

# A Novel Homozygous Missense Mutation (Ile583Asn) in a Consanguineous Marriage Family with Hereditary Factor XII Deficiency: A Case Report

Shuting Jiang<sup>1</sup> Yuan Chen<sup>1</sup> Haixiao Xie<sup>1</sup> Meina Liu<sup>1</sup> Xiaoyong Zheng<sup>1</sup> Mingshan Wang<sup>1</sup>

<sup>1</sup>Department of Clinical Laboratory, Key Laboratory of Clinical Laboratory Diagnosis and Translational Research of Zhejiang Province, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China

**Address for correspondence** Mingshan Wang, MD, Department of Clinical Laboratory, Key Laboratory of Clinical Laboratory Diagnosis and Translational Research of Zhejiang Province, The First Affiliated Hospital of Wenzhou Medical University, Shangcai Village, Ouhai District, Wenzhou 325000, China (e-mail: wywms@126.com).

Hamostaseologie 2023;43:142–145.

## Abstract

**Background** Hereditary coagulation factor XII (FXII) deficiency is an autosomal recessive disorder. At present, the contribution of severe FXII deficiency to the development of thromboembolism is still undetermined. There are limited reports on the relationship between the FXII defect and thromboembolism.

**Case Presentation** A 27-year-old woman came to our hospital for the treatment of shoulder trauma and cervical disc herniation caused by a car accident. The shoulder trauma was treated with five stitches. After physical examination, imaging examination, and routine coagulation examination, cervical disc herniation was treated conservatively. Combined with the examination results, the patient was diagnosed with FXII deficiency. Unfortunately, the patient was readmitted 10 days after the trauma with edema in the lower limbs and secondary varicose veins. The D-dimer increased to 6.22 mg/L. Thrombus in the inferior vena cava and right common iliac was shown by lower limb venography. According to the patient's medical history, the *F12* gene was analyzed by direct sequencing. The patient was also screened for other thrombotic risk factors. Genetic analysis showed that the patient had a c.1748T > A (p.Ile583Asn) homozygous missense mutation in exon 14 of the *F12* gene. No other hereditary thrombophilia risk factors screened were positive in the patient.

**Conclusion** The p.Ile583Asn missense mutation in exon 14 of the *F12* gene might be responsible for the reduction of the FXII level in the patient.

## Keywords

- ▶ factor XII deficiency
- ▶ gene mutation
- ▶ venous thromboembolism
- ▶ bioinformatics

## Introduction

Human coagulation factor XII (FXII), a serine protease precursor, is mainly synthesized by the liver and released into circulating plasma in the form of inactive zymogen.<sup>1</sup> The mature FXII protein contains 596 amino acid residues.<sup>2</sup> FXII precursor cleaves at R353-V354 and becomes activated FXII (FXIIa).<sup>3</sup> FXIIa plays a vital role in the fibrinolysis pathway,

complement activation, and inflammatory response.<sup>4</sup> Besides, extensive research has revealed that FXIIa has biological activity related to cell protection and repair.<sup>5</sup>

Hereditary FXII deficiency is an autosomal recessive disorder with abnormal FXII levels mainly caused by mutations in the *F12* gene.<sup>6</sup> Although it leads to a significantly prolonged activated partial thromboplastin time (aPTT) in vitro, patients do not show bleeding tendency.<sup>7</sup> Most

received  
July 18, 2022  
accepted after revision  
September 26, 2022

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Georg Thieme Verlag KG,  
Rüdigerstraße 14,  
70469 Stuttgart, Germany

DOI <https://doi.org/10.1055/a-1962-1490>.  
ISSN 0720-9355.

patients are accidentally discovered by health checks or preoperative coagulation screening tests.<sup>8</sup> Some research has found that the FXII defect may be related to diseases such as thrombosis and cerebral infarction.<sup>9</sup> Here, we report a novel mutation in a family with hereditary FXII deficiency.

