

## Case Report

# A novel factor X gene mutation Val (GTC) 384Ala (GCC) in a Chinese family resulting in congenital factor X deficiency

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**Abstract:** FX is a vitamin K-dependent coagulation protease critically essential for the coagulation cascade. FXD (congenital deficiency of factor X) is a rare coagulation disorder that inherited as an autosomal recessive trait. Here we reported a patient with bleeding diathesis from infant. The proband with pseudotumor in cerebral articular and cavity were identified as encapsulated hemocele ultimately. FX sequence analysis revealed that the patient carried a novel homozygous missense mutation that resulted in the Val384Ala substitution. Further investigation of the novel mutation would deepen our understanding of the bleeding mechanism involved in FXD.

**Keywords:** FX deficiency, FXD, gene mutation, coagulation disorder

## Introduction

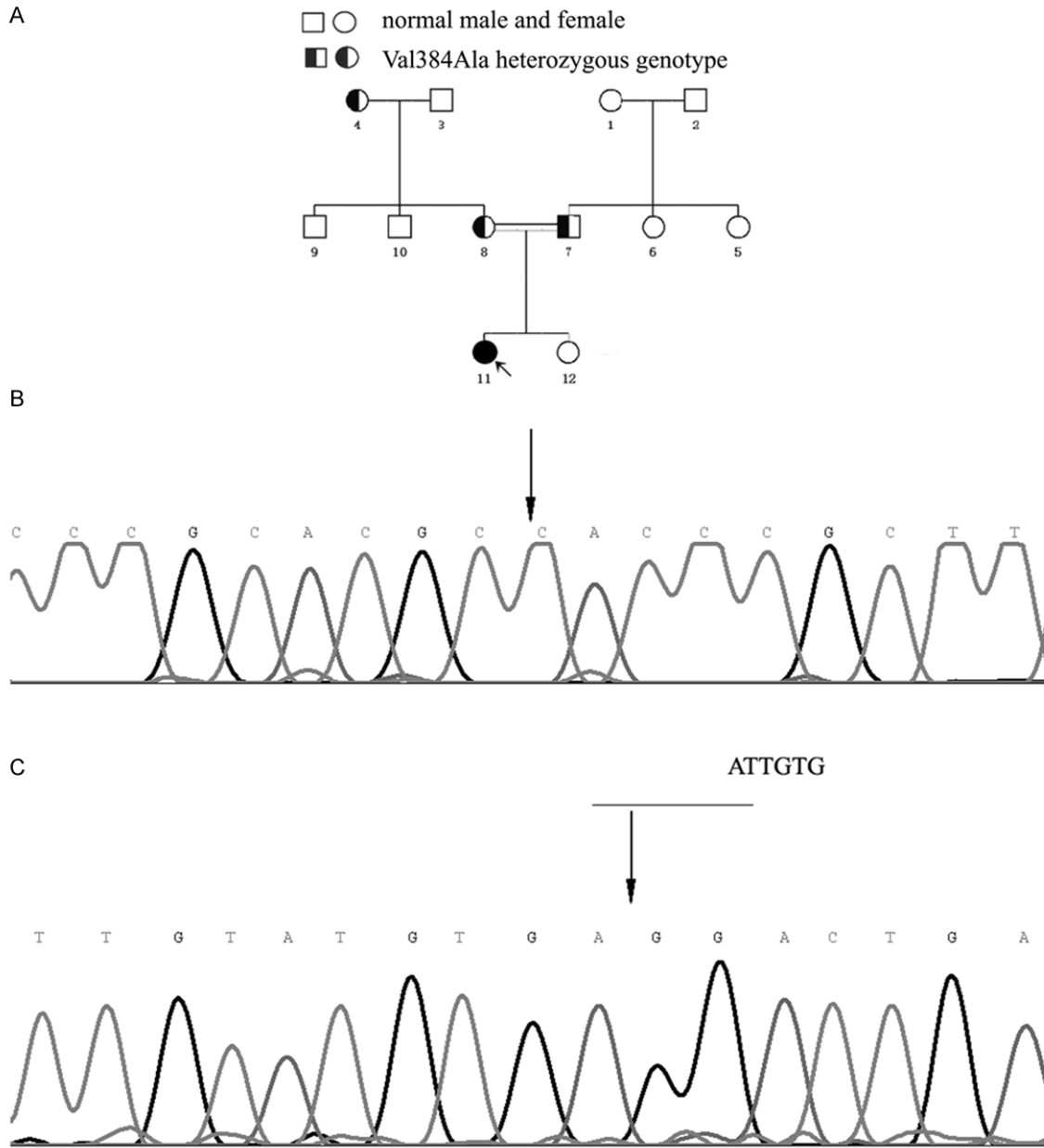
Human coagulation factor X (FX), a vitamin K dependent serine protease, is essential for blood coagulation. The gene of factor X consisting of eight exons is located on the chromosome 13q34 [1]. To date, more than 100 mutations of FX gene have been reported in the world scope [2]. Most of the mutations in the gene can cause congenital deficiency of factor X (FXD). FXD is a rare coagulation disorder that inherited as an autosomal recessive trait. In the general population, the reported incidence is approximately 1:10<sup>6</sup>. In some areas where consanguineous marriages are popular, the frequency is increased with eight- to 10-fold [3]. The ratio of male to female is 1:1. The severity of FXD is associated with the onset age of the disease. Furthermore, the complete deficiency of FX could not survive, which is confirmed by the embryonic or perinatal lethality of FX knock-out mice [4, 5]. A recent study for clinical manifestation of FXD on large scales showed that almost all the homozygous and compound-heterozygous patients present bleeding symptoms. The incidence of bleeding disturbance in heterozygous patients is 13% [6]. The symp-

