CASE REPORT

Congenital Factor XI deficiency in an elderly Japanese male accompanied by nonsense mutation p.Trp519* and novel missense mutation p.Ile618Phe

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Abstract : Objective : In the present study, we identified a genetic mutation in a patient with asymptomatic congenital Factor XI (FXI) deficiency, with an FXI activity of <1%. The mutation was accidentally discovered when the patient was 80 years old. Methods : We performed genome sequencing (GS) on using a whole blood sample from the patient. The nucleotide sequences obtained were compared to the FXI reference GS and mutations were assessed using BioEdit. Results : Notably, exon 14 was not amplified ; therefore, all other exons were analyzed. Four heterozygous nucleotide mutations were noted : c.1556G>A, c.1812G>T, c.1839G>A, and c.1852A>T ; c.1556G>A and c.1852A>T were associated with amino acid substitutions p.Trp519* and p. Ile618Phe, respectively. Some cases of the amino acid substitution p.Trp519* have been registered in the database ; however, to the best of our knowledge, p.Ile618Phe was likely discovered for the first time in this study. Conclusion : Because both gene mutations were heterozygous, the patient had compound heterozygous mutations that decreased FXI activity. J. Med. Invest. 73 : 281-285, February, 2026

Keywords **:** *congenital Factor XI deficiency, compound heterozygous, old age onset*

INTRODUCTION

Factor XI (FXI) is a coagulation factor that is involved in hemostasis. FXI is converted to activated FXI (FXIa) by activated Factor XII (FXIIa) and its cofactor, a high-molecular-weight kininogen, *in vivo*. FXIa converts Factor IX (FIX) to activated FIX (FIXa) in the presence of Ca2+ (1). FXI is a homodimer consisting of two subunits linked by disulfide bonds, with one subunit containing 607 amino acid residues and a molecular weight of approximately 80 kDa (2). Each monomer has four apple domains comprising 90 or 91 amino acid residues, with a serine protease domain at the C-terminal (2). The FXI gene *F11* located on chromosome 4q35 has a total length of approximately 23 kb and contains 15 exons (3). FXI deficiency, also known as Rosenthal disease, occurs because of mutations or deletions in the *F11* gene. This disease was first described in 1953 by Rosenthal in a family experiencing bleeding related to surgery and dental procedures (4).

The prevalence of severe FXI deficiency is estimated to be approximately 1 in 1 million individuals ; however, it is more prevalent in the Ashkenazi and Iraqi Jewish populations, where heterozygosity approaches 1 in 11 individuals (8–9%). Notably, homozygosity or compound heterozygosity is observed in 1 in 450 individuals (0.2%) (5). Clinically, FXI deficiency is often asymptomatic, whereas mild to moderate bleeding is be observed in some instances. Here, we report a case of congenital FXI deficiency that was accidentally discovered in an elderly patient. Genetic analysis revealed a nonsense mutation (p.Trp519*) and a novel missense mutation (p.Ile618Phe), indicating a compound heterozygous state. This study expands the spectrum of known *F11* mutations and highlights the importance of genetic analysis in diagnosing FXI deficiency, particularly in asymptomatic individuals. This study was approved by the Ethics Committee of the Tokushima University Hospital (approval numbers : 3767-3 and 4659).

Received for publication August 5, 2025 ; accepted December 11, 2025.

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CASE PRESENTATION

An 80-year-old male visited our hospital for a detailed examination of a right lung tumor. He had a history of atrial fibrillation and was administered warfarin. Initially, no bleeding was observed when warfarin was administered. Subsequently, the patient visited the hospital with persistent bloody sputum and nosebleeds. Incidentally, he had stopped taking warfarin at this time. He was eventually diagnosed with squamous cell carcinoma of the lung through transbronchial lung biopsy ; however, pre-procedural examination showed a significant prolongation of activated partial thromboplastin time (APTT). According to the patient, this was the first time he had realized that his APTT had been prolonged. Table 1 lists the examination data at the time of referral. ADVIA2120i (Siemens Healthcare Diagnostics) was used for hematologic tests, STACIA (PHC Holdings Corporation) for coagulation tests, ACL-TOP500 (Instrument Laboratory Co., Ltd.) for coagulation factor activity tests and cross-mixing tests (CMT), and LABOSPECT 008 (Hitachi High-Tech Co., Ltd.) for biochemistry tests.

Initially, we suspected acquired hemophilia because of the advanced age of the patient as well as the malignant tumor. However, most coagulation factor activities were normal, except for FXI activity (<1%) ; therefore, either congenital or acquired

FXI deficiency was suspected. Based on the CMT results, the immediate response showed a factor deficiency pattern, with no change after 2 h of incubation (Figure 1). Therefore, we concluded that the patient had congenital FXI deficiency.

