–20 IU/dl.³ Individuals with levels between 20 IU/dl and the lower limit of the normal range, generally 65–80 IU/dl, are classified as having partial or mild deficiency.³

The gene (F11) of FXI contains 15 exons and 14 introns, and is located on the long arm of chromosome 4 (4q35).⁴ Homozygotes or compound heterozygotes typically show severe FXI deficiency, whereas heterozygotes show partial or mild deficiency.⁵ FXI deficiency has been predominantly diagnosed in Ashkenazi Jews.⁶ Other clusters of FXI-deficient groups have been observed among Iraqi Jews and Arabs, and among Basques and Caucasians (United Kingdom and France).⁵ In Ashkenazi Jews, the c.403G>T (p.Glu135*; so-called type II mutation) and the c.901T>C (p.Phe301Leu; type III mutation) genetic variants within the F11 gene are prevalent and strongly associated with FXI deficiency.⁷ These variants were also investigated in an unselected population of 3,879 Italian individuals with an allele frequency of 0.00064 (type II) and 0.00051 (type III), respectively, and in 31 Italian deficient-FXI patients, the type II mutation was more prevalent than the type III mutation.⁸ In FXI deficiency, bleeding episodes are typically injury related, particularly those involving loci with higher fibrinolytic activity, such as the oral cavity, nose, tonsils, and urinary tract.^{9,10} Menorrhagia is the most frequent

spontaneous episode in women with severe deficiency,⁵ whereas postpartum hemorrhage occurs in ~20% of affected women.^{11,12} Some patients with low levels of FXI may not bleed at all,¹³ whereas other subjects can show a different susceptibility to bleeding in the presence of similar hemostatic challenges.^{9–11} Postoperative bleeding events are common in subjects with severe FXI deficiency, whereas individuals with partial or mild FXI deficiency show a weak tendency for postoperative blood loss.³ Thus, a clear understanding of the relationship between the F11 genotype and phenotype of individuals with FXI deficiency is still needed. Herein, we report our findings in subjects of Caucasian ancestry with FXI deficiency to provide additional insights into this bleeding disorder.

MATERIALS AND METHODS

Subjects

Individuals with alterations in activated partial thromboplastin time referred to the Atherosclerosis and Thrombosis Unit of IRCCS 'Casa Sollievo della Sofferenza' were described. All subjects examined were from Southern Italy. All patients provided informed written consent for the use of their clinical and bio-molecular data. A detailed collection of present and past clinical history was performed to investigate the presence of any bleeding events. In detail, all the participants were requested to provide details of the conditions potentially causing bleeding, such as surgical procedures, pregnancy, and any injuries, or any spontaneous blood losses. In the case of a referred bleeding episode, medical records were requested

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Table 1. Clinical and molecular findings of the families investigated

