Favourable outcome of multisystem venous thrombosis associated with novel SERPINC1 mutation after treated with dabigatran: a case report and literature review

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Case Report

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Abstract

Background: Thrombophilia is a group of disorders that predispose to thrombosis, involving the interaction between genetic and acquired factors, mainly manifested as recurrent venous thromboembolism (VTE). Mutations in *SERPINC1* lead to deficiency in antithrombin (AT) which is an endogenous anticoagulant of normal hemostasis and could result in VTE. Herein, we report a case of hereditary thrombophilia manifested by recurrent thrombosis involving the deep veins of the lower extremities, splanchnic veins, and cerebral vein.

Case presentation: A 61-year-old male patient with recurrent thrombosis involving the deep veins of the lower extremities, splanchnic veins, and cerebral vein. Laboratory tests revealed a type I AT deficiency in this patient and further whole exome sequencing (WES) identified a novel heterozygous frameshift duplication (c.233_236dup, p.Val80Alafs*26) in *SERPINC1* gene. After diagnosis, the patient was treated with dabigatran and obtained a perfect therapeutic effect.

Conclusion: A novel frameshift variation (c.233_236dup, p.Val80Alafs*26) within the SERPINC1 gene was identified in a multisystem VTE patient, which may play a significant role in human hereditary AT deficiencies. Our study enriches the insights of genetic factors for VTE and will facilitate the genetic diagnosis of this disease.

Background

Thrombophilia caused by inherited or acquired conditions is a group of diseases predisposing patients to thrombosis [1]. The main clinical symptom is recurrent venous thromboembolism (VTE). VTE typically occurs in deep veins of the legs and arms, but sometimes the thrombosis occurs in uncommon sites, such as the splanchnic veins, cerebral veins and retinal vein [2]. Thrombophilia is etiologically multifactorial and involves an interaction between inherited and acquired factors. The acquired risk factors include antiphospholipid antibody syndrome, malignancy, oral contraceptive use, hormonal replacement therapy, surgery, obesity, smoking, prolonged travel, immobility and pregnancy [3]. Furthermore, mutations in anticoagulant or procoagulant protein associated genes play important roles in pathologic development of thrombophilia [4]. Genetic testing is useful for confirming diagnosis of hereditary thrombophilia.

Antithrombin (AT) is an endogenous anticoagulant that acts as a major clotting inhibitor by inactivating thrombin and factor Xa, IXa [5]. Inherited deficiency of AT is an uncommon autosomal dominant disorder with a 5 to 17 per 1000 individuals prevalence in the general population [3]. According to the quantity and quality of AT protein produced, AT deficiency is classified as type I with reduced protein production and type II with abnormal protein structure and function [5]. *SERPINC1* mutations or variants can lead to premature termination of the AT protein, thereby resulting in coagulation disorder/dysfunction.

Here, we report a case of hereditary thrombophilia manifested by recurrent thrombosis involving the deep veins of the lower extremities, splanchnic veins, and cerebral veins. In the past 5 years, the patient suffered multiple thrombosis-related diseases, including acute mesenteric vascular obstruction, cerebral venous sinus thrombosis, deep venous thrombosis (DVT) and pulmonary embolism (PTE). A novel heterozygous mutation (c.236_237insGGCG p.V80Afs*26) in *SERPINC1* was identified which could lead to AT deficiency [6]. After diagnosis, the patient was treated with dabigatran and a perfect therapeutic effect was obtained. All the information were collected from the patient after informing consent.

