A novel compound heterozygous mutation of F7 gene identified in an infant with hereditary factor VII deficiency and literature review

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Abstract

Hereditary factor VII (FVII) deficiency is a rare autosomal recessive disorder, characterized by decreasing the coagulation activity of FVII in plasma and heterogeneous with bleeding in different degrees. Hereditary factor VII deficiency is usually caused by missense mutations in the F7 gene, which may affect the structure and function of FVII. Here we present a case of hereditary factor VII deficiency in an infant who was found to have a prolonged prothrombin time(PT)and 2.0% of FVII activity. Molecular studies revealed a novel compound heterozygous mutation of the F7 gene, which confirmed the diagnosis of hereditary factor VII deficiency.

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abbreviations

FVII factor VII

PT prothrombin time

APTT activated partial thromboplastin time

Abstract Hereditary factor VII (FVII) deficiency is a rare autosomal recessive disorder, characterized by decreasing the coagulation activity of FVII in plasma and heterogeneous with bleeding in different degrees. Hereditary factor VII deficiency is usually caused by missense mutations in the F7 gene, which may affect the structure and function of FVII. Here we present a case of hereditary factor VII deficiency in an infant who was found to have a prolonged prothrombin time(PT)and 2.0% of FVII activity. Molecular studies revealed a novel compound heterozygous mutation of the F7 gene, which confirmed the diagnosis of hereditary factor VII deficiency.

Keywords Hereditary factor VII deficiency F7 gene compound heterozygous mutation FVII activity

Introduction Coagulation factor VII is a vitamin K-dependent glycoprotein with 406 amino acid residues[1],which is synthesized and secreted by hepatocytes. It circulates in the blood in zymogen form and initiates the extrinsic pathway of coagulation.

Hereditary coagulation factor VII deficiency is a rare autosomal recessive hemorrhagic disorder, with an estimated prevalence of 1/500 000[2]. All age groups can be affected with FVII deficiency. A few patients have a history of consanguineous marriage. The disease was first reported by Alexande in 1951[3]. Up to now, the updated database includes 287 types of gene mutations, including deletion, duplication, insertion, insertion / deletion rearrangement and single nucleotide variants [4]. Single nucleotide variants are the most common type (88.0%) with missense representing 74.0% of these variants [5]. However, the clinical hemorrhage of FVII deficiency is not exactly proportional to the activity of FVII [6]. The cause is not identified. FVII activity of homozygous or compound heterozygous gene mutations generally are between 1.0% and 5.0%, and the clinical hemorrhage is often severe, while the heterozygous gene mutation is generally asymptomatic[7]. Thus, a comprehensive analysis of genotype of hereditary coagulation factor VII deficiency is essential.

Now we report an infant with hereditary factor VII deficiency which has a novel compound heterozygous mutation of F7 gene.

Case report

A one-month-old female presented at the pediatric hematology department with a complaint of PT prolongation. According to her parent, she was born to nonconsanguinous marriage without any birth complications and had no remarkable umbilical cord bleeding after birth, shortly she was admitted to local hospital for jaundice. Meanwhile, she was found to have PT prolongation, She was managed conservatively with vitamin K and phototherapy, and then was discharged from hospital due to the remarkably improvement of jaundice. In addition to follow-up jaundice, coagulation function also needed to review. A day ago, reexamination of coagulation function showed that PT was still abnormal, thus she was admitted to our department for further diagnosis and treatment. On physical examination, she has a normal appearance, with a temperature of 36.6, a pulse rate of 120 beats per minute, respiratory rate of 30 breaths per minute, and oxygen saturation 100% on room air. Her body weight was 4.8kg. No ecchymosis or bleeding spots were seen on the skin. Respiratory, circulatory system and abdominal examination was unremarkable, and no neurological abnormalities were noted. Routine investigations including hematology, biochemistry were within reference ranges. Coagulation studies revealed the PT was 88.4 seconds. After intramuscular injection of vitamin K, the PT was still significantly prolonged. Therefore, we did a further examination. A coagulation factor profile showed deficiency of factor VII, which had 2.0% of normal activity, other factors (factors II, V, VIII, X, IX, XI and XII) had normal activity in functional assays. And at the same time, we tested the coagulation function and FVII activity levels of her parents, the coagulation function were unremarkable in both of her parents, the FVII activity levels of her father and mother were 50.0% and 48.0% respectively (Table 1).