Family subject, year of birth	FXI:C (U dL ⁻¹)	Amino acid	Gene region	Domain	Genotype	Symptoms	Challenges
<i>Family 1</i>							
P1, F, 2005	< 1	p.Ala108Thr c.325+1G>A	Exon 4	Apple 2	Comp	Asymptomatic	
Father, 1980	32	c.325+1G>A	Intron 4	—	Hetero	Epistaxis	
Mother, 1986	35	p.Ala108Thr	Exon 4	Apple 2	Hetero	Asymptomatic	
<i>Family 2</i>							
P2, F, 1987	38.4	p.Glu135 ^a	Exon 5	Apple 2	Hetero	Asymptomatic	
<i>Family 3</i>							
P3, M, 1937	42	p.Glu135 ^a	Exon 5	Apple 2	Hetero	Asymptomatic, ^a idiopathic superficial vein thrombosis	Knee prosthesis implantation; multiple tooth extraction; tonsillectomy; surgery for inguinal hernia
<i>Family 4</i>							
P4, F, 1977	34.3	p.Glu135 ^a	Exon 5	Apple 2	Hetero	Asymptomatic	Appendicectomy; gynaecological laparoscopy
<i>Family 5</i>							
P5, F, 1959	< 1	p.Glu135 ^a p.Cys136Arg	Exon 5 Exon 5	Apple 2 Apple 2	Comp Hetero	Asymptomatic	Two pregnancies
<i>Family 6</i>							
P6, M, 1990	34	p.Thr150Met	Exon 5	Apple 2	Hetero	Epistaxis	
Father, 1966	52	p.Thr150Met	Exon 5	Apple 2	Hetero	Asymptomatic	
Sister, 1978	118.5	No mutation	NA	NA	NA	Asymptomatic	
<i>Family 7</i>							
P7, M, 2005	37	p.Thr150Met	Exon 5	Apple 2	Hetero	Asymptomatic	Genito-urinary surgery
Father, 1974	43	p.Thr150Met	Exon 5	Apple 2	Hetero	Asymptomatic	
<i>Family 8</i>							
P8, F, 2005	45.3	p.Arg160His	Exon 5	Apple 2	Hetero	Asymptomatic	Adeno-tonsillectomy
Mother, 1975	43.1	p.Arg160His	Exon 5	Apple 2	Hetero	Asymptomatic	
Sister, 2005	47.3	p.Arg160His	Exon 5	Apple 2	Hetero	Asymptomatic	Adeno-tonsillectomy
<i>Family 9</i>							
P9, M, 1992	33.6	p.Cys230Arg	Exon 7	Apple 3	Hetero	Asymptomatic	Surgery for sinus pilonidalis
Father, 1964	84.2	No Mutation	NA	NA	NA	Asymptomatic	
Mother, 1962	33.9	p.Cys230Arg	Exon 7	Apple 3	Hetero	Asymptomatic	
<i>Family 10</i>							
P10, F, 1998	3.8	c.595+3A>G p.Phe301Leu	Intron 6 Exon 9	— Apple 4	Comp Hetero	Asymptomatic	
Father, 1963	51	p.Phe301Leu	Exon 9	Apple 4	Hetero	Asymptomatic	
Mother, 1962	84.8	c.595+3A>G	Intron 6	—	Hetero	Asymptomatic	
<i>Family 11</i>							
P11, F, 2005	5.5	p.Phe301Leu p.Trp519 ^a	Exon 9 Exon 13	Apple 4 Catalytic	Comp Hetero	Surgery-related bleeding	Abdominal surgery for intestinal atresia (transfusions required)
Father, 1972	114	p.Trp519 ^a	Exon 13	Catalytic	Hetero	Asymptomatic	
Mother, 1981	84.8	p.Phe301Leu	Exon 9	Apple 4	Hetero	Asymptomatic	
Brother, 2010	47.4	p.Trp519 ^a	Exon 13	Catalytic	Hetero	Asymptomatic	
<i>Family 12</i>							
P12, F, 1986	7	p.Glu315Lys p.Trp519 ^a	Exon 9 Exon 13	Apple 4 Catalytic	Comp Hetero	Vaginal bleeding at the 16th week of pregnancy	Pregnancy
Father, 1963	35.8	p.Trp519 ^a	Exon 13	Catalytic	Hetero	Asymptomatic	
Mother, 1964	38.9	p.Glu315Lys	Exon 9	Apple 4	Hetero	Asymptomatic	Appendicectomy
Sister, 1988	28.9	p.Glu315Lys	Exon 9	Apple 4	Hetero	Asymptomatic	
<i>Family 13</i>							
P13, F, 2005	37.2	p.Arg326His	Exon 9	Apple 4	Hetero	Asymptomatic	
Mother, 1969	59.7	p.Arg326His	Exon 9	Apple 4	Hetero	Asymptomatic	
<i>Family 14</i>							
P14, F, 1964	45	p.Gly418Val	Exon 11	Catalytic	Hetero	Easy bruising, ^a cerebellar ischemia in oral contraceptive	Appendicectomy; adeno-tonsillectomy; abdominoplasty

Table 1. (Continued)

Family subject, year of birth	FXI:C (U dL ⁻¹)	Amino acid	Gene region	Domain	Genotype	Symptoms	Challenges
Family 15							
P15, F, 1992	36	p.Trp151Gly	Exon 13	Catalytic	Hetero	Asymptomatic	Four pregnancies; appendicectomy; hysterectomy; arthroscopic rotator cuff repair
Father, 1965	36	p.Trp515Gly	Exon 13	Catalytic	Hetero	Asymptomatic	
Mother, 1968	40	p.Trp515Gly	Exon 13	Catalytic	Hetero	Asymptomatic	
Family 16							
P16, F, 2014	33.6	p.Glu315Lys	Exon 9	Apple 4	Hetero	Asymptomatic	
Mother, 1987	36.3	p.Ala561Asp	Exon 14	Catalytic	Hetero	Asymptomatic	
		p.Glu315Lys	Exon 9	Apple 4	Hetero		
		p.Ala561Asp	Exon 14	Catalytic	Hetero		

