Genetic and clinical characterization of factor VII deficiency: insights from 34 Turkish patients

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Background **Factor VII (FVII) deficiency is a rare autosomal recessive bleeding disorder caused by pathogenic variants in the *F7* gene. Clinical manifestations vary widely, ranging from asymptomatic cases to severe bleeding episodes, including gastrointestinal bleeding and intracranial hemorrhage.**

Objective **This study aims to evaluate the clinical and molecular characteristics of Turkish patients diagnosed with FVII deficiency and explore genotype–phenotype correlations.**

Methods **A cohort of 34 patients with FVII deficiency was examined. Clinical symptoms were documented, and genetic analysis of the *F7* gene was performed to identify pathogenic variants.**

Results **A total of 16 different variants were identified, including four novel variants: c.-5_4delTCinsCA, c.686T>C (p.Leu229Pro), c.728T>C (p.Ile243Thr), c.733delA (p. Thr245ProfsTer20). Monoallelic variants were found in 50% of patients, while biallelic pathogenic variants were detected in 20.6%. No pathogenic variants were identified in 29.4% of the patients. There was a poor correlation between FVII activity levels and clinical severity.**

Conclusion **This study highlights the importance of molecular diagnostics in the management of FVII deficiency, providing valuable insights into genotype-phenotype relationships. Our findings contribute to the understanding of the genetic diversity and clinical spectrum of FVII deficiency, particularly within the Turkish population. *Blood Coagul Fibrinolysis* 36:303–308 Copyright © 2025 Wolters Kluwer Health, Inc. All rights reserved.**

Blood Coagulation and Fibrinolysis 2025, **36**:303–308

Keywords: bleeding disorders, *F7* gene, factor VII deficiency, genetic variants, Turkish population

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Received 11 September 2024 **Revised** 20 May 2025 **Accepted** 27 June 2025

Introduction

Hereditary bleeding disorders affect over 7.5 million individuals worldwide. Congenital factor VII (FVII) deficiency is a rare autosomal recessive bleeding disorder caused by pathogenic variants in the *F7* gene, with a frequency of 1 in 500 000 individuals [1]. Despite its rarity, FVII deficiency can lead to significant morbidity and mortality. The clinical phenotype is highly diverse, ranging from asymptomatic or very mild forms to severe and potentially life-threatening manifestations, such as gastrointestinal bleeding, hemarthrosis, intramuscular bleeding, and central nervous system bleeding [2,3,4]. Postoperative bleeding can also occur, and coagulation tests are generally not helpful in predicting the risk of bleeding. Unlike other common factor deficiencies, residual plasma FVII activity does not always correlate with bleeding severity [2,5,6,7].

Although FVII deficiency is defined as a decrease in factor VII levels below 50%, there is no strong correlation between clinical findings and factor levels. However, a more severe phenotype is typically observed in patients with factor VII activity below 10% [6]. The *F7* gene, mapped to chromosome 13q34 [8], contains nine coding exons approximately 12.8 kb long and encodes a FVII protein consisting of 406 amino acids [9,10]. To date, over 300 different variants have been reported, the majority being single nucleotide variants, including base changes, splicing site mutations, small deletions, and insertions. Missense variants have been identified in more than 70% of cases [11,12].

It has been established that certain benign variants can modulate FVII levels, potentially mimicking heterozygous

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FVII deficiency in individuals who are actually homozygous for such variants. Among these, the minor alleles of rs5742910 and rs6046 have been consistently associated with lower plasma FVII activity levels in various populations. Studies have shown that these polymorphisms can lead to reduced transcription or altered mRNA stability, resulting in a functional decrease in FVII levels. However, these benign variants do not typically result in a clinical bleeding phenotype. Their presence should be considered when evaluating patients with low FVII levels but without any identified pathogenic variants [13,14].

Recent advancements in molecular genetics have significantly improved the diagnosis and identification of the underlying causes of genetic disorders, including FVII deficiency. Unraveling the molecular mechanisms responsible for congenital FVII deficiency is essential for predicting the risks associated with the disorder. It also facilitates the identification of carriers and offers tailored genetic counseling.

In this study, we present the clinical findings and molecular test outcomes of 34 patients from unrelated families diagnosed with FVII deficiency. We highlight the importance of molecular diagnostics in managing this rare bleeding disorder. Our findings offer insights into the genetic etiology of FVII deficiency, which can aid in the management strategies for affected individuals.