toms of FXD vary from easy bruising, recurrent nose bleeding, menorrhagia, hematuria, spontaneous abortion, postpartum bleeding, to excessive bleeding during or following surgery or trauma, haematoma, haemarthrosis, pseudotumors, even intracranial bleeding or gut haemorrhage [6]. In this report, we described a Chinese family with FXD. The Val384Ala substitution resulted in the proband severe FX deficiency.

## Case report

The first symptoms of the proband, a 16-year-old girl, presented as headache, nausea, without vomiting, however. She suffered recurrent epistaxis from infancy. From puberty, she began to undergo menorrhagia. Two years ago, she accepted operation on periosteum cyst and be treated with fresh frozen plasma and concentrated red cells for postoperative hemorrhage. CT of her brain revealed a 5 × 6 × 6cm tempus dextrum cyst mass. A routine preoperative coagulation screening test showed that the proband had a prolonged prothrombin time (PT) and activated partial thromboplastin time (APTT). Fibrinogen concentration, platelet co-

## FX deficiency



**Figure 1.** A. Pedigree of the FX deficiency family. The arrow denotes the proband, the “4” represents the grandmother, “7” and “8” represent the parents, and the “12” represents the sister. B. The arrow indicates 28140 T-C homozygous mutation in FX gene of the proband. C. -343- -384 homozygous deletion of six nucleotides in the proband. The change was not pathogenic but a polymorphism.

unt, and platelet aggregation were normal. Coagulation factors were normal except for FX. FX coagulation activity (FX: C) was 2.4% and FX antigen was 10.8%. Her parents were not consanguineous marriage. The pedigree was shown in **Figure 1A**. No apparent bleeding tendency was noted in her family history. The phenotype of the proband was diagnosed as FX deficiency (type I). The management was conservative. She was given fresh plasma infusion and received dehydration therapy to depress

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intracranial pressure. The repeated CT revealed cyst mass regression. The patient had a good prognosis.