Abbreviations: F, female; M, Male; NA, not applicable; P, Proband. ^aNo acquired or inherited thrombophilia.

to collect as much information as possible. The diagnosis of the deficiency was performed on two consecutive blood withdrawals. Individuals with FXI activity levels < 15 IU/dl were defined as severely deficient, whereas those with levels of 20–50 IU/dl were defined as moderately deficient.

The present study was carried out according to the Principles of the Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects and approved through the local ethics committee.

Coagulation tests

Blood samples were collected in Na-citratd tubes. The samples were centrifuged at 2,500g for 15 min to obtain plasma aliquots. The FXI activity levels were determined using a one-stage clotting assay (Siemens, Marburg, Germany), standardized using a homemade normal plasma pool. The reference interval, based on a locally performed reference range, was 70–150 IU/dl. The assay was performed using a BCS automated coagulation analyzer (Siemens AG). The detection limit of the FXI:C assay was < 1 IU/dl. Reference intervals were obtained from the dosing plasma of 100 healthy blood donors from the local healthy population.

DNA analysis

DNA was extracted using standard procedures. The PCR reaction was performed in a total volume of 50 µl containing 100 ng of genomic DNA, 1 U of HotStartTaq Plus DNA Polymerase (QIAGEN, Valencia, CA, USA), 1 × PCR Buffer, 1 × Q-Solution, 0.2 mm dNTPs, and 0.4 µm of forward and reverse oligonucleotides. A typical PCR cycling protocol was optimized under the following conditions: an initial activation step of 5 min at 95 °C, followed by 35 cycles at 94 °C for 1 min, 63 °C for 55 s, 72 °C for 1 min, and a final extension of 10 min at 72 °C. Direct sequencing of the coding regions, intron–exon boundaries, and 5' and 3' non-translated regions of the F11 (GenBank accession number NT_022792) was performed to detect mutations. The sequences were obtained using a BigDyeTerminator v3.1 Cycle Sequencing kit and the ABI PRISM 3130 Genetic Analyzer Sequencer (PE Biosystems, Foster City, CA, USA).

In silico predictions

Multiple alignment of F11 sequences was generated using the computer program MUSCLE (version 3.6)¹⁴ on the HomoloGene automated system (<http://www.ncbi.nlm.nih.gov/homologene>). Deleterious and damaging effect of missense mutations was predicted using the web-based tools SIFT (Sorting Intolerant from Tolerant, <http://sift.bii.a-star.edu.sg/>), and Polyphen-2 (Polymorphism Phenotyping v2, <http://genetics.bwh.harvard.edu/pph2/>).^{15,16} Residue change was classified as damaging with SIFT prediction scores ranging from 0.00 to 0.05 and with Polyphen-2 prediction according to the score ranging from (0 to 1), with 1 as the damaging prediction score. In SIFT, the median sequence information, measuring the diversity of the sequences used for prediction, is considered significant when lower than 3.25. The 'median info' is the median of conservation values in the alignment at the position of the substitution. If a substitution is predicted as damaging, with a median conservation value greater than 3.25, then SIFT highlights the lack of diversity in the selected sequences.¹⁵

RESULTS

Clinical features and bleeding history

We studied 16 (12 females and 4 males) unrelated subjects with reduced FXI activity (Table 1). Clinical and laboratory information are reported in Table 1. Five out of 16 individuals had severe deficiency (< 15 IU/dl). The remaining 11 individuals showed levels between 33 and 46 IU/dl. Two (P11 and P12) out of 5 individuals with severe deficiency displayed a bleeding tendency, which was observed after abdominal surgery (P11) and during pregnancy (P12), respectively.