To confirm the diagnosis of congenital FXI deficiency, we performed genome sequencing (GS) using a whole blood sample. Primers were designed for each of the 15 exons and exon-intron boundaries of the FXI gene *F11* (Supplementary Table S1). The QIAamp DNA Blood Mini Kit (Qiagen N. V.) was used to extract DNA according to the manufacturer's instructions and samples were sent to Macrogen Japan Co., Ltd. for DNA sequencing. A DNA Engine Dyad PTC-220 Peltier Thermal Cycler (Bio-Rad Laboratories, Inc.) and KOD one PCR master mix (TOYOBO Co., Ltd.) were used for PCR, and a 3730xl DNA Analyzer (Thermo Fisher Scientific, Inc.) and BigDye Terminator v3.1 cycle sequence kit (Thermo Fisher Scientific, Inc.) were used for sequencing. The PCR conditions were as follows : the sample was first heated at 94 ℃ for 30 s, then 35 cycles of 30 s at 94 ℃, 30 s at 55–57 ℃, and 30–60 s at 72 ℃ were repeated, and finally heated at 72 ℃ for 60 s. The nucleotide sequences obtained were compared to the FXI reference genome sequence (Accession number : NG_008051.1) and mutations were assessed using BioEdit (ver. 7.2.5). FXI mutations were also reviewed in the European Association for Haemophilia and Allied Disorders Coagulation Factor Variant Database (EAHAD-CFDB : https://dbs.eahad.org/). Notably, exon 14 was not amplified ; therefore, all other exons were analyzed. Four heterozygous nucleotide mutations were noted : c.1556G>A in exon 13 and c.1812G>T, c.1839G>A, and c.1852A>T in exon15 (Figure 2). The c.1812G > T and c.1839G > A mutations observed in exon 15 were not accompanied by amino acid substitutions. In contrast, c.1556G>A in exon 13 is a nonsense heterozygous mutation that changes a tryptophan residue to a stop codon (p.Trp519*). Furthermore, c.1852A>T in exon 15 is a missense heterozygous mutation with an amino acid substitution from an isoleucine to a phenylalanine residue (p.Ile618Phe).

DISCUSSION

Congenital FXI deficiency can be divided into type 1, where both FXI activity and antigen levels are reduced, or type 2, where only the activity level is reduced. When conducting our study, 1275 cases and 403 unique *F11* gene variants were registered in the EAHAD-CFDB. Approximately half of the patients with congenital FXI deficiencies were type 1, with genetic mutations

Table 1. Laboratory data

【CBC】			【Coagulation】		
WBC	5100	/μL	PT	13.1	sec
RBC	3.29	$\times10^6$/μL	PT-INR	1.06	
Hb	9.4	g/dL	APTT	69.6	Sec
HCT	28.3	%	Fib activity	543	mg/dL
MCV	86.2	fL	FVIII activity	>150.0	%
PLT	220	$\times10^3$/μL	FIX activity	124.3	%
seg	80.0	%	FXI activity	<1	%
lymph	16.0	%	FXII activity	99.9	%
mono	2.0	%	vWF activity	233	%
eosino	2.0	%	dRVVT	1.2	
baso	0.0	%	FXIII activity	116	%

【Biochemistry】					
AST	22	U/L	AMY	91	U/L
ALT	12	U/L	Na	140	mmol/L
LDH	200	U/L	K	4.7	mmol/L
ALP	111	U/L	Cl	106	mmol/L
γ-GT	33	U/L	Ca	9.2	mg/dL
T-bil	0.4	mg/dL	IP	3.6	mg/dL
TP	7.2	g/dL	CRP	1.59	mg/dL
BUN	31	mg/dL	BSC	106	mg/dL
Cre	1.99	mg/dL	SCC antigen	6.19	ng/mL
IgG	1317	mg/dL	SLX antigen	38.1	U/mL
IgM	80	mg/dL	NSE	26.4	ng/mL
IgA	308	mg/dL	ANA	(-)	

Abbreviation
PT : prothrombin time, APTT : activated partial thromboplastin time, dRVVT : dilute Russell's viper venom time, BSC : blood sugar concentration, SCC antigen : squamous cell carcinoma antigen, SLX antigen : sialyl lewis X antigen, NSE : neuron-specific enolase, ANA : anti-nuclear antibody.

