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*OBM Genetics*

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Original Research

# Prenatal Diagnosis of Severe Factor VII Deficiency in the Setting of Maternal Breast Cancer

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**Academic Editor:** Ying S. Zou

**Special Issue**: Molecular, Cellular, and Genomic Insights into Thrombosis and Hemostasis

*OBM Genetics*
2026, volume 10, issue 2
doi:10.21926/obm.genet.2602343

**Received:** January 23, 2026
**Accepted:** May 12, 2026
**Published:** May 26, 2026

**Abstract**

Congenital factor VII (FVII) deficiency is the most common rare bleeding disorder (RBD), presenting with various clinical manifestations. Given the heightened risk of life-threatening bleeding and fatal hemorrhagic complications, prompt detection of the disorder is critical, especially in cases with low FVII levels and a history of familial severe clinical presentations. In such cases, prenatal diagnosis (PND) emerges as a life-saving option. In this study, we reported two PNDs in a family with a positive family history of severe FVII deficiency (<1%) and a positive history of breast cancer in the mother at the time of the second PND. Sanger sequencing of the entire *F7* gene was performed to detect the underlying gene variant in the affected girl and her parents. An FVII activity assay was performed to determine the plasma FVII levels in the girl and her parents. Chorionic villus sampling for fetal DNA acquisition was performed. DNA extraction and polymerase chain reaction (PCR)-sequencing of exon 1 of the

*F7* gene were performed on fetal DNA samples. An FVII activity assay was performed on the neonate to determine the severity of FVII deficiency. In the next two years, clinical presentations of the two children were collected. Molecular analysis revealed the c.1A>G (p.Met1Val) variant in exon 1 of the affected girl, who was homozygous for this variant in the *F7* gene and had severe FVII deficiency (<1%). Both parents were heterozygous for this variant, with FVII levels of 33% and 50% in the mother and father, respectively. PND revealed that both fetuses were homozygous for the c.1A>G variant, leading to termination of the second pregnancy. During the third pregnancy (Second PND), while the mother was being cared for for breast cancer, the homozygous child was born without complications, and the mother underwent mastectomy following delivery. Over the following two years, the child has remained asymptomatic, and the mother has also remained healthy after the mastectomy. Successful PND of severe FVII deficiency was achieved through c.1A>G variant detection, with coordinated multidisciplinary care enabling favorable maternal and fetal outcomes despite concurrent breast cancer treatment.

**Keywords**
Factor VII deficiency; prenatal diagnosis; intracranial hemorrhage; rare bleeding disorder; breast cancer

## 1. Introduction

Congenital factor VII (FVII) deficiency is one of the most severe rare bleeding disorders (RBDs), with an estimated incidence of one per 500,000 in the general population [1]. The clinical spectrum of FVII deficiency is remarkably heterogeneous, with patients presenting with a wide range of clinical manifestations, including hemarthrosis, hematoma, post-surgical bleeding, epistaxis, gastrointestinal (GI) bleeding, intracranial hemorrhage (ICH), and other bleeding manifestations [2-4]. The most severe clinical manifestations are often observed in patients with FVII coagulant activity levels (FVII:C) below 1% [3]. Paradoxically, some patients with severe FVII deficiency may not experience severe bleeding episodes, demonstrating the complex phenotype-genotype relationship in this disorder [3]. A recent systematic review demonstrated a weak correlation between FVII activity and the severity of clinical presentations, which may explain the mild bleeding tendency in some patients with severe FVII deficiency or, conversely, severe presentations in those with moderate FVII deficiency [3].

The pathophysiology of FVII deficiency involves variants in the *F7* gene on chromosome 13, which encodes FVII, a vitamin K-dependent glycoprotein essential for initiating the extrinsic coagulation pathway. Based on the Human Gene Mutation Database (HGMD), over 398 variants have been identified in the *F7* gene, each contributing to varying degrees of functional impairment and clinical severity [5]. As with other RBDs, the diagnosis of FVII deficiency is based on a combination of detailed family history, clinical presentation, and comprehensive laboratory evaluation.