Sequence variants

We identified 15 sequence variants (Table 1). All the mutations were previously described. In detail, 14 sequence variants were located in the F11 coding region, responsible for 11 missense and 2 nonsense mutations, and 2 sequence variants were located within a splice donor site. To our knowledge, the c.1682G>A (p.Ala561Asp) allele variation is novel. Based on SIFT (score 0.00; median conservation value of 2.36) and Polyphen-2 (score 1.00) predictions, the change p.Ala561Asp could have a damaging effect on FXI structure. We identified the p.Ala561Asp combined *in cis* (analysis of trio family showed that the mother and the father were a heterozygous carrier and wild type for the p.Glu315Lys and p.Ala561Asp missense changes, respectively) with p.Glu315Lys mutation in a P16 individual who showed FXI levels of 33.6%. In addition, multiple alignment of FXI amino acid sequences revealed that the p.Ala561 is a highly conserved residue across compared species (Figure 1). The 2 splice site variants were previously described to affect the normal splicing process of exons 4 and 6.^{17,18} No mutations were observed in regions controlling gene expression (5' non-translated flanking regions) or mRNA stability (3' non-translated region). Overall, mutations dispersed over the entire gene with no evidence of clustering at specific coding and non-coding regions (Table 1) but primarily involved residues in the Ap2 or Ap4 domains (Figure 2). The c.325G>A (p.Ala108Thr) variant alters the physiological donor splice site, resulting in the skipping of exon 4.¹⁷ The most common F11 mutations identified in Ashkenazi Jews, i.e., p.Glu135* (type II; 26.5%, 4/15) and p.Phe301Leu (type III; 13.3%, 2/15), were detected in 6 probands.

Clinical data and genetic findings

With respect to the bleeding phenotype, 4 probands (2 with a severe and 2 a moderate deficiency) showed bleeding complications. All severe FXI patients (*n* = 5) were combined heterozygotes and in 4 of these individuals, to our knowledge, the combination was not previously described. The only 2 severely deficient

NP_000119.1	546	QKRYRGHKITHKMICAGYREGGKDACKGDSGG-----PLSCKHNEVW	587
XP_001165847.1	546	QKRYRGHKITHKMICAGYREGGKDACKGDSGG-----PLSCKHNEVW	587
XP_001090398.2	695	QKRYRGHKITHKMICAGYREGGKDACKGDSGGVDPDSHTFPDGIASSLFW	744
NP_001128595.1	545	QIRYKGHKITHKMICAGYREGGKDACKGDSGG-----PLSCKHNEVW	586
NP_001008665.1	546	QAGYREHRTSKMVCAGYREGGKDACKGDSGG-----PLSCKHNEVW	587
NP_082342.1	545	QTRYRRHKITHKMICAGYKEGGKDTCKGDSGG-----PLSCKYNGVW	586
NP_001041313.1	477	QTRYRRHKITHKVICAGYKEGGKDTCKGDSGG-----PLSCKHNGVW	518
XP_420678.3	554	QARYRKRRIIDREICAGYDEGGKDACKGDSGG-----PLSCRHEEVW	595
XP_004911242.1	551	QGNYEQTRIDKILCAGYKRGKIDSKGDSGG-----PLACVVDEIHW	592

Figure 1. Multiple alignment of Factor XI (FXI) amino acid sequences. The Alanine-543 (numbering is reported without the signal peptide of 18 residues) is highlighted. Species compared are the following NP_000119.1 *H.sapiens*, XP_001165847.1 *P.trogloctydes*, XP_001090398.2 *M.mulatta*, NP_001128595.1 *C.lupis*, NP_001008665.1 *B.tamms*, NP_082342.1 *M.musculus*, NP_001041313.1 *R.norvegicus*, XP_420678.3 *G.gallus*, and XP_004911242.1 *tropicalis*.

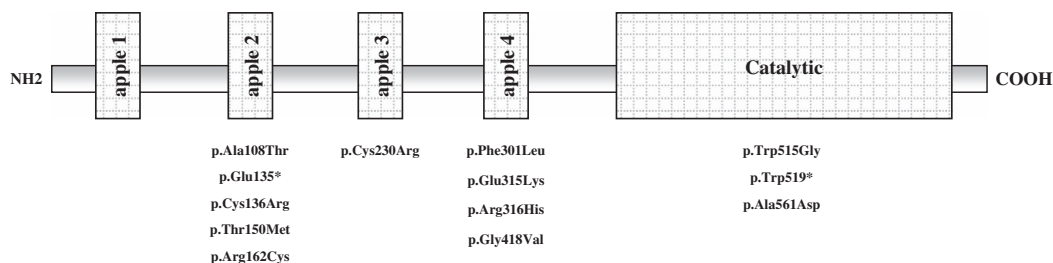


Figure 2. Distribution along the Factor XI (FXI) domains of the missense mutations identified.