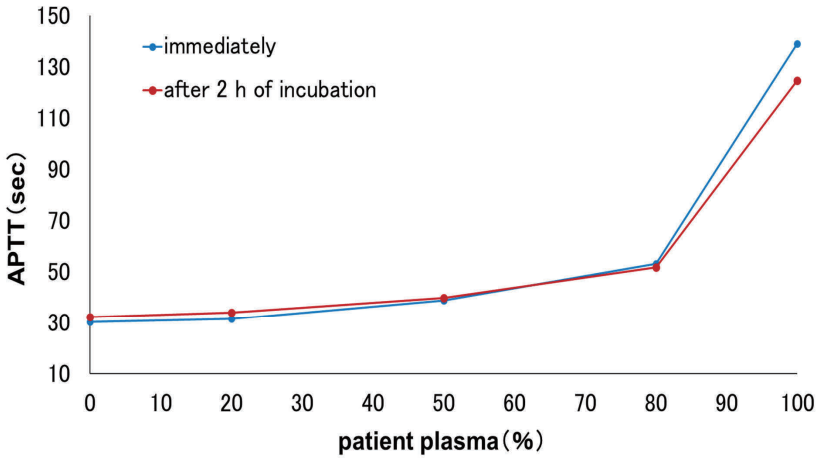

Figure 1. Cross-mixing test. A cross-mixing test was conducted using patient and control plasma at different concentrations : 0%, 20%, 50%, 80%, and 100%. In 100% plasma, the APTT measured after 2 hours of incubation was shorter than that of the immediate measurement. We speculate that this may be because of the lack of contact factors such as FXI, FXII, and prekallikrein, which destabilizes coagulation factor activation by influencing the first reagent of APTT, resulting in variable APTT.

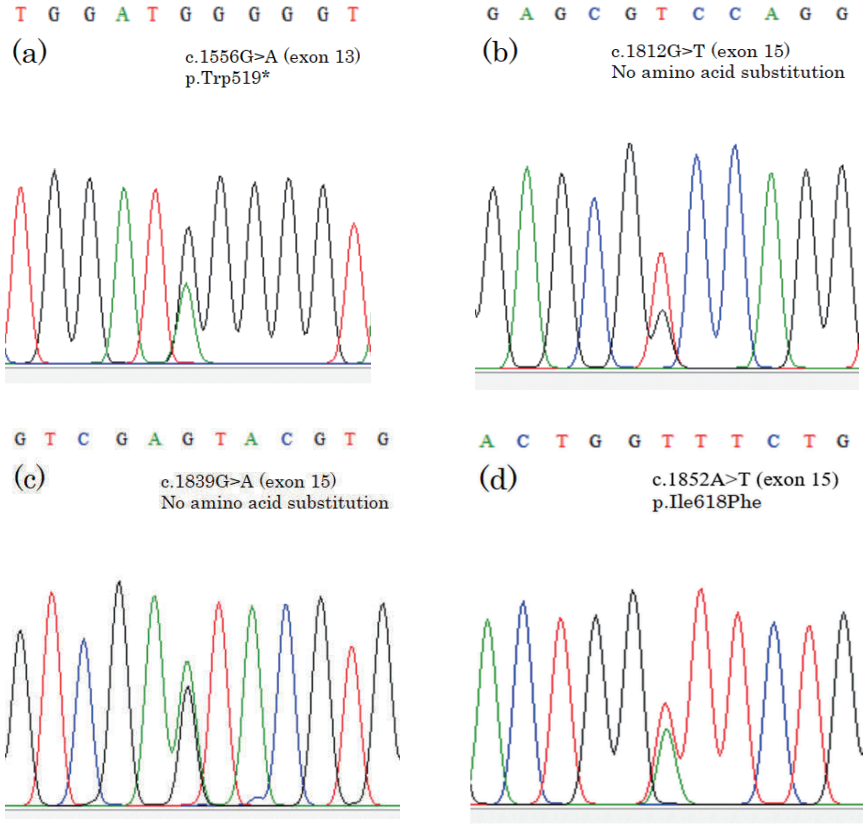

Figure 2. Mutations identified in the *F11* gene of the patient. (a) c.1556G>A., (b) c.1812G>T., (c) c.1839G>A, and (d) c.1852A>T.

found in various regions of the *F11* gene. In contrast, the frequency of type 2 was significantly low, and mutations associated with type 2 tended to be concentrated in the serine protease domain. Glu135*, which is present in the A2 domain, is the most commonly reported mutation ; however, it is classified as type 1 and not type 2 (6, 7). The mutation p.Trp519*, which was observed in our patient, has been reported in 25 cases of EAHAD-CFDB (Supplementary Table S2). In all cases, FXI activity was low in both homozygous and compound heterozygous mutations. In contrast, in the case of a single patient with a heterozygous mutation, the decrease in FXI activity was not significant, with some patients showing no decrease. Although a few cases exist in which FXI antigen levels were measured, these levels decreased in all cases. Notably, the presence or absence of bleeding in patients was unrelated to FXI activity or antigen levels. This is speculation because we were unable to measure FXI antigen

levels ; however, based on previous reports, we considered that this case may correspond to be type 1.