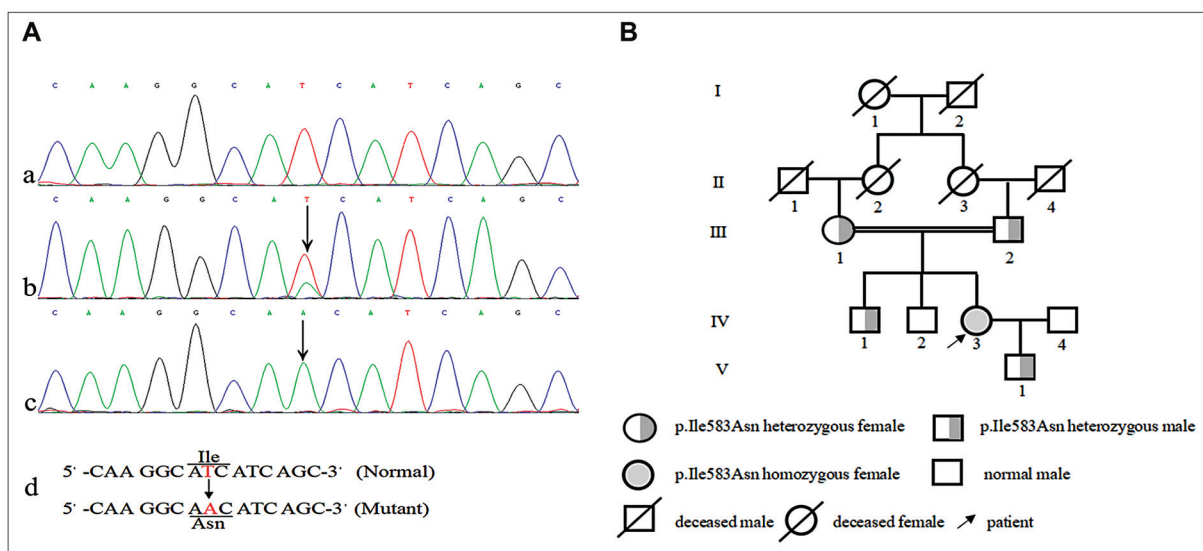
## Case Presentation

The 27-year-old female patient was prepared for treatment in our hospital due to shoulder trauma and cervical disc herniation caused by a car accident. The shoulder trauma was treated with five stitches, and there was no abnormal bleeding from the wound. Through physical examination, imaging examination, and routine coagulation examination, cervical disc herniation was treated conservatively after a comprehensive evaluation. It is worth noting that aPTT was significantly prolonged to 180 seconds (normal range: 29.0–43.0 seconds) by matched commercially available kits on the Stago-STA-R automatic coagulometer (Diagnostica Stago, France). The abnormal result of aPTT could be corrected by normal plasma. The lupus anticoagulant ratio was 1.02 (normal range: 0.80–1.20), which excluded the presence of lupus anticoagulant. Further examinations showed that FXII activity (FXII:C) and FXII antigen (FXII:Ag) decreased to 3 and 5%, respectively. Other coagulation indexes were in the normal range. The plasma plasminogen activity (PLG:A) was increased to 135% (normal range: 80–120%) by chromogenic substrate assay. Combined with the examination results, the patient was diagnosed with FXII deficiency. Unfortunately, the patient was readmitted 10 days after the trauma with edema in the lower limbs and secondary varicose veins. The D-dimer (D-D) was 6.22 mg/L (normal range: 0.00–0.50 mg/L), and the modified Wells DVT scale score was 2 points. Thrombus in the inferior vena cava and right common iliac was shown by lower limb venography. Low-molecular-weight heparin calcium of

0.4 mL (5,000 U) was injected subcutaneously every 12 hours. Six days later, the patient's general condition improved, and the treatment was changed to rivaroxaban 15 mg twice a day for 3 weeks. Then it was changed to 20 mg once a day for 3 months. During outpatient follow-up, the patient's general condition was good, with no bleeding or thrombotic events.

The patient delivered one fetus naturally at the age of 25 years. She was not pregnant during this visit to our hospital, did not take contraceptive pills, and had regular menstruation and normal blood pressure. The *F12* gene was analyzed by direct sequencing, considering the patient's medical history. At the same time, the patient was also screened for other thrombotic risk factors such as protein C activity (PC:A), protein S activity (PS:A), antithrombin activity (AT:A), factor V Leiden mutation, and prothrombin G20210A mutation. Genetic analysis showed that the patient had a c.1748T > A (p.Ile583Asn) homozygous missense mutation in exon 14 of the *F12* gene (–Fig. 1A). No other hereditary thrombophilia risk factors screened were positive in the patient. After reviewing the literature and Human Gene Mutation Database (<http://www.hgmd.cf.ac.uk/ac/index.php>), the p.Ile583Asn mutation has not yet been reported. The predicting consequences of online bioinformatics software of p.Ile583Asn mutation are pathogenic.

Seven family members of three generations were enrolled in this study (–Fig. 1B). Consanguineous marriage was confirmed. Other members had no history of abnormal bleeding or thrombosis. The phenotype of all family members is shown in –Table 1. Her mother (III<sub>1</sub>), father (III<sub>2</sub>), elder brother (IV<sub>1</sub>), and son (V<sub>1</sub>), who were heterozygote for p.Ile583Asn mutation, showed slightly prolonged aPTT and the level of FXII decreased to about half of the normal range. There were no abnormalities in the other indexes of the family members. One hundred healthy individuals aged 16 to 60 years were recruited as normal controls. Informed consent was signed by all the individuals.



**Fig. 1** The sequence diagrams of p.Ile583Asn mutation (A) and the family tree of inherited FXII deficiency (B). (a) The sequences of wild-type; (b) the sequences of heterozygote; (c) the sequences of homozygote; (d) comparison of wild-type and mutant amino acid sequences. The position of the mutant base is marked with an arrow.