P03951	FA11_HUMAN	551	--GHKITHKMICAGYRE--GGKDACKGDSDGGLSC--KHNEVHVLGITSWEGECAQRE	603
P00742	FA10_HUMAN	395	--SFITQNMFCAGYDT--KQEDACQDSDSGGPHVT--RFKDTYFVTGIVSWGECARKG	447
P00740	FA9_HUMAN	387	--KFTIYNMFCAGFHE--GGRDSCQDSDSGGPHVT--EVEGTSFLTGIISWEGECAIKG	439
P08709	FA7_HUMAN	378	GDSPNITEYMFAGYSD--GSKDSCKGDSDSGGPHAT--HYRGTWYLTGIVSWGQCATVG	432
P00734	THRB_HUMAN	541	--RIRITDNMFCAGYKPDGKRGDACEGDSDSGGPFVWKSPPNINRYQMGIVSWGECDRDG	598
P04070	PROC_HUMAN	378	--SNMVSENMLCAGILG--DRQDACEGDSDSGGPHVA--SFHGTWLVGLVSWGECGLLH	430

Figure 3. Multiple alignment of Factor XI (FXI) amino acid sequence with other serine proteases involved in the coagulation system, using Clustal Omega program. Highlighted within dashed box the well conserved Cysteine–Alanine–Glycine ('CAG') sequence. P03951 Uniprot ID Coagulation factor XI; P00472 Uniprot ID Coagulation factor X; P00740 Uniprot ID Coagulation factor IX; P08709 Uniprot ID Coagulation factor VII; P00734 Uniprot ID Prothrombin; P04070 Uniprot ID Vitamin K-dependent protein C.

patients who bled, carried the p.Glu315Lys/p.Trp519* (P11) and p.Phe301Leu/p.Trp519* mutations (P12), respectively (Table 1).

DISCUSSION

Consistent with other reports, the cohort of probands and relatives described herein is highly heterogeneous in terms of clinical and genetic findings. Among individuals with moderate deficiency, 7 individuals underwent surgical procedures either at fibrinolytic (e.g., tonsillectomy and genitourinary disorders) or non-fibrinolytic sites (e.g., pilonidal sinus) without suffering from any bleeding manifestations. In addition, 1 (P15) individual had four uneventful pregnancies. Two thrombotic events (1 idiopathic superficial vein thrombosis and 1 cerebellar ischemia during oral contraceptives) were also recorded in 2 out of 10 (20%) probands with moderate deficiency, suggesting that the occurrence of a thrombotic event is not a rare circumstance in subjects with this biochemical phenotype.

Women with FXI deficiency often experience significant obstetric and gynecological morbidity.^{19,20} Kadir *et al.*¹⁹ studied obstetric outcomes in women with FXI deficiency of Ashkenazi Jewish ancestry and observed a higher incidence of pregnancy complications in those with von Willebrand's disease than in those with FXI deficiency. In the women in the present study cohort (11 probands and 12 relatives), we recorded 10 pregnancies, 1 of which was complicated by a bleeding episode at the 16th week of gestation in a P12 patient. Notably, two pregnancies in 1 woman with severe deficiency (P5) were uneventful. The P12 patient was diagnosed at our center during her first pregnancy for

unexplained vaginal bleeding that was successfully treated with tranexamic acid. Consistent with the data reported thus far, we detected the low prevalence of bleeding episodes during pregnancy and puerperium. Furthermore, tranexamic acid is confirmed to be efficacious in managing bleeding complications related to pregnancy.