After informed consent, plasmas from the proband and 4 other family members (her grandmother-in-law, parents and her sister) were collected in 1:10 sodium citrate 3.8%, centrifuged at 2000 rpm for 15 min and stored in aliquots at -80°C until used. FX coagulation activity (FX: C) assay involved a one-stage PT and FX antigen

## FX deficiency

**Table 1.** Family member's coagulation parameters

	Sister	Grandmother-in-law	Mother	Father	Proband
PT (s)	11.3	11.1	13.5	13.4	27.6
PT% (%)	96	100	86	88	21
INR	1.02	1.00	1.08	1.07	3.35
APTT (s)	45.8	51.7	38.0	36.2	57.5
FIB (g/L)	2.55	4.05	2.82	2.32	3.95
FX: C (%)	35	29	44	53	2.40

Reference Ranges: PT 11.8-14.8s; PT% 50-150%; INR 0.80-1.20; APTT 28.0-41.0s; FIB 2.00-4.00g/L; FX: C 50-150%.

(FX: Ag) was measured with a sandwich enzyme-linked immunoadsorbent assay (ELISA) as previously described [7]. Genomic DNA was prepared from the whole blood using the standard phenol-chloroform protocol. FX gene was amplified using PCR with the primers designed according to the published sequence of FX (GenBank accession number AF503510). PCR products were purified and then sequenced. Reverse sequencing was applied to confirm any mutation. To eliminate the frequent polymorphisms, all mutations were also investigated in 100 alleles in a Chinese normal control population.

**Table 1** showed the coagulation parameters of the proband and her family members. The proband had a prolonged PT (27.6 s vs. 12.5 s) and APTT (57.5 s vs. 37.6 s). Compared with normal level, her FX: Ag was 10.7% and FX: C was 2.4%. The proband's activity levels of factor II, V, VII, VIII, XI, XII and fibrinogen were all within normal ranges. DNA sequencing revealed that the proband was homozygous for a T to C transversion at nucleotide 384 in exon 8 of the FX gene, resulting in an amino acid substitution of valine (GUC) to alanine (GCC) (**Figure 1B**). Another variation was -343- -384 homozygous deletion of six nucleotides that located in promoter of factor X gene (**Figure 1C**). Gene polymorphism analysis revealed that the change was not pathogenic because there was no association between FX levels and polymorphisms in the promoter of FX gene [8]. The proband's grandmother and her parents were heterozygous for the same missense mutation, while her sister was a normal subject.

### Discussion

The proband was found to be homozygote for FX deficiency, showing low levels of FX activity (2.4%) and FX antigen (10.7%). Tracing the other pedigree members, we found that the homozy-

gous mutation in the proband was derived from her father and mother respectively. The family members manifested as asymptomatic subjects, suggesting an autosomal recessive heredity. FH Herrmann et al [6] showed that almost all the homozygous patients had spontaneous bleeding symptom while proportion of symptomatic heterozygous to the total heterozygous subjects was merely 13%, which was consistent with the proband and her family.

The classification of congenital FX deficiency could be as follows: Type I (cross-reacting material (CRM) negative). Type II (CRM positive with inert protein). Type III (CRM positive with disre-active protein). Type IV (cases of FX deficiency associated with FVII deficiency usually due to chromosome 13 abnormalities) [9]. It was known that a few homozygote patients with severe bleeding disorder investigated thus far were affected by CRM- (type I) FX deficiency [10, 11]. Generally, intracranial haemorrhage (ICH) and haemarthrosis occurred in severe deficiency of FX. The proband was homozygous for Val384Ala. It was noteworthy that the proband was CRM- deficiency and revealed by pseudotumor. Actually, the pseudotumors in articular cavity were encapsulated hematocele. However, the hemorrhage heterogeneity was only partially explained by molecular analysis of the FX gene. Maybe the mutations in the same domain led to different phenotype [12]. Meanwhile other factors could also contribute to the clinical phenotype [13].

In conclusion, we hereby reported a novel mutation of FX gene in a Chinese family resulting in FX deficiency. The bleeding mechanism and genotype-phenotype correlation of the same mutation warrant further studies.

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**Disclosure of conflict of interest**

None.

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