



A New SNP locus c. 247 C > T of *F12* can Significantly Prolong aPTT: a Case Report

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Abstract

Factor XII deficiency is a rare condition of the coagulation system with autosomal-recessive inheritance. Affected patients are often asymptomatic and are diagnosed incidentally during preoperative investigations or during hospitalization on the basis of an isolated, prolonged activated partial thromboplastin time (aPTT). We report a 39-year-old female who was admitted to hospital for early artificial abortion and abnormal blood coagulation function. We found a novel nonsense mutation (c.247C>T, p. Gln83*) in one of the exon coding regions of the *F12* gene on chromosome 5 in a patient with a prolonged aPTT.

Keywords: Factor XII deficiency; aPTT-activated partial thromboplastin time; Hemostasis.

INTRODUCTION

Factor XII (Hageman factor) is a single chain glycoprotein (molecular mass of 80 kDa), that circulates in the blood in the inactive zymogen form. The *F12* gene is located at 5q33-qter, and contains 14 exons and 13 introns [1]. It encodes a single chain of 615 amino acids requiring post-translation modification for conversion to a mature 596-amino acid zymogen in the liver. Factor XII deficiency is a rare condition of the coagulation system with autosomal-recessive inheritance. Its exact prevalence is unknown as affected individuals are asymptomatic under normal conditions, but its incidence is estimated to be 1 in 1 million [2]. The condition is occasionally discovered in individuals with an isolated, prolonged activated partial thromboplastin time (aPTT) or during unexplained coagulopathy due to lack of bleeding diathesis [3]. The molecular mechanism of factor XII deficiency needs further investigation. Approximately 53 types of gene mutation are included in the Human Gene Mutation Database for factor XII deficiency [4]. Here, we present a case of factor XII deficiency associated with novel gene mutation (c.247C>T, p. Gln83*).

CASE PRESENTATION

A 39-year-old female with menstrual cessation for 48 days was admitted to the hospital for surgical abortion in the first trimester period on August 2, 2022. She decided to terminate the pregnancy because the pregnancy was unplanned and she already had two children. Baseline coagulation tests showed an isolated, prolonged aPTT=96.7 s (normal=25.1–36.5 s), PT=12.4 s (normal=9.4–12.5 s), international normalized ratio (INR)=0.99 (normal=0.79–1.25), thrombin time (TT)=13.6 s (normal=10.3–16.6 s), fibrinogen=3.62g/L (normal=2.38–4.98g/L), and D-Dimer=147 ng/ml (normal= 0–243 ng/ml). The patient had no obvious bleeding symptoms on most days and prolongation of

aPTT was only discovered during preoperative screening. Blood routine tests showed that RBC = $3.90 \times 10^{12}/L$ (normal = $3.80\text{--}5.10 \times 10^{12}/L$), HB = 125 g/L (normal = 115–150 g/L), WBC = $6.5 \times 10^9/L$ (normal = $3.5\text{--}9.5 \times 10^9/L$), and platelets = $260 \times 10^9/L$ (normal = $125\text{--}350 \times 10^9/L$). Liver function, kidney function, serum electrolytes, and antinuclear antibodies were normal. To further clarify the cause of the isolated prolongation of aPTT, the patient underwent mixing studies, coagulation factor activity assays, and genetic testing. Mixing studies showed correction for coagulation parameters, indicating the absence of any inhibitors. Intrinsic coagulation factors assays performed using the coagulation method on the fully automatic coagulation analyzer ACL TOP700 revealed severe factor XII deficiency of 4.8% (normal=70–150%). No other coagulation abnormality was detected. After conducting a sanger sequencing assay on coagulation-related genes, a nonsense mutation (c.247C>T, p. Gln83) was found in the exon region of the factor XII gene in chromosome 5 (Figure 1). The homozygosity of the mutation suggested that it was the cause of factor XII deficiency in this individual. The patient was diagnosed with factor XII deficiency based on the results of the relevant tests and underwent surgical abortion with minimal bleeding.