In the present study, most of the identified genetic variants are missense mutations, consistent with the data reviewed by Duga *et al.*²¹

More than 50% (8/15) of the probands in the present case series carried mutations in the Ap2 domain, described as a key determinant of interactions between FXI and high-molecular-weight kininogen, a molecule that facilitates the activation of FXI on platelets.²² Mutations in the Ap2 domain are not frequently identified in FXI-deficient patients (<http://www.factorxi.org>), although these mutations frequently occurred in an Italian series.²²

In the present cohort, type II mutation was significantly present, consistent with other studies^{8,22} reporting the high prevalence of this mutation in Italian patients. Interestingly, we observed the type III mutation in 2 patients. To date, only 2 Italian patients with the p.Phe301Leu have been described^{8,23} and both individuals were compound heterozygotes showing a bleeding tendency. In the present study, p.Phe301Leu was detected in combination with nonsense or splice site mutations. These mutations are responsible for a null allele, explaining the hemorrhagic phenotype. We propose that the p.Phe301Leu associated with a null allele could determine low FXI levels, thereby predicting a bleeding phenotype.

The p.Glu315Lys mutation was previously characterized and implicated in lowering the secretion rate of FXI to 4.5% of that of the wild type.²⁴ This mutation has primarily been identified in French patients as well as in an Israeli Arab heterozygous 15-year-old female showing menorrhagia and epistaxis.^{24,25} Bleeding was also observed in a Belgian woman who showed compound heterozygosity involving p.Glu315Lys and p.Cys545Tyr, and bleeding episodes after tooth extractions. The proband P12, showing p.Glu315Lys in association with a nonsense mutation in the catalytic site (p.Trp519*), suffered from vaginal bleeding during pregnancy (at the 16th week), whereas her mother, carrying only p.Glu315Lys, did not bleed during surgery. We propose that in this family, the presence of a nonsense mutation combined with the p.Glu315Lys is a determinant for the occurrence of bleeding complication. Notably, bleeding tendency was also recorded in proband P11, who displayed the p.Trp519* mutation together with another variant in the Ap4 domain, p.Phe301Leu. However, the presence of the homozygosity for the p.Trp519*, described in a Japanese patient who underwent gastrectomy, was not associated with bleeding episodes.²⁶ The Ap4 domain has a crucial role in FXI zymogen activation, ensuring the proper folding and dimerization of FXI.²⁷ The p.Glu315Lys variation combines *in cis* with the novel mutation p.Ala561Asp. In the present and previous studies, p.Glu315Lys heterozygous subjects showed FXI levels similar to those observed in the P16 subject: the novel mutation p.Ala561Asp *in cis* does not apparently influence the FXI levels or clinical phenotype. However, prediction models suggest a deleterious effect, and Ala-561 is in the middle of the Cysteine–Alanine–Glycine sequence. The ‘Cysteine–Alanine–Glycine’ sequence is highly conserved among serine proteases (Figure 3), suggesting a main functional and structural role for these residues in this class of proteins. Missense changes involving the Cysteine–Alanine–Glycine residues either of the other serine proteases of the coagulation system or of F11 have been described.^{28–38} Therefore, we speculated that p.Ala561Asp, when present in homozygosity or *in trans*, could influence plasmatic levels and/or bleeding tendency. In the present study, bleeding episodes were not recorded in the proband P10, who showed p.Phe301Leu combined with the c.595+3 A>G, whereas bleeding complications were reported when this missense mutation is combined with p.Trp519* (P11 and P12), as previously described. With respect to the c.595+3 A>G mutation, alterations in the splicing process have previously been demonstrated¹⁷ and described in an asymptomatic Italian subject showing compound heterozygosity; in the homozygous state, alterations in the splicing process were described in an Italian patient who showed a bleeding episode after knee arthroscopy.²² To our knowledge, the only heterozygosity for c.595+3 A>G was described in two Caucasian patients who never bled.^{39,40}

The p.Gly418Val variant has been previously identified in FXI-deficient patients who showed dental or gingival bleeding; one of these patients was of Italian origin.⁴⁰ We detected this variant in a moderately deficient woman with easy bruising (P14), but with no bleeding episodes during surgery; notably, she suffered from cerebellar ischemia when she was taking birth control pills, suggesting that the bleeding tendency may not be enough to avoid thrombotic events, at least in the presence of triggers. The data in the present study confirm the wide heterogeneity of the clinical and biochemical findings in subjects showing the FXI deficiency. A novel potentially deleterious mutation in the catalytic domain was reported. Additional studies are needed to better define the genotype–phenotype relationship in FXI-deficient subjects.

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COMPETING INTERESTS

The authors declare no conflict of interest.

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