Although on-demand therapy remains the primary approach for treatment in FVII deficiency, secondary prophylaxis should be considered for those with a history of severe bleeding. Furthermore, primary prophylaxis should be considered for those at risk of life-threatening bleeding

[6, 7]. Plasma-derived products are the most widely available therapeutic options for the management of patients with FVII deficiency; however, recombinant activated FVII (rFVIIa) is the treatment of choice due to its lower volume requirements and the elimination of the risk of blood-borne diseases. Treatment options include fresh-frozen plasma, 4-factor prothrombin complex (4F-PCC) concentrate, and rFVIIa, with the choice depending on bleeding severity, patient characteristics, and product availability [2].

Due to the severity of the disorder and the high rate of life-threatening bleeding, early diagnosis and appropriate management of affected patients are essential. In this regard, and due to the risk of fatal ICH at the time of birth or shortly after birth, prenatal diagnosis (PND) can be considered a life-saving strategy in those with a positive family history of congenital FVII deficiency, particularly those with a positive family history of life-threatening bleeding [2, 7]. PND typically involves chorionic villus sampling (CVS) or amniocentesis, followed by molecular genetic analysis to identify known familial mutations. This approach enables informed decision-making regarding pregnancy management and prepares specialized care teams appropriately if the pregnancy continues.

Considering all the above issues, we report two PNDs in a family with severe congenital FVII deficiency and a known *F7* gene variant, complicated by maternal breast cancer during the second pregnancy. We also provide follow-up data on the patient and her mother's breast cancer management, which represents a unique case study for clinicians who may encounter patients with FVII deficiency in complex clinical scenarios.

## 2. Materials and Methods

### *2.1 Demographic Data and Study Protocol*

The present prospective investigation focused on a family with a 12-year-old girl with severe FVII deficiency, referred for the PND program in the second and third pregnancies. Informed consent was obtained from this family, and the study received approval from the Ethics Committee of Babol University of Medical Sciences (IR.MUBABOL.REC.1402.142). A comprehensive questionnaire was also completed by expert staff to collect demographic and clinical data of the family members (Table S1). Initially, the FVII activity of both parents and their daughter was measured using the Stago kit (Sta, Diagnostica Stago, France) with a fully automated instrument (Sta-Compact Max 2, USA). The antigen level of FVII was determined using Nordic BioSite kits from Taby, Sweden. When their daughter was seven years old, the family experienced a second pregnancy, in which PND revealed homozygous FVII deficiency, prompting the family to choose termination. The family's third pregnancy occurred when their first daughter was 11 years old. Two years before this unplanned pregnancy, the mother received a diagnosis of low-grade breast cancer, but declined to pursue the required treatment due to the economic burden of the treatment. Despite this, they opted to proceed with the pregnancy, and her medical team decided to address the breast cancer after delivery. After delivery of the child, the newborn received rFVIIa (Aryoseven, Tehran, Iran) a few hours post-delivery, and the child's clinical presentation was assessed for the next 2 years. FVII activity levels were measured two days after rFVIIa infusion.

### *2.2 Molecular Study*

2.2.1 DNA Extraction and Polymerase Chain Reaction

As previously mentioned, for the diagnosis of FVII deficiency in the parents and affected sibling, polymerase chain reaction (PCR)-sequencing was performed. For this purpose, DNA was extracted using a DNA extraction kit (Viogene, Taipei, Taiwan). The quantity and quality of DNA were determined by spectrophotometry and agarose gel electrophoresis, respectively. PCR was conducted with designed primers covering all exons, exon/intron boundaries, and the promoter region. Sanger sequencing was performed using an Applied Biosystems sequencer (ABI, Foster City, CA). DNA sequence analysis was performed using Chromas Lite version 2.6.6 (Technelysium Pty Ltd., Australia).

### *2.3 Prenatal Diagnosis*

The PND for both the second and third pregnancies was performed at 9-10 weeks of gestation using chorionic villus sampling for fetal DNA acquisition. DNA was extracted using a QIAGEN Mini DNA kit (Qiagen, Hilden, Germany). To rule out contamination of fetal DNA with maternal DNA, short tandem repeat (STR) linkage analysis was performed, as previously described in detail [8]. Exon 1 of the *F7* gene was amplified by PCR using the specific primer (Table 1). Sanger sequencing was performed to detect the pertinent variant in exon 1.