Case Presentation

A 61-year-old male patient was transferred to the gastrointestinal surgery department of our hospital for further treatment due to severe abdominal infection after he was performed a massive resection of small intestine for vascular ileus in December 2015. The results of the coagulation function test showed that the D-dimer (2.28; reference range, 0-0.5) was prolonged while thrombin time (TT), prothrombin time (PT) and active partial thromboplastin time (APTT) were normal. The plasma levels of AT antigen (58mg/dl; reference range, 80-120mg/dl) and AT activity (54%; reference range, 80–120%) were reduced. Abdomen enhanced computed tomography (CT) scan and computed tomography venography (CTV) revealed the several peripheral thromboembolus have been filled in the portal vein (Fig. 1A), splenic vein (Fig. 1B), superior mesenteric vein (Fig. 1C). Pulmonary artery CT angiography (CTA) demonstrated the massive thrombosis of the left pulmonary artery (Fig. 1F, G). Color Doppler ultrasound showed thrombosis in bilateral femoral vein and the left popliteal vein, which suggested DVT in both lower extremities (Fig. 1H). His family history was unremarkable except for sudden death of his nephew and niece from possible pulmonary embolism. He received standard thrombolytic therapy. Initially, he had achieved significant improvement in recanalization of the venous thrombosis. The patient was prescribed with oral dabigatran and was discharged. However, the patient was referred to the department of neurology for status epilepticus after ceasing dabigatran by himself in March 2017. Brain CT and magnetic resonance imaging (MRI) revealed bilateral frontal hemorrhagic infarction (Fig. 2A, B, C). Brain enhanced MRI (Fig. 2E, F) and MRI Venography (MRV) (Fig. 3A, B) documented multiple thrombosis in the right transverse sinus, sigmoid sinus, and superior sagittal sinus. CTA in head was unremarkable with no vascular malformation, aneurysm or stenosis (Fig. 2D). A total of 4mg clonazepam was immediately administered intravenously as antiepileptic therapy. He received lamotrigine titrated to 75 mg bid and levetiracetam titrated to 1000 mg bid, after which clinical signs of seizure activity ceased. Simultaneously, he received standard anticoagulation treatment with low-molecular-weight heparin (LMWH) for the first 14 days once again, followed by the addition of oral dabigatran 110 mg Bid for 3 days, and then oral dabigatran only.

To identify the etiology of this patient showed multisystem VTE, serial blood tests were performed. Routine biochemical, renal, hepatic, blood lipid profile, homocysteine, thyroid profiles, tumor markers, electrocardiogram and transthoracic echocardiography were normal. The coagulation profile of the patient was determined, which included thrombin time, international normalized ratio (INR), fibrinogen

degradation products, factor V, VII, VIII, IX, protein C, S, rheumatoid factor, lupus anticoagulant, antiphospholipid antibodies, anticardiolipin antibodies, antinuclear antibodies, and antineutrophil cytoplasmic antibodies, but no abnormality was found. The D-dimer (2.35; reference range, 0-0.5) was slightly elevated. The plasma levels of AT antigen (43mg/dl; reference range, 80-120mg/dl) and AT activity (33%; reference range, 80–120%) were found to be decreased. The patient was subjected to whole exome sequencing (WES) to identify potential pathogenic variants. A novel heterozygous frameshift duplication (c.233_236dup, p.Val80Alafs*26) in the *SERPINC1* gene was identified, which was also validated by Sanger sequencing (Fig. 4). The *SERPINC1* gene encoding AT protein, which is the most important serine protease inhibitor in plasma that regulates the blood coagulation cascade. The truncating mutation in *SERPINC1* in the patient can lead to premature termination of the AT protein, thereby resulting in coagulation disorder/dysfunction.

The recovery of myodynamia and daily ability were significantly achieved within one year after the treatment. His seizures were kept under control by a combination therapy with lamotrigine and levetiracetam. Due to the inherited AT deficiency, oral dabigatran was continued with semiannual follow-up, including blood tests, Doppler ultrasound in the peripheral vessels and brain MRV. Blood tests revealed that the repeated measurement of plasma AT antigen and activity were constantly lower than normal. Other coagulation tests were unremarkable. Abdomen CTV in 2019 revealed recanalization of the portal vein, splenic vein, superior mesenteric vein thrombosis (Fig. 2D, E). The Color Doppler ultrasound in 2021 showed partial recanalization of bilateral superficial femoral vein and the popliteal vein thrombosis. Brain MRV improved even if recanalization was not completed after 2 years of the onset of the cerebral infraction (Fig. 3C, D). The last follow-up visit in February 2022 indicated that the patient recovered significantly.