Materials and method

Patients

In this study, we retrospectively evaluated the bleeding symptoms, INR, and FVII levels, along with the *F7* gene sequence analysis results, of 34 patients diagnosed with FVII deficiency (FVII < 50%) who underwent genetic analysis between 2019 and 2021 at the Department of Pediatric Genetic Diseases, Ege University Faculty of Medicine. The study received approval from the Ethics Committee of Ege University Faculty of Medicine. Informed consent was obtained from all patients and/or their families for participation in the study, in accordance with the Declaration of Helsinki.

In this manuscript, *genetic analysis* refers to the evaluation of previously performed genetic testing results within the context of a broader genotype-phenotype investigation. The decision to initiate genetic testing was made by the treating physician based on clinical necessity and was not guided by a standardized protocol. For inclusion in this study's genetic analysis, patients were selected among those who had undergone genetic testing and met the following predefined clinical and laboratory criteria: confirmed diagnosis of FVII deficiency (FVII activity < 50%) and availability of clinical follow-up data. No additional selection criteria were applied. Other potential factors influencing the bleeding phenotype, including coexisting coagulation disorders, platelet function abnormalities, and underlying medical conditions, were evaluated in all patients. No additional causes contributing to bleeding symptoms were identified.

Molecular analysis

A sequencing analysis was performed to evaluate the 9 coding exons and exon-intron junctions of the *F7* (NM_000131.4) gene. This method did not allow for the assessment of copy number variations (CNVs). The following steps were applied for sequencing analysis.

Genomic DNA was isolated from peripheral blood cells using the QIAamp DNA Blood Mini Kit (Qiagen Ltd, Crawley, United Kingdom), following the manufacturer's instructions. The purity and concentration of the isolated DNA were measured using the Qubit system. After verifying the purity and concentration, DNA was stored at -80°C until sequencing analysis.

The "Factor VII NGS Sequencing Kit" (Multigen Saglik Hizmetleri Ltd, Izmir, Turkey) was used for DNA analysis by amplifying all exonic regions, exon-intron boundaries, and the promoter region of the *F7* gene. Following amplification, samples were prepared with the Illumina Nextera XT sample preparation kit and loaded onto the device. Sequence analysis was performed on the Illumina MiSeq (Illumina Co., San Diego, USA) platform. In the MiSeq system, the target was to obtain at least 500 coverage in the targeted gene regions. The bam files from the MiSeq were visually evaluated using the IGV program.

Variant classification and pathogenicity assessment

Variants were classified according to the American College of Medical Genetics and Genomics (ACMG) guidelines published in 2015 [15]. The classification process included evaluating the variant's frequency in population databases (e.g., gnomAD), computational predictions (e.g., SIFT, PolyPhen-2), functional studies when available, and its presence in disease-specific databases such as HGMD (Human Gene Mutation Database), ClinVar, and EAHAD (European Association for Haemophilia and Allied Disorders Database). Each variant was categorized as pathogenic, likely pathogenic, uncertain significance (VUS), likely benign, or benign based on the ACMG framework. Variants classified as likely benign or benign according to ACMG criteria were not considered in this study.

Results

In this study, we evaluated 34 patients diagnosed with FVII deficiency. Clinical and molecular analysis results are summarized in Table 1. The cohort included 15 females and 19 males, aged between 6 and 24 years. Based on Factor VII levels, 7 patients had FVII levels <10%, 3 patients had FVII levels between 10–20%, and 24 patients had FVII levels >20%.

Bleeding symptoms varied among the patients. Eighteen patients presented with at least one of the following symptoms: easy bruising (EB), epistaxis (EP), gum

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Table 1 **Clinical details and *F7* sequence analysis results of the patients with FVII deficiency**