**Table 1** Primer characterization for exon 1 of the *F7* gene.

| Primer | Sequence | Product size |
|---|---|---|
| Forward | GGCTCACCTAAGAAACCAGC | 613 |
| Reverse | TTTGCCCACTGCCCTTCC | |

## 3. Results

### *3.1 Characteristics of the Family Members*

Mather and father carried the c.1A>G variant heterozygously, with FVII activity levels of 32% and 50%, respectively, consistent with heterozygous FVII deficiency. The mother and father were diagnosed at ages 35 and 39 years old, respectively. As first cousins, neither parent had a known family history of FVII deficiency or abnormal bleeding. The father experienced easy bruising, while the mother had mild bleeding episodes, including easy bruising and gum bleeding.

When their first daughter turned nine, the mother was diagnosed with invasive ductal carcinoma of the right breast but refused treatment due to financial constraints. Two years later, during her third pregnancy, the family underwent PND as a preventive measure.

Although each pregnancy had only a 25% chance of resulting in severe FVII deficiency, the third fetus also tested positive for the homozygous variant. The baby girl was born healthy, and the mother subsequently underwent a total mastectomy. Her medical team decided against chemotherapy but recommended adjuvant radiation. Nearly two-year follow-up testing showed no signs of cancer recurrence.

Their first daughter was first suspected of having a bleeding disorder at premature birth when she experienced prolonged bleeding after a routine blood draw. Coagulation tests showed an isolated prolonged PT (16.5 seconds; normal range 11.5-15 seconds) (Diagnostica Stago, France). Genetic testing confirmed homozygous FVII deficiency (c.1A>G) (Figure 1) with severely reduced FVII activity (<1%). She has never required replacement therapy and has remained asymptomatic, experiencing only easy bruising throughout her 13 years of life (Table 2).