Discussion And Conclusions

Thrombophilia is a group of disorders in which blood has an increased tendency to clot. It is a multicausal disease triggered by interactions between inherited and acquired conditions. The acquired risk factors include antiphospholipid antibody syndrome, malignancy, oral contraceptive use, hormonal replacement therapy, surgery, obesity, smoking, prolonged travel, immobility and pregnancy[3]. The reported patient had no acquired risk factors while the plasma levels of AT antigen and activity were significantly decreased. As the acute thrombosis event may cause a transient reduction in AT level, which could be misread to suggest AT deficiency, measurements were repeated after the patient had recovered. The results revealed that the levels of AT antigen and AT activity were still significantly reduced, which demonstrated the patient had AT deficiency. Moreover, A mutation (c.233_236dup p.Val80Alafs*26) in the *SERPINC1* gene, encoding AT, was identified by WES. The deletion mutation can lead to a frameshift at the 80th codon (Val) and premature termination at the 26th downstream amino acid of the *SERPINC1* protein (p.Val80Alafs*26), resulting in a failure in expression of AT. Thus, we believe that multisystem VTE in this case should be associated with AT deficiency caused by *SERPINC1* mutation.

The genetic burden of thrombophilia is estimated from 35 to 60%, indicating a strong heritability affecting the function of coagulation or antithrombin system [7]. Generally, inherited thrombophilia is mainly attributed by either the loss of anticoagulant function (i.e., mutations in *SERPINC1, PROC* genes)[8], or the gain of procoagulant function (i.e., mutations in *F5, F2* genes)[9]. Among all of those mutations, the factor V Leiden mutation in *F5* is the most common inheritance-related cause of thrombophilia. *F2*-related thrombophilia is the second most common genetic form of thrombophilia, occurring in about 1.7-3% of the European and US general populations[2]. Hereditary AT deficiency has a prevalence of 1:500–5000 in the general population[10]. AT is the endogenous anticoagulant of normal hemostasis, which regulates the coagulation cascade by inhibiting serine proteases of the intrinsic pathway (i.e., thrombin, factors IXa, Xa and XIa) [11]. Up to 80% of cases with suspicion of inherited AT deficiency are caused by defects of *SERPINC1* that encodes AT[11]. In this case, only the *SERPINC1* gene mutation was detected by WES.

Inherited AT deficiency is divided into type I deficiency, in which both the functional activity and antigenic levels AT are proportionately reduced (quantitative deficiency), and type II deficiency, in which normal antigen levels are found in association with low AT activity due to a dysfunctional protein (qualitative deficiency) [5]. Further specialized tests help to subclassify type II deficiencies. As the plasma AT antigen and activity were both decreased significantly, it was suggested that this patient had type I AT deficiency. Clinically, the thrombotic events often occur at an earlier age if someone has a genetical AT deficiency. VTE occurred in 85% of AT deficient relatives before 55 years of age in family studies [12]. Moreover, homozygous individuals with type I AT deficiency have a higher risk of severe venous thromboembolism (VTE) in childhood[13]. However, this patient as well as part patients in other cases are older than 60[14], which indicates the pathogenesis mechanisms of genetical AT deficiency may also involve with acquired risk factors.

SERPINC located on chromosome at q23.1–23.9 d spreads 13.5 kb, is composed of seven extrons and six introns [15]. According to the Human Gene Mutation Database (HGMD), more than 250 mutations in the *SERPINC1* have been already identified, and missense or nonsense mutations constitute more than 50% to the genetic defects, followed by small deletions, gross deletions, and small insertions [16]. Most mutation change single protein-building blocks in AT, resulting in disrupting in its ability to control coagulation. In addition, genetic mutations could alter the domains of antithrombin-associated conformational instability, leading to protein polymerization [17]. Missense and null mutations are widely reported in VTE families. For example, there is a G to T substitution at nucleotide position 13,268, resulting in the replacement of the normal alanine residue at position 384 by serine and the synthesis of a dysfunctional AT with a reduction in anti-IIa activity[18, 19]. A heterozygous missense mutation (c.848_849insGATGT) is partly responsible for the AT deficiency in a server VTE patients[20]. The combination of different *SERPINC1* mutations or variants are also involved in multiple thrombophilic disorder [21]. There are some correlations between AT deficiency phenotype and genotype. Generally, Type I deficiency is caused by nonsense mutations or short insertions and deletions within *SERPINC1* which