Exon 13 is located at the C-terminus of FXI that is a serine protease domain (2). The three amino acids, His413, Asp462 and Ser557, are responsible for serine protease activity (2). As all amino acids downstream from position 519 are not translated in p.Trp519*, the phenotype is presumed to occur due to loss of serine protease activity. The association between clinical symptoms and this mutation is not well understood, and in some cases, homozygous patients did not exhibit bleeding (8-10). However, in other cases, heterozygous patients showed moderate bleeding symptoms even with 64% FXI activities (11). In the present case, the patient experienced bloody sputum and nosebleeds leading up to the initial visit, and was diagnosed with anemia following tests. We suspected that these symptoms are because of his underlying lung tumor and are unlikely to be related to the decrease in FXI activities. Moreover, the anemia was also considered to be because of his advance age and persistent bloody sputum and nosebleeds. However, the highly elevated von Willebrand Factor (vWF) and Factor VIII (FVIII) activities exhibited by the patient may compensate for the reduced hemostatic ability resulting from decreased FXI activities.

The p.Ile618Phe mutation observed in exon 15 is a novel mutation that has not been recorded in the EAHAD-CFDB. However, two other amino acid substitutions at the same position as this mutation have been reported. First, Micheal *et al*. described gene mutation c.1853T>G and the resulting amino acid substitution p.Ile618Ser (12). This study referred to both homozygous and heterozygous mutations, with FXI activities of <2% in homozygous and <23% in heterozygous patients, respectively. The antigen levels of FXI and patient bleeding symptoms are unknown. Second, gene mutation c.1853T>C and the resulting amino acid substitution p.Ile618Thr was reported. Although this mutation is registered in the EAHAD-CFDB, the reference is unknown, and details such as FXI activities and antigen levels are unknown. In addition, other amino acid substitutions, such as homozygous p.Trp617Arg (13) and compound heterozygous p.Leu619Pro (with p.Gln47Pro) (14), which occur at positions close to p.Ile618Phe, have been reported. The homozygous mutation p.Trp617Arg decreased both FXI activities and antigen levels to <1%, and compound heterozygous mutations p.Gln47Pro and p.Leu619Pro decreased FXI activities to 2% and antigen levels to <5%. Considering these reports, because p.Trp519* and p.Ile618Phe mutations are heterozygous, it is unlikely that they would significantly decrease FXI activities and antigen levels on their own. However, in the present case, we believe that FXI activities were decreased to <1% because of compound heterozygous p.Trp519* and p.Ile618Phe. These mutations were considered to be congenital ; therefore, we offered genetic investigation to the daughter of the patient. However, we were unable to obtain her consent and genetic investigation could not be performed.

In conclusion, we encountered a case of congenital FXI deficiency with p.Trp519* and p.Ile618Phe mutations that likely reduced the FXI activities of the patient.

CONFLICT OF INTEREST

There are no conflicts of interest to declare.

PATIENT CONSENT STATEMENT

Written informed consent was obtained from the patient for the publication of this paper.

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Supplementary Table S1. used primers for mutation regions

Target	Forward primer	Rverse primer
exon 13	CCTGAGGGAGGAAAATACACG	AAAGGTTCCGCTCTTCATTTCTA
exon 15	CTGAAGATGGGAAGCGTCTG	TTGGACTCCATAGAAGCGTGA

Supplementary Table S2. pTrp519* mutations in EAHAD-CFDB

		activity (%)	Ag levels (%)	clinical severity	additional variants
1	Homozygous	<5	<1	Asymptomatic	
2	Heterozygous	22	26	Not reported	p.Gly235Ser
3	Heterozygous	None	None	Not reported	
4	Heterozygous	2	None	Asymptomatic	p.Gln244*
5	Heterozygous	64	None	Moderate	
6	Heterozygous	34	None	Mild	
7	Heterozygous	36	None	Moderate	
8	Homozygous	2	1	Asymptomatic	
9	Heterozygous	53	None	Not reported	
10	Heterozygous	53	None	Not reported	
11	Heterozygous	2	None	Asymptomatic	p.Arg326His
12	Heterozygous	6	None	Mild	p.Phe301Leu
13	Heterozygous	114	None	Asymptomatic	
14	Heterozygous	47	None	Asymptomatic	
15	Heterozygous	7	None	Mild	p.Glu315Lys
16	Heterozygous	36	None	Asymptomatic	
17	Heterozygous	28	None	Moderate	
18	Heterozygous	38	None	Asymptomatic	
19	Homozygous	6	None	Asymptomatic	
20	Heterozygous	59	None	Asymptomatic	
21	Heterozygous	20	6	Not reported	
22	Heterozygous	55	None	Not reported	
23	Heterozygous	<1	None	Moderate	p.Glu341Lys
24	Heterozygous	<1	None	Mild	p.Asp526Glnfs*27
25	Heterozygous	2	None	Mild	c.1136-4delGTTG