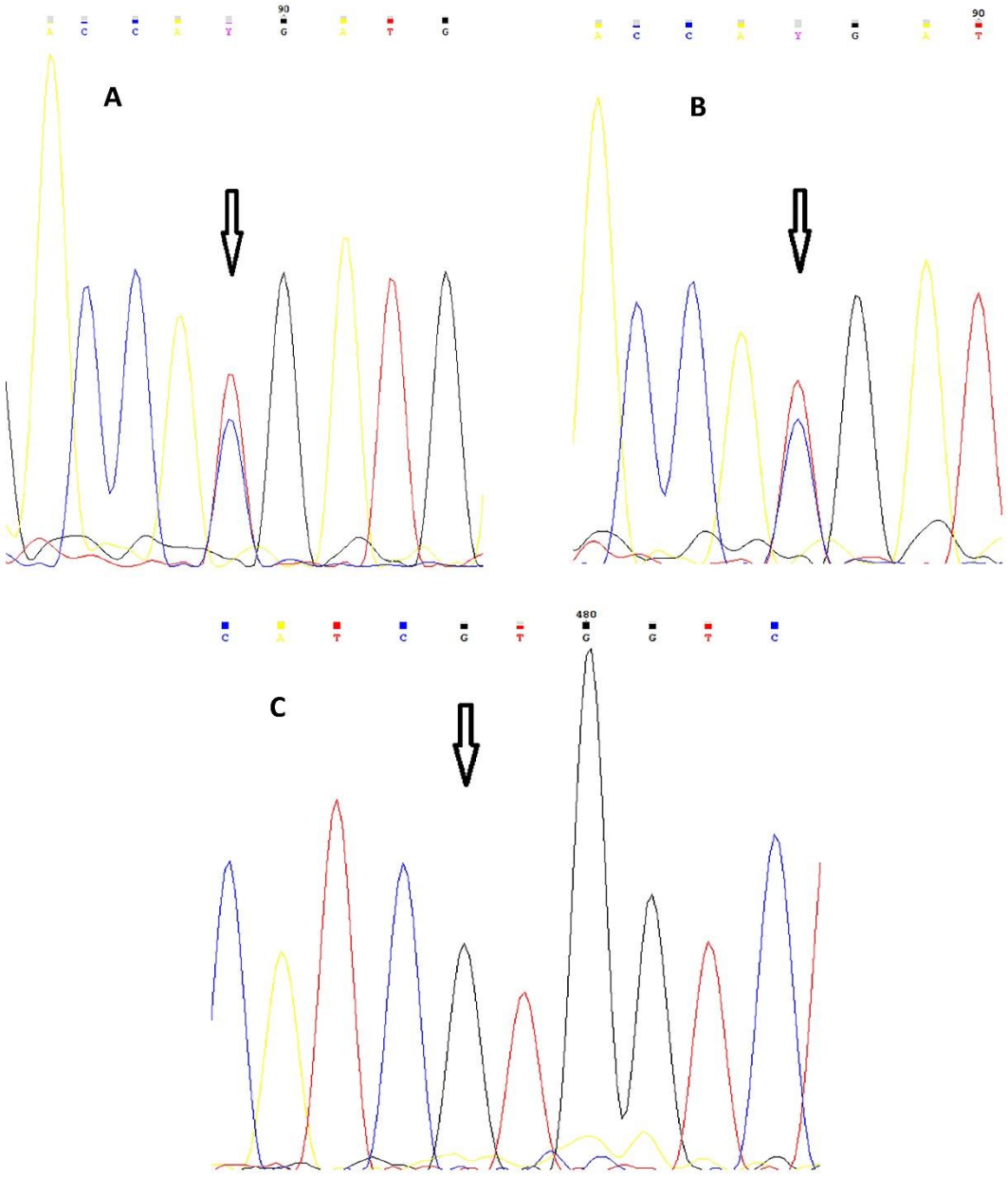


**Figure 1** Reverse sequencing of DNA in the parents (A and B) and forward sequencing of the daughter (C) revealed heterozygous and homozygous states, respectively, in exon 1 (c.1A>G; p.Met1Val).

**Table 2** Molecular, laboratory and clinical characteristics of the family members.

| Case | FVII activity (%) | Age at diagnosis | FVII antigenic assay (%) | Nucleic acid variant | Protein exchange | Inheritance | Clinical manifestations |
|---|---|---|---|---|---|---|---|
| **First daughter** | 1 | Birth | 8 | c.1A>G | p.Met1Val | Homozygous | Easy bruising |
| **Second pregnancy** | - | - | - | c.1A>G | p.Met1Val | Homozygous | Terminated |
| **Third pregnancy** | <1 | Birth | - | c.1A>G | p.Met1Val | Homozygous | Asymptomatic |
| **Father** | 50 | 39 | 51 | c.1A>G | p.Met1Val | Heterozygous | Easy bruising |
| **Mother** | 32 | 35 | 43 | c.1A>G | p.Met1Val | Heterozygous | Easy bruising, oral cavity bleeding |

### *3.2 Prenatal Diagnosis*

The first PND detected a homozygous c.1A>G variant in the fetus that was compatible with severe FVII deficiency. The first pregnancy was terminated as a result of the family's decision.

Similarly, the second PND revealed homozygous FVII deficiency in the affected fetus. As previously mentioned, the mother was diagnosed with invasive ductal carcinoma of the right breast. Following consultation with an oncologist, hematologist, and gynecologist, a healthy full-term delivery was achieved. After prenatal confirmation of homozygous FVII deficiency in the fetus — a condition associated with a significant risk of life-threatening bleeding, including intracranial hemorrhage, in the neonatal period — a multidisciplinary team decision was made to administer rFVIIa prophylactically at birth. At birth, the neonate received rFVIIa (Aryoseven, Tehran, Iran) as prophylactic replacement therapy a few hours after delivery; FVII activity was subsequently measured two days after infusion to confirm an adequate response. The child's clinical course was then assessed over the following two years. The mother was discharged from the hospital two days later without any bleeding complications. Follow-up of the neonate and her sister over the following two years revealed no abnormal bleeding. Except at birth, neither the neonate nor her sister has received any replacement therapy in the past two years.