lead to frameshifts and result in a failure in expression of AT. Type II deficiency is usually caused by missense mutations affecting residues that are involved in AT function[22]. In this study, we reported the case of a severe multisystem VTE patient with type I AT deficiency caused by a heterozygous frameshift mutation of *SERPINGC1*. The c.233_236dup of *SERPINGC1* is a frameshift that contributes to the protein synthesis termination, leading to protein destruction and type I AT deficiency, which has not been reported yet. Hotpot in *SERPINC1* gene is rare but also been detected in other Chinese cohorts, including genetic variants c.881G > T (p.Arg294Leu) and c.883G > A (p.Val295Met)[23–26].

The initial management of VTE in patients with AT deficiency should generally be no different from its management in those without AT [27]. Occasionally, it is worthwhile to consider AT concentrate in the individual with severe thrombosis [28]. In determining the length of oral anticoagulation therapy, the circumstances of the thrombotic event, all the patients risk factors for recurrence and all risk factors for bleeding should be weighed together. It is suggested that individuals carried with hereditary AT deficiency and already developed to VTE should receive long-term anticoagulation [27].

Based on this recommendation, a long-term oral anticoagulant dabigatran was applied in this case. No thromboembolic and bleeding event occur during the 5-year follow-up period. Dabigatran is a reversible, potent, competitive direct thrombin inhibitor. In comparison to similar anticoagulant strategy like warfarin, the benefits of dabigatran include decreased risk in major ischemic and bleeding event, as well as good compliance since there is no need of regularly laboratory test in monitoring clotting indices [29]. More importantly, we have shown the successful treatment with dabigatran of multisystem VTE associated with hereditary type I AT deficiency. However, long-term effectiveness and safety of dabigatran for hereditary AT deficiency need to be confirmed in a big number of cases.

There are also some limitations in this case. A disadvantage of direct sequence analysis is that it is inadequate for revealing large gene rearrangements in all coding regions of *SERPINC1* gene. Multiplex Ligation-dependent Probe Amplification (MLPA) should be performed simultaneously. Genetic counseling for his whole family is necessary. We are not able to determine AT deficiency in the asymptomatic family members based on these genetic data. Bioinformatic analysis is highly useful in clinical laboratories with limited experimental facilities. However, functional studies are extremely desirable to evaluate the possible effects of a genetic variation. Further studies are required to verify the frameshift for mutations described in *SERPINC1*, which may include recombinant models, analysis of *SERPINC1* transcripts and minigene models.

In conclusion, we have identified a novel frameshift variation within the *SERPINC1* gene in a multisystem VTE patient, suggesting frameshift mutations may play a significant role in human hereditary AT deficiencies. Our study enriches the insights of genetic factors for VTE and will facilitate the genetic diagnosis of this disease. In type I AT deficiency, oral anticoagulant dabigatran may be promising in prevention of VTE. However, further studies with larger sample size should be performed.

Abbreviations

APTT: active partial thromboplastin time

AT: antithrombin

CT: computed tomography

CTA: computed tomography angiography

CTV: computed tomography venography

DVT: deep venous thrombosis

INR: international normalized ratio

LMWH: low-molecular-weight heparin

MLPA: Multiplex Ligation-dependent Probe Amplification

MRI: magnetic resonance imaging

MRV: magnetic resonance imaging venography

PT: prothrombin time

PTE: pulmonary embolism

TT: thrombin time

VTE: venous thromboembolism

WES: whole exome sequencing

Declarations

Acknowledgements

Not applicable.

Authors' contributions

YL and TH contributed equally to this work. YL and TH collected and interpreted the patient data. XJ A helped write the initial draft of the manuscript. WZ and HZ proposed the study design. QH supervised the project from initiation to completion. All author(s) read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate

Informed consent was obtained from the patient for publication and the study was approved by the institutional ethics committees of Tongji Hospital.

Consent for publication

The patient provided informed consent for the publication of this study.

Competing interests

The authors declare that they have no competing interests.