No	Gender	Consanguinity	Age	Menstruation	Bleeding manifestation	ISTH-BAT score	Medical intervention for bleeding	Surgery without FVII replacement	Surgery with FVII replacement	FVII prophylaxis	INR	FVII level (% activity)	*F7* NM_000131.4 variants	Zygosity
1	F	No	15	Normal	Asy	0	No	No	Yes, no AB	No	1.5	23	c.1123C>T (p.Arg375Trp) c.1151C>T (p.Thr384Met)	Compound het
2	M	No	14	–	GI, EP, GB	16	Yes	No	Yes, no AB	No	4.46	4.7	c.1061C>T (p.Ala354Val)	hom
3	F	Yes	7	–	JS	3	Yes	No	No	Three times a week	5.1	2	c.1256C>T (p.Thr419Met)	hom
4	F	Yes	13	–	Asy	0	No	No	No	No	1.76	10	**c.728T>C (p.Ile243Thr)**	hom
5	M	Yes	24	–	JS, GB, IC, IB	24	Yes	No	Yes, no AB	Three times a week	5.9	4.2	c.430+1G>A	hom
6	M	Yes	11	–	EP	1	No	No	No	No	2.44	5	c.911C>T (p.Ala304Val).	hom
7	F	Yes	13	MN	EP	1	Yes	No	No	No	NA	1,1	c.1256C>T (p.Thr419Met)	hom
8	M	Yes	10	–	Asy	0	No	No	Yes, no AB	No	1.33	24	**c.-5_-4delTCinsCA**	het
9	M	No	13	–	Asy	0	No	No	No	No	1.41	32	c.1025G>A (p.Ser342Asn)	het
10	F	No	8	–	EB	5	No	No	Yes, no AB	No	1.47	35	c.1295G>A (p.Ala429Thr)	het
11	M	No	11	–	EP, UCP	3	No	No	Yes, no AB	No	1.29	36	**c.728T>A (p.Ile243Asn)**	het
12	F	No	10	–	EP	1	No	No	No	No	1.6	17	c.715G>A (p.Gly239Arg)	het
13	M	No	21	–	Asy	0	No	No	Yes, no AB	No	1.9	20	**c.733delA (p.Thr245ProfsTer20)**	het
14	M	NA	9	–	NA	NA	NA	NA	NA	NA	NA	22	c.911C>T (p.Ala304Val)	het
15	M	NA	9	–	NA	NA	NA	NA	NA	NA	NA	41	c.973G>A (p.Glu325Lys)	het
16	M	No	14	–	EB	1	No	No	No	No	1.48	15	c.469G>A (p.Gly157Ser)	het
17	M	Yes	19	–	EB	1	No	No	No	No	1.23	32	c.911C>T (p.Ala304Val).	het
18	M	NA	10	–	Asy	0	No	No	Yes, no AB	No	1.56	41	c.911C>T (p.Ala304)	het
19	F	No	20	Normal	Asy	0	No	No	No	No	NA	21.8	**c.686T>C (p.Leu229Pro)**	het
20	F	No	12	NA	NA	NA	NA	NA	NA	NA	NA	31.4	c.1151C>T (p.Thr384Met)	het
21	F	No	19	NA	NA	NA	NA	NA	NA	NA	NA	46	c.1109G>T (p.Cys370Phe)	het
22	M	No	13	–	NA	NA	NA	NA	NA	NA	NA	34.4	c.1151C>T (p.Thr384Met).	het
23	F	No	19	Normal	EB	1	No	No	No	No	1.23	32	c.911C>T (p.Ala304Val).	het
24	F	No	10	–	Asy	0	No	No	Yes, no AB	No	1.56	41	c.911C>T (p.Ala304Val)	het
25	F	Yes	15	MN	GI, ICB, EP, MN	19	Yes	No	Yes, no AB	Two times a week	5.41	2	Normal	
26	F	Yes	13	MN	ICB	5	Yes	Yes	No	No	2	6.9	Normal	
27	M	No	14	–	EB, EP, GB	3	Yes	No	No	No	1.46	27	Normal	
28	M	Yes	11	–	EB, PCB	4	No	Yes, PCB	No	No	1.28	41	Normal	
	M	No	15	–	EB	1	No	No	No	No	1.3	28	Normal	
30	M	No	16	–	Asy	0	No	No	Yes, no AB	No	1.35	38	Normal	
31		No	7	–	Asy	0	No	No	Yes, no AB	No	1.2	47	Normal	
32	F	No	19	Normal	Asy	0	No	No	No	No	1.4	29	Normal	
33	M	No	6	–	EP	1	No	Yes, no AB	No	No	1.15	48	Normal	
34	M	NA	15	–	EB	1	No	No	No	No	1.31	28	Normal	

Novel variants are written in bold. INR and factor VII levels represent measurements taken at the time of genetic testing. AB, abnormal bleeding; Asy, asymptomatic; EB, easy bruising; EP, epistaxis; F, female; GB, gum bleeding; GI, gastrointestinal; Het, heterozygous; Hom, homozygous; IB, intramuscular bleeding; ICB, intracranial bleeding; INR, international normalized ratio; JS, joint swelling; M, male; MN, menorrhagia; PCB, postcircumcision bleeding; UCP, umbilical cord bleeding.