## 4. Discussion

FVII deficiency is one of the most severe bleeding disorders associated with a variety of life-threatening bleeding complications, such as ICH, GI bleeding, and occasionally umbilical cord bleeding [9-11]. Patients with homozygous F7 gene variants usually have a severe FVII deficiency, but the phenotype is heterogeneous. In this study, a homozygous variant has been detected in the fetus. The c.1A>G variant identified in this family affects the translation initiation codon of the *F7* gene, substituting the methionine start codon with valine (p.Met1Val) and thereby abolishing canonical translation initiation. This variant is not novel; it has been previously reported in the published case series of hereditary FVII deficiency, including in Iranian patients [12]. The c.1A>G variant was the most common variant observed in an Iranian cohort in one study. The study found five patients with the homozygous c.1A>G variant and severe clinical presentations and severe FVII deficiency (<1%), similar to our reported cases [12].

Due to the potential life-threatening bleeding, PND represents a potentially life-saving strategy in FVII deficiency, particularly in those with severe FVII deficiency or those with a positive family history of life-threatening bleeding [13]. Our case highlights several important considerations regarding PND in families with severe FVII deficiency. In this study, the parents decided to undergo PND for their subsequent pregnancies due to their first daughter's severe FVII deficiency, despite her mild bleeding tendency. This decision was driven by the understanding that severe FVII deficiency, even in the absence of significant bleeding episodes, carries the potential for life-threatening complications. PND has been rarely reported in families with RBDs, including FVII deficiency. In the literature, 10 PNDs have been reported, most of which involved families with a family history of severe FVII deficiency and ICH [7, 13-15].

In one reported case, the family had a child with FVII deficiency who experienced two episodes of ICH and one GI bleeding episode, which prompted them to request PND in the subsequent pregnancy, which resulted in the detection of a non-mutant healthy fetus [16]. The contrast with

our case is notable, as our family's decision was based on proactive risk assessment rather than reactive response to severe bleeding complications.

A positive history of congenital bleeding disorders is a significant reason for requesting PND not only in FVII deficiency but also in other bleeding disorders, such as hemophilia [17]. A comparative study of Iranian and Italian families with hemophilia that assessed their attitude toward PND and termination of pregnancy revealed that only about 15% of Iranian families knew of PND in hemophilia. At the same time, this percentage was significantly higher in Italian families [17]. Another significant finding of this study was the higher rate of pregnancy termination in Iranian patients compared to Italian patients (58.2% vs 16.7%). The main reasons for termination of pregnancy in Iranian families were concerns about the quality of care and hope for achieving effective treatment in the future [17].

In our study, the decision-making process evolved between the two PNDs. In the first PND, despite the affected child's mild bleeding tendency, the main reason for termination of pregnancy was the positive family history of severe FVII deficiency. The confirmed PND of homozygous *F7* c.1A>G variant, along with the psychological burden of anticipating a second severely affected child within the same family, generated considerable distress. The family's limited financial resources compounded this emotional and psychological burden, and the clinical guidance received at the time of the second pregnancy supported termination as a reasonable course of pregnancy termination. However, in the second PND, despite the homozygous state of the fetus and concurrent maternal breast cancer, the parents decided not to terminate the pregnancy. The main reason for continuing the pregnancy was the mild bleeding tendency in the affected child without the need for any replacement therapy. This shift in decision-making reflects the family's growing understanding of their daughter's clinical course and their confidence in managing the condition.

The two-year follow-up of both children in our study showed that molecular findings and family history are important factors that should be considered when requesting PND and making decisions about termination of pregnancy. In this study, both children, despite having severe deficiencies in FVII levels, are essentially asymptomatic. This observation supports the concept that biochemical severity does not always correlate with clinical severity in FVII deficiency, as previously reported in the literature [18].

On the other hand, several studies have shown that those with a positive family history of severe bleeding episodes are more likely to experience severe bleeding in subsequently affected children [14, 18-20]. This paradox highlights the complexity of genotype-phenotype correlations in FVII deficiency and the challenges families and clinicians face in making informed decisions about pregnancy management.

It should be considered that severe bleeding disorders can result in intrauterine bleeding, as we have observed in a neonate with homozygous FXIII deficiency that experienced ICH during delivery [21]. Therefore, after detection of an affected fetus with a high risk of central nervous system (CNS) bleeding, such as in afibrinogenemia, FII, FXIII, FX, and FVII deficiencies, special precautions such as selection of the best mode of delivery and intrauterine infusion of deficient factors or immediate post-delivery replacement therapy should be considered to minimize the risk of CNS bleeding and related adverse consequences. In our case, the administration of rFVIIa immediately after birth represents a precautionary measure that was successful in preventing immediate bleeding complications.