**Table 1** Coagulation assay results of the family members

Family members	PT (S)	aPTT (S)	FIB (g/L)	FXII:C (%)	FXII:Ag (%)	Thromboembolic history
IV <sub>3</sub> (patient)	13.8	180	3.5	3	5	+
III <sub>1</sub>	13.1	87	2.7	52	58	–
III <sub>2</sub>	13.4	85	3.1	56	51	–
IV <sub>1</sub>	12.9	76	3.3	48	50	–
IV <sub>2</sub>	13.0	35	2.4	92	101	–
IV <sub>4</sub>	13.8	39	3.0	80	97	–
V <sub>1</sub>	13.5	75	3.2	45	44	–
Normal range	12.6–14.4	29.0–43.0	2.0–4.0	72–113	72–113	

Abbreviations: PT, prothrombin time; aPTT, activated partial thromboplastin time; FIB, fibrinogen; FXII:C, FXII activity; FXII:Ag, FXII antigen. Notes: The FVIII activity, FIX activity, and FXI activity of the family members were normal and not listed in the table.

## Discussion

The human *F12* gene is located in the 5q33-qter domain of the autosome, which spreads about 12 kb in size and includes 14 exons and 13 introns.<sup>10</sup> Congenital FXII deficiency can be divided into two types: The cross-reacting material–negative group (CRM<sup>−</sup>) is characterized by synchronously decreased FXII:C and FXII:Ag, whereas CRM-positive group (CRM<sup>+</sup>) has the feature of decreased activity but borderline-normal or normal antigen.<sup>11</sup> In this study, the FXII:C and FXII:Ag of the patient were significantly reduced simultaneously. Genetic analysis showed that the patient had a c.1748T > A homozygous missense mutation in exon 14 of the *F12* gene, which led to the replacement of isoleucine (ATC) with asparagine (AAC) at amino acid position 583 (p.Ile583Asn). In addition, none of the members had liver or kidney function abnormalities or other coagulation abnormalities. Thus, we preliminarily considered that the p.Ile583Asn mutation might be responsible for the reduction of FXII:C and FXII:Ag.

FXII is glycosylated at multiple sites (SwissProt entry P00748). The Thr309 is a putative O-linked glycosylation site.<sup>12</sup> In addition, the Asn230 and the Asn414 are two important N-linked glycosylation sites.<sup>13</sup> The heavy chain consists of 353 amino acid residues and carries six structural domains.<sup>14</sup> The light chain consists of 243 amino acid residues, with only one domain containing the H393-D442-S544 catalytic triad.<sup>14</sup> In this study, isoleucine is a nonpolar hydrophobic amino acid, and asparagine is a polar neutral amino acid. Moreover, the molecule of asparagine is larger than isoleucine, which may affect the charge situation and the molecular space conformation. Ile583 is located in the catalytic domain of the light chain. The mutation of Ile583 to Asn may affect the normal structure/function of the FXII protein.

According to the American College of Medical Genetics and Genomics (ACMG), the evidence of the pathogenicity of the c.1748T > A mutation in this family includes the following—(1) Strong evidence of pathogenicity (PS2): the patient has a new mutation and no family history. (2) Moderate evidence of pathogenicity (PM2): absent from controls in exome sequencing project, 1000 genomes or ExAC. (3)

Supporting evidence of pathogenicity (PP1): co-segregation with the disease in multiple affected family members in a gene definitively known to cause the disease. (4) Supporting evidence of pathogenicity (PP3): multiple lines of computational evidence support a deleterious effect on the gene or gene product. Combining the above variant evidence and classifications, the pathogenicity of the c.1748T > A mutation is most likely a pathogenic variant.

The genetic risk factors for thrombophilia include deficiency of AT, PC, or PS; factor V Leiden mutation; and prothrombin G20210A mutation.<sup>15</sup> Acquired thrombophilia risk factors include surgery, trauma, immobility, and indwelling catheter.<sup>16</sup> Early research suggested that the initiation of the endogenous coagulation pathway by FXIIa did not participate in physiological hemostasis and might be related to pathological thrombosis and cardiovascular disease.<sup>17</sup> Venous thromboembolism (VTE) is a multifactorial disease, involving interactions between inherited predispositions to thrombosis and acquired risk factors.<sup>18</sup> In our study, the patient's FXII level was significantly reduced, and plasma PLG:A was increased. The increase of PLG:A indicates that the fibrinolytic activity of the patient is reduced. For patients with recurrent VTE without obvious triggers or at a younger age, clinicians should pay attention to the general survey of anticoagulant proteins and coagulation factors and the detection of thrombus-related genes. If the presence of physiological defects is confirmed, the other family members should be further screened.

To sum up, we reported a novel homozygous missense mutation site (Ile583Asn) in the *F12* gene, which might be responsible for the reduction of the FXII level in the patient.

### Ethics Approval

Our study was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University (201217).

### Funding

This work was funded by the Project of Key Laboratory of Clinical Laboratory Diagnosis and Translational Research of Zhejiang Province (2022E10022) and the Project of

Wenzhou Public Welfare Science and Technology (Y2020110).

#### Conflict of Interest

The authors declare that they have no conflict of interest.

#### Acknowledgement

We are grateful to the patient and her family members for their cooperation.

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