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Table 2 Genetic variants identified in the *F7* gene in patients with factor VII deficiency

F7 (NM_000131.4) variants (novels in bold)	Exon	Mutation type	Pathogenicity	Affected domain
c.-5_-4delTCinsCA	P	Promoter	VUS	Regulatory region
c.430+1G>A	5	Splice	Pathogenic	Splice site
c.469G>A (p.Gly157Ser)	6	Missense	Likely Pathogenic	Gla domain
c.686T>C (p.Leu229Pro)	8	Missense	Likely Pathogenic	EGF-like domain
c.715G>A (p.Gly239Arg)	8	Missense	Pathogenic	EGF-like domain
c.728T>C (p.Ile243Thr)	8	Missense	Likely Pathogenic	EGF-like domain
c.733delA (p.Thr245ProfsTer20)	8	Frameshift	Likely Pathogenic	EGF-like domain
c.911C>T (p.Ala304Val)	9	Missense	Pathogenic	Serine protease
c.973G>A (p.Glu325Lys)	9	Missense	Likely Pathogenic	Serine protease
c.1025G>A (p.Ser342Asn)	9	Missense	Likely Pathogenic	Serine protease
c.1061C>T (p.Ala354Val)	9	Missense	Pathogenic	Serine protease
c.1109G>T (p.Cys370Phe)	9	Missense	Pathogenic	Serine protease
c.1123C>T (p.Arg375Trp)	9	Missense	Likely Pathogenic	Serine protease
c.1151C>T (p.Thr384Met)	9	Missense	Pathogenic	Serine protease
c.1295G>A (p.Ala429Thr)	9	Missense	Likely Pathogenic	Serine protease
c.1256C>T (p.Thr419Met)	9	Missense	Pathogenic	Serine protease

VUS, variant of unknown significance

bleeding (GB), gastrointestinal bleeding (GI), joint swelling (JS), intracranial bleeding (ICB), intramuscular bleeding (IB), menorrhagia (MN), umbilical cord bleeding (UCP), and postcircumcision bleeding (PCB). Eleven patients were asymptomatic, and bleeding history was not available for five patients. All asymptomatic patients had FVII levels $\geq$10%. Among the patients with FVII levels <10%, six out of seven required medical intervention for bleeding events at healthcare facilities, and three were using prophylactic FVII replacement therapy. None of the patients in this study was found to have inhibitors.

Based on the *F7* gene sequence analysis results, biallelic pathogenic variants were identified in seven patients (20.6%): five with FVII levels <10%, one with FVII levels between 10% and 20%, and one with FVII levels >20%. Monoallelic variants were detected in 17 patients (50.0%), including 2 with FVII levels between 10% and 20% and 15 with FVII levels >20%. In 10 patients (29.4%), including 2 with FVII levels <10% and 8 with FVII levels >20%, no pathogenic variants were identified in the *F7* gene sequence analysis.

F7 gene sequence analysis identified a total of 16 different variants, including 14 missense, 1 frameshift, 1 splice, and 1 promoter mutation. Among these, four variants (c.-5_-4delTCinsCA, c.686T>C (p.Leu229Pro), c.728T>C (p.Ile243Thr), and c.733delA (p.Thr245ProfsTer20)) were novel. The most frequently identified variant was c.911C>T (p.Ala304Val), detected in seven alleles. The majority of the variants were located in exon 9, and their pathogenicity classification was performed according to ACMG guidelines. The affected protein domains, including the serine protease domain, EGF-like domains, and Gla domain, were also determined. These findings are summarized in Table 2.

Discussion

This study presents a comprehensive analysis of the clinical and molecular features of 34 patients diagnosed with FVII deficiency, a rare autosomal recessive bleeding disorder. Our findings highlight the significant heterogeneity in clinical presentation and molecular etiology associated with this condition. The clinical spectrum in our cohort ranged from asymptomatic cases to severe bleeding episodes, including gastrointestinal bleeding, hemarthrosis, and intracranial hemorrhage. This variability aligns with previous studies emphasizing the unpredictable nature of FVII deficiency and the lack of correlation between FVII activity levels and bleeding severity [3,5,6].