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Figures

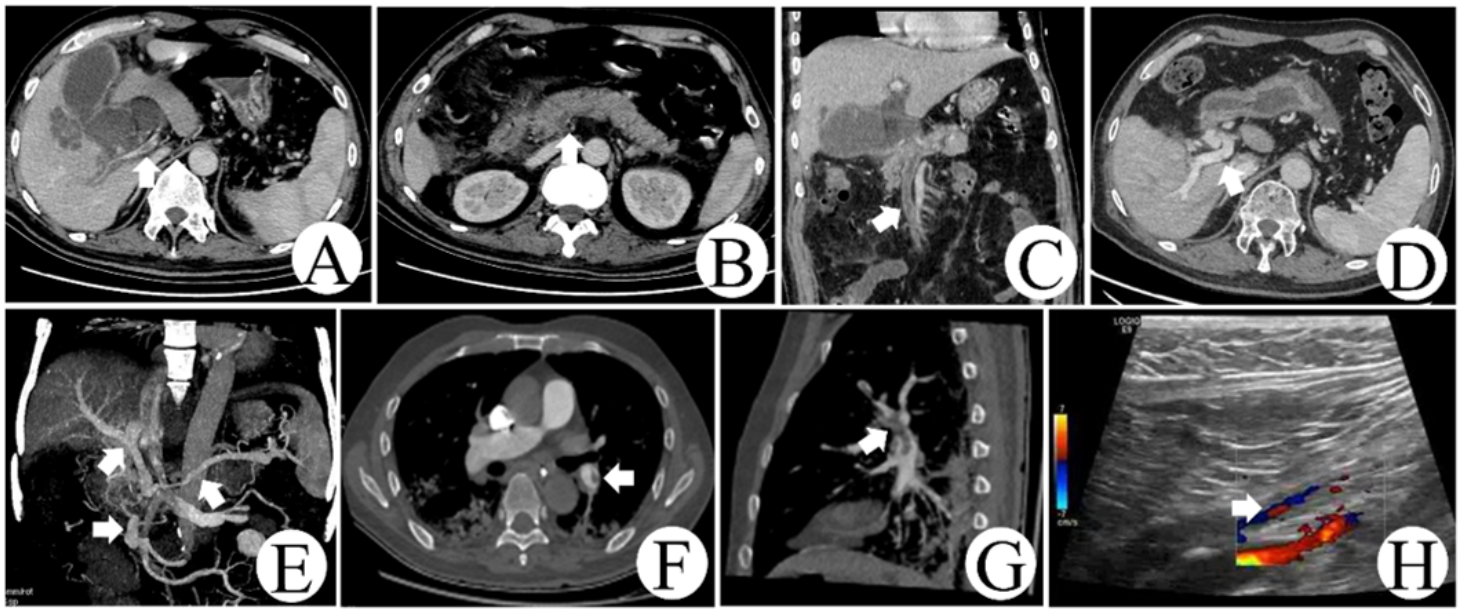

Figure 1

A triphase abdomen computed tomographic revealed filling defect in the major portal vein (A) and a low-density area in splenic vein (B). Coronal reconstruction of the abdominal computed tomography exhibited a low-density area in superior mesenteric vein (C). After 2 years of anticoagulation treatment with oral dabigatran, a triphase abdomen computed tomographic demonstrated complete recanalization of the portal vein thrombosis (D) and coronal maximum intensity projection showed the formation of aberrant collateral vessels and partial recanalization of the splenic vein, superior mesenteric vein thrombosis (E). At admission, transverse (F) and sagittal (G) computed tomography pulmonary angiography demonstrated filling defect in the left pulmonary artery. Color Doppler ultrasound showed thrombosis in bilateral femoral vein and the left popliteal vein.