Daffos et al. detected severe FVII deficiency in a fetus through fetal blood sampling [22]. The parents chose to continue the pregnancy, leading to an intrauterine infusion of FVII concentrate, which resulted in increased FVII levels within the normal range before and at the time of delivery, resulting in a successful, event-free delivery [22]. This approach demonstrates the feasibility of intrauterine treatment, though such interventions require specialized expertise and careful risk-benefit assessment.

Despite its rarity, fetal ICH has been reported in severe RBDs, including FXIII, FVII, and FV deficiencies [4, 23, 24]. For fetuses at risk of life-threatening bleeding, precautionary measures should be taken during pregnancy, delivery, and post-delivery. Additionally, after delivery and during childhood, when the risk of head trauma is high, precautions should be considered. These precautions can include prevention of head trauma and even factor replacement therapy to decrease the risk of life-threatening bleeding. Although the risk of ICH is lower in FVII deficiency than in FXIII deficiency, the rate of ICH is relatively high in severe FVII deficiency [23]. When considering all these factors, PND can be a life-saving intervention. However, in the absence of adequate precautions, invasive PND programs or even less aggressive methods, such as cell-free fetal DNA sampling, can be accompanied by complications [4, 13, 21].

Our case also presents the unique challenge of managing a high-risk pregnancy in the context of concurrent maternal malignancy. The mother's breast cancer diagnosis added complexity to the decision-making process, requiring multidisciplinary collaboration between hematologists, oncologists, and obstetricians. The successful management of both conditions demonstrates the importance of comprehensive care coordination in complex clinical scenarios.

Limitations of our study include the small sample size and relatively short follow-up period. Long-term outcomes and the potential for delayed bleeding complications in the affected children remain to be determined. Additionally, the psychosocial impact of PND decision-making and the burden of caring for children with bleeding disorders were not systematically assessed.

## 5. Conclusion

This study demonstrates the complexity of PND decision-making in families with severe FVII deficiency. While severe FVII activity levels may indicate high risk for bleeding complications, the clinical phenotype can be surprisingly mild, as observed in both affected children in our study. The evolution of the family's decision-making between the two PNDs, from termination to continuation, reflects the importance of individualized counseling based on family-specific factors, including the clinical course of previously affected children.

Our experience suggests that PND remains a valuable option for families with severe FVII deficiency. Still, decisions should be based on a comprehensive assessment of molecular findings, family history, clinical phenotype of affected relatives, and family preferences. The successful management of pregnancy and delivery in the context of concurrent maternal breast cancer highlights the importance of multidisciplinary care. Long-term follow-up of affected children is essential better to understand the natural history of severe FVII deficiency and to provide more accurate prognostic information for future families facing similar decisions.

Healthcare providers should offer balanced counseling that acknowledges both the potential risks of severe FVII deficiency and the possibility of a mild clinical course, enabling families to make informed decisions that aligned their values and circumstances.

## Author Contributions

M. Sh contributed to the conception and design of the study, drafted the manuscript, and approved the final version. N. S contributed to clinical management of the case, provided critical revision of the manuscript, and approved the final version. S. F assisted with data collection, literature review, and manuscript preparation. A. D supervised the study, contributed to interpretation of the findings, critically revised the manuscript, and approved the final version.

## Competing Interests

The authors have declared that no competing interests exist.

## AI-Assisted Technologies Statement

Artificial intelligence (AI)–based tools were used solely for language editing and grammatical refinement during the preparation of this manuscript. Specifically, Claude was utilized to enhance the clarity and readability of the English text. The scientific content, data analysis, interpretation, and conclusions were developed independently by the author(s). All AI-assisted revisions were critically reviewed and approved by the author(s), who take full responsibility for the accuracy and integrity of the final manuscript.

## Additional Materials

The following additional materials are uploaded at the page of this paper.

1. Table S1: Domains and items of the data collection questionnaire administered to family members enrolled in the prenatal diagnosis program for congenital factor VII deficiency.

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