Interestingly, all asymptomatic patients in our study had FVII levels above 10%, suggesting a potential threshold below which clinical symptoms are more likely to manifest. This aligns with Sharma *et al.*, who reported that severe bleeding tendencies were primarily observed in patients with FVII levels below 10% [6].

Genotypic and phenotypic correlations in factor VII deficiency

Although *F7* gene variant distribution data for many countries and regions worldwide have been reported [5,13,16–18], no studies have specifically analyzed variant distribution and genotype–phenotype relationships in Turkish FVII deficiency cases. Halimeh *et al.* conducted a large-scale genotype–phenotype study involving 785 unrelated White women with congenital FVII deficiency, demonstrating significant phenotypic variability [5]. Preisler *et al.* performed a comprehensive genetic analysis of 704 unrelated patients, identifying a wide range of pathogenic variants and emphasizing the importance of copy number variations (CNVs) and large deletions, which are often overlooked in routine genetic screening [13]. Pshenichnikova *et al.* analyzed 31 Russian patients, identifying five novel *F7* variants and highlighting the role of polymorphisms (rs5742910, rs6046) in modulating FVII activity, which may contribute to phenotypic variability even in individuals without pathogenic mutations [17]. Quintavalle *et al.* conducted a large genotype–phenotype study on 123 unrelated Italian patients, emphasizing regional differences in variant distribution [18].

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Research on variant distribution in the *F7* gene and associated databases indicates that single nucleotide variants (missense, nonsense, small insertions and deletions, and splice site variants) detectable by sequence analysis are responsible for most cases of FVII deficiency [13,17]. Studies analyzing global and population-specific distributions of *F7* variants have highlighted geographical differences and founder effects in certain regions [16].

Missense variants constituted 62% of the identified variants in Quintavalle *et al.*'s study [18]. Similarly, Preisler *et al.* found that missense variants were the most frequently observed type, comprising 71% of identified variants among 704 unrelated FVII deficiency patients [13]. In our study, missense variants were the most common type, accounting for 81.3% (13/16) of all identified variants.

Pathogenic *F7* variants were distributed throughout the gene, suggesting that each protein domain plays a crucial functional role. However, pathogenic variants were most commonly found in the serine protease domain, followed by the EGF-like and Gla domains, consistent with previous studies emphasizing the functional importance of these regions [13,17]. Studies have demonstrated that serine protease domain mutations tend to have stronger phenotypic consequences due to their direct role in enzymatic activity, whereas EGF-like and Gla domain variants may lead to milder phenotypes, as they primarily affect cofactor interactions and calcium binding [16].

A relatively large number of novel *F7* variants have been described in FVII deficiency studies worldwide. Shahbazi *et al.* identified 4 novel variants among 8 different *F7* gene variants in an Iranian cohort [19]. Similarly, in a study from Pakistan, 5 out of 10 variants were novel [20]. In a larger multinational study, Quintavalle *et al.* reported that 20 out of 48 variants were novel [18].

In our study, one-fourth of the identified *F7* variants (4 out of 16) were novel, including c.-5_-4delTCinsCA, c.686T>C (p.Leu229Pro), c.728T>C (p.Ile243Thr), and c.733delA (p. hr245ProfsTer20). Among these, c.728T>C (p. Ile243Thr) was found in homozygous form in Patient 4, a 13-year-old girl who had not yet started menstruation. Despite having a FVII level of 10%, she exhibited no bleeding symptoms, reinforcing the lack of a strict correlation between FVII levels and clinical phenotype. The other novel variants were detected in a heterozygous state, with FVII levels ranging from 20% to 36%, and all heterozygous patients remained asymptomatic.

Monoallelic variants were detected in 17 patients (50.0%), including two with FVII levels between 10% and 20% and 15 with FVII levels >20%. This is consistent with Quintavalle *et al.*, who reported that most patients with heterozygous variants were either asymptomatic or had mild symptoms. In contrast, homozygous or compound heterozygous variants were more frequently associated with severe phenotypes [18]. Preisler *et al.* similarly found that homozygous or compound heterozygous variants were predominantly associated with severe FVII deficiency (FVII:C <10 IU/dl), whereas heterozygous variants were more common in patients with mild or moderate deficiency [13]. In our cohort, 10 out of 34 patients (29.4%) had documented parental consanguinity. Among the six patients with homozygous variants, five had consanguineous parents, reinforcing the role of consanguinity in the inheritance of FVII deficiency.