Methods and results

After informed consent had been obtained, genomic DNA was extracted from peripheral blood samples of the index patient and from her parents for molecular genetic analysis of the F7 gene. No other laboratory testing was performed at that time. Compound heterozygous mutations in the proband were identified: A>G

mutation at position 572-2 and G>A mutation at position 1280, resulting in aberrant mRNA alternative splicing and Gly427Asp substitution respectively. Heterozygosity for c.572-2A>G was confirmed in the proband's mother; heterozygosity for c.1280G>A was confirmed in the proband's father(Fig.1).

Literature review

To investigate the clinical features of hereditary FVII deficiency in compound heterozygous mutation, we conducted case report of relevant literature on hereditary FVII deficiency. CNKI, WanFang, and PubMed databases were searched for relevant articles published nearly five years using the keywords of "compound heterozygous mutation; FVII deficiency" in Chinese and English, respectively. There were 3 Chinese articles[8–10] and 5 English articles[11–15] concerning hereditary FVII deficiency on case report. Complete clinical data from 11 cases of hereditary FVII deficiency were analyzed, including 3 males and 8 females. All patients showed mild to severe bleeding tendencies except 1 patient who was clinically asymptomatic. The symptoms were epistaxis in 5 cases, gum bleeding in 6 cases and bleeding in other sites. FVII activity ranged from <1.0% to 25.0%, and FVII <5.0% was in 7 cases (S1)

Discussion

FVII is a crucial component of the exogenous coagulation cascade. It is synthesized in the liver and secreted in the form of 49 kDa single chain glycoprotein. It is a vitamin K-dependent coagulation factor. Hereditary coagulation factor VII deficiency is an autosomal recessive disorder. Human F7 gene is located on the chromosome 13 (13q34), lies adjacent to the factor X gene. It is composed of 9 exons and 8 introns [16]. The clinical heterogeneity ranges from lethal to mild or even asymptomatic forms. Mild symptoms include epistaxis, ecchymosis of skin and mucous membrane, gingival bleeding, menorrhagia and post-traumatic bleeding. Some individuals experience life-threatening events such as central nervous system bleeding, gastrointestinal bleeding and joint bleeding. The incidence of severe cases is 4.4% - 8.0% [17]. In the neonatal period, the central nervous system and gastrointestinal bleeding are the main causes, which can develop serious nervous system complications, poor prognosis and high mortality. With regard to the severity of hereditary coagulation FVII deficiency, depending on the number of causative gene mutations, the effect of mutation sites on the function site and gene polymorphism, which is not directly related to the activity of FVII [18-19]. The activity of FVII was 1.0%-5.0% in homozygous and complex heterozygous mutation patients and life-threatening events such as intracranial hemorrhage and gastrointestinal hemorrhage often occur [7].

In our case, proband's PT was prolonged and activated partial thromboplastin time(APTT) was normal. The activity of FVII was significantly reduced. After polymerase chain reaction Sanger sequencing, compound heterozygous mutation of F7 gene was detected: c.572-2A>G and c.1280G>A. The mutation of c.572-2A>G may lead to the aberrant mRNA alternative splicing of F7 gene, which is included in the ExAC database and reported in the HGMD database[20]. The mutation is a possible pathogenic mutation. The mutation of c.1280G>A resulted in the transformation of amino acid 427 from glycine to aspartic acid (p.gly427asp), which was not reported in gnomAD, ExAC and 1000G databases, and no case was reported in HGMD database. The mutation was a possible pathogenic mutation. The results of family verification showed that the father and mother of the subjects carried c.1280G>A and c.572-2a > G respectively, which was consistent with the rule of genetic co-segregation. The activity of FVII was less than 5.0%, but there was no obvious manifestation of intracranial hemorrhage and gastrointestinal hemorrhage. It may be related to the protein structure and function change is not obvious or does not affect the function of FVII protein. We need to further explore.

Conclusion

Thus, PT prolongation in infant should not only consider vitamin K deficiency, but also should consider congenital coagulation factor deficiency. In our case, the prolongation of PT is caused by mutation in the F7 gene, this mutation is a novel compound heterozygous mutation, which has not been reported in the literature. Therefore, it can be included in the gene mutation library to provide a basis for the study of the disease. And there was no overt bleeding tendency of this compound heterozygous mutant gene.

Conflicts of interest

There are no conflicts of interest.

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Figure legend

Fig.1 A The pedigree of the two-generation Chinese family investigated in this study showing the proband, mother and father. Molecular analyses were carried out in the index patient, her mother and her father. The proband is indicated with an arrow.

B Sanger sequencing validation of the F7 gene mutation. The position of mutational base is indicated with an arrow.

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