DISCUSSION

Factor XII acts as an initiating step orchestrating enzymatic conversion of factor XII. It is important for the initiation of the intrinsic pathway *in vitro* (in the laboratory coagulation test). When it makes contact with a negatively charged surface *in vitro*, the attached precursor is cleaved by kallikrein at Arg353Val354, which in turn activates factor XII protein [5]. *In vitro* prolongation of aPTT does not necessarily may not indicate an increased risk of coagulopathy *in vivo* because other coagulation factors can compensate for the lack of factor XII. The physiologic function of factor XII *in vivo* has remained unclear since it was discovered. Further investigations will be required to identify novel roles of factor XII so that therapies can be found for certain disease states, such as thrombosis, inflammation, and infections.

The variation (c.247C>T, p. Gln83*) in the coding region of the exon of the *F12* gene was localized to 176832775 on chromosome 5 of the patient, and it would lead to nonsense-mediated mRNA decay of the *F12* gene transcript or premature termination of its amino acid sequence, which theoretically would result in loss of protein function. The variation has not been reported previously and is absent from large-scale population frequency databases. The c.247 C > T point mutation would result in the substitution of glutamate (GAG) with the termination codon TAG. Based on available evidence, we have classified this variation as a potential pathogenic mutation. Premature termination of the amino acid sequence of factor XII would lead to reduced activity and prolonged aPTT. The discovery of the novel *F12* mutation provides a basis for performing comparative molecular analyses to clarify further the role of factor XII in

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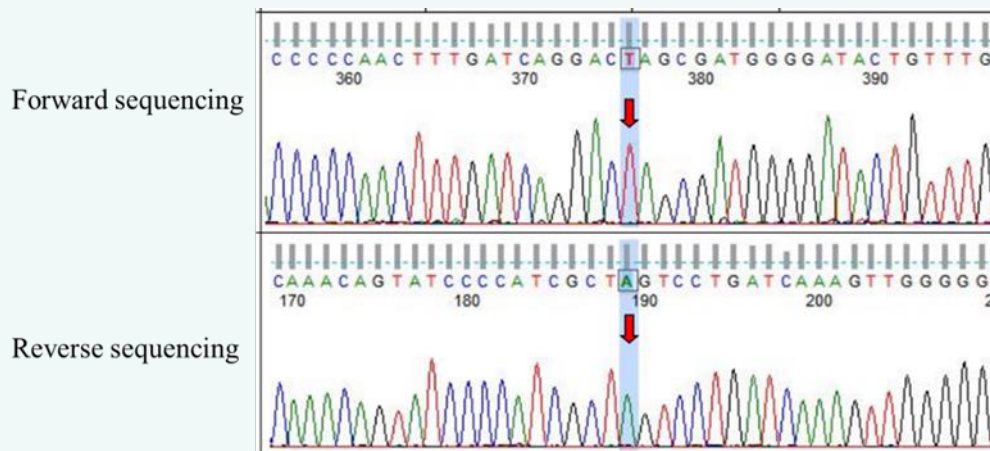


Figure 1: A nonsense mutation (NM-000505.4: c.247 C>T) in one of the exon coding regions of the F12 gene

hemostatic and thrombotic processes.

The aPTT assay is routinely employed by surgeons and others in preparation for planned invasive procedures. aPTT may be prolonged for multiple reasons, such as use of unfractionated-heparin, antiphospholipid syndrome, Von Willebrand variants, and deficiency in IX, XI, and XII factors. A mixing study and a coagulation factor assay are frequently used to confirm factor XII deficiency.

In this study, we found a novel nonsense mutation (c.247C>T, p. Gln83*) in one of the exon coding regions of the *F12* gene on chromosome 5 in a patient with a prolonged aPTT. The nonsense mutation would lead to premature termination of the amino acid sequence and loss of factor XII protein function.

STATEMENT OF ETHICS

Informed consent was obtained from the patient.

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AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Li Haining, Feng Changzhou, Zhou Ying, and Zhang Huanhuan. The first draft of the manuscript was written by Li Haining, Yang Jin, and Zhang Chu. All authors commented on previous versions of the manuscript. All authors

read and approved the final manuscript.

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