Large deletions in FVII deficiency have been reported in the literature, but they are rare. Quintavalle *et al.* identified large deletions in 6.2% of cases, many of which were previously unreported. Their study also demonstrated that the lowest FVII levels and most severe phenotypes were observed in patients with truncated variants [18]. Similarly, Hewitt *et al.* described a patient with severe FVII deficiency who carried a single nucleotide variant on one allele and an *F7* gene deletion on the other allele. Interestingly, standard sequencing misclassified the variant as homozygous, while segregation analysis later revealed that a large deletion was responsible for the severe phenotype [21]. These findings highlight the importance of screening for large deletions in FVII-deficient patients with homozygous single nucleotide variants and severe bleeding symptoms, as failure to detect these variants may lead to misclassification and misdiagnosis [22].

Despite comprehensive sequencing, a significant proportion of FVII-deficient patients do not have detectable pathogenic variants. Quintavalle *et al.* found no identifiable *F7* variants in 42% of patients with FVII deficiency [18]. Similarly, in our study, we could not identify pathogenic variants in 10 out of 34 cases (29.4%), including 2 patients with FVII levels <10% and 8 with FVII levels >20%. The unexpectedly low FVII level (6.9%) in one patient, despite no detectable *F7* gene variant, suggests that other mechanisms may be involved. One possibility is the presence of deep intronic variants that create cryptic splice sites, which are undetectable by standard sequencing techniques. Another possibility is the presence of large deletions or copy number variations (CNVs), which require multiplex ligation-dependent probe amplification (MLPA) or quantitative PCR (qPCR) for detection. Preisler *et al.* emphasized the role of CNVs and large deletions in severe FVII deficiency, underscoring the need for comprehensive structural variant analysis in genetic screening [13]. Additionally, regulatory region mutations affecting *F7* gene expression, which were not evaluated in our study, could explain these findings. Another consideration is that genes beyond *F7* might be responsible for FVII deficiency in these cases, as suggested by Preisler *et al.*, who proposed that variants in other coagulation-related genes could contribute to unexplained FVII deficiencies [13]. Lastly, acquired FVII deficiency remains a potential factor in some

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cases, though no clear evidence of an acquired etiology was detected in this study. Furthermore, it is well documented that common *F7* polymorphisms, particularly rs5742910 and rs6046, can influence FVII activity levels, even in individuals without pathogenic variants. Pshenichnikova *et al.* demonstrated that these polymorphisms play a role in modulating FVII activity and may contribute to phenotype variability in individuals with FVII deficiency [17].

Limitations and future directions

This study has several limitations. First, it is retrospective, and data were collected from medical records, which may introduce selection bias. Second, the sample size is relatively small, limiting the generalizability of findings. Third, our sequencing approach did not include gene-internal CNVs or large deletions, which require additional methods such as MLPA or qPCR for detection.

Additionally, Preisler *et al.* highlighted that large deletions in *F7* are often overlooked, yet can result in severe phenotypes [13]. Future studies should incorporate MLPA, qPCR, and whole-genome sequencing (WGS) to capture structural variants and deep intronic mutations. Moreover, we did not systematically evaluate common *F7* polymorphisms (rs5742910, rs6046), which have been shown to modulate FVII levels and influence clinical phenotype [5,17]. Further research incorporating genome-wide analyses and functional assays will enhance our understanding of disease severity and diagnostic accuracy.

Conclusion

Despite its limitations, our study provides valuable insights into the genetic spectrum of FVII deficiency in the Turkish population. By identifying four novel *F7* variants, we contribute to the growing understanding of genotype-phenotype correlations. Future research integrating MLPA, WGS, and functional studies will improve genetic diagnostics and clinical management, ultimately enhancing the quality of life for individuals with FVII deficiency.

Acknowledgements

None.

Author contributions: T.A., B.D.O., E.I., F.O.: conception and design, acquisition of data, analysis and interpretation of data, writing original draft. E.A.D., N.S., C. A., A.K., M.S.E., M.A., D.A., F.T.K., G.T.K., E.U., A.O., K.K.: acquisition of data, analysis and interpretation of data. T.A., F.O.: manuscript revising.

Funding: No specific funding.

Conflicts of interest

The authors declare no competing interests.

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