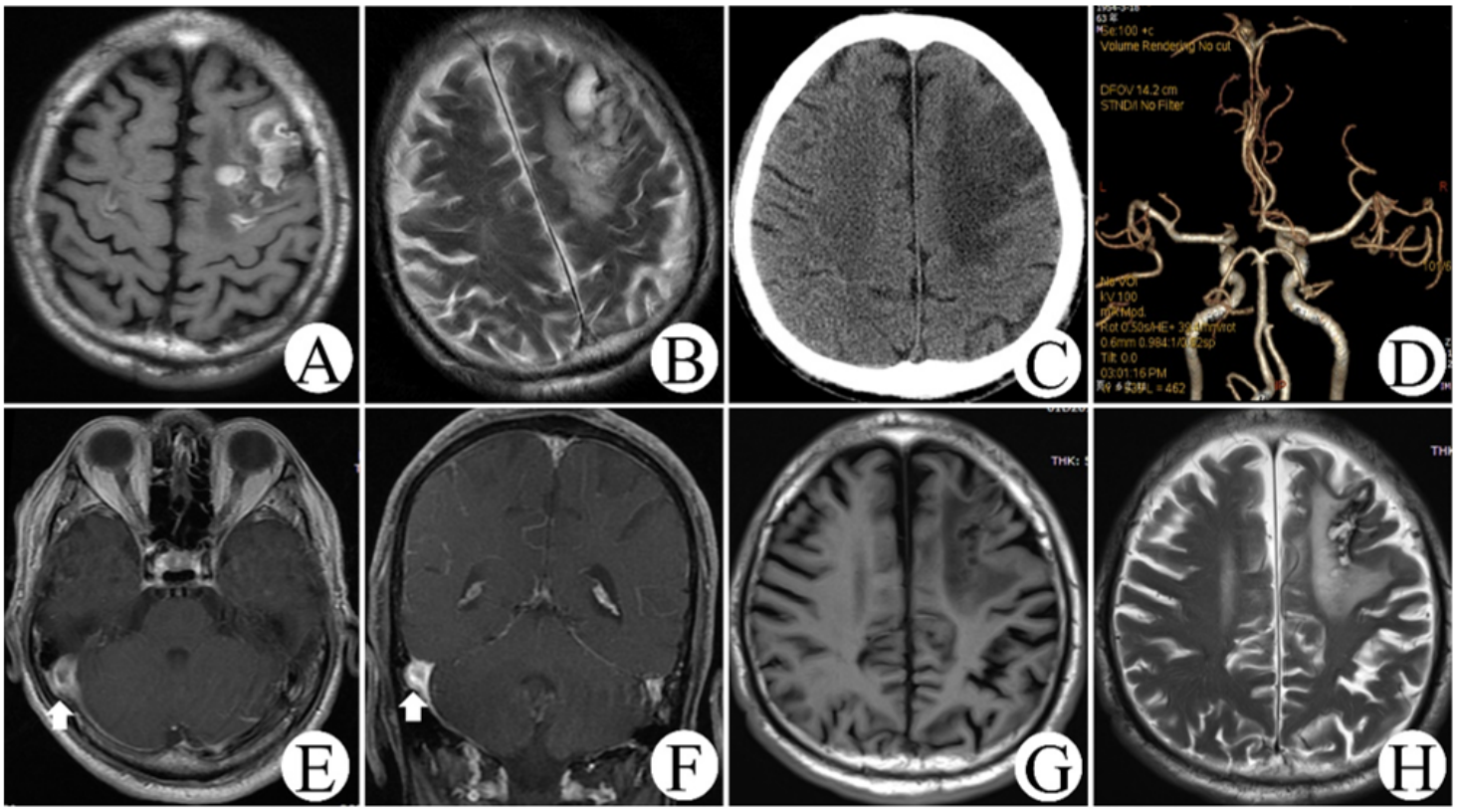

Figure 2

The T1-weighted magnetic resonance images (A), the T2-weighted magnetic resonance images (B) and CT images (C) demonstrate bilateral frontal hemorrhagic infarction. Axial (E) and coronal (F) contrast-enhanced T1-weighted magnetic resonance imaging demonstrate filling defect and a δ sign in the right transverse sinus, sigmoid sinus. The computed tomography angiography in brain is unremarkable except for hypoplasia of the left anterior cerebral artery A1 segment (D). The repeated T1-weighted magnetic resonance images (G) and the T2-weighted magnetic resonance images (H) reveal encephalomalacia in right frontal lobe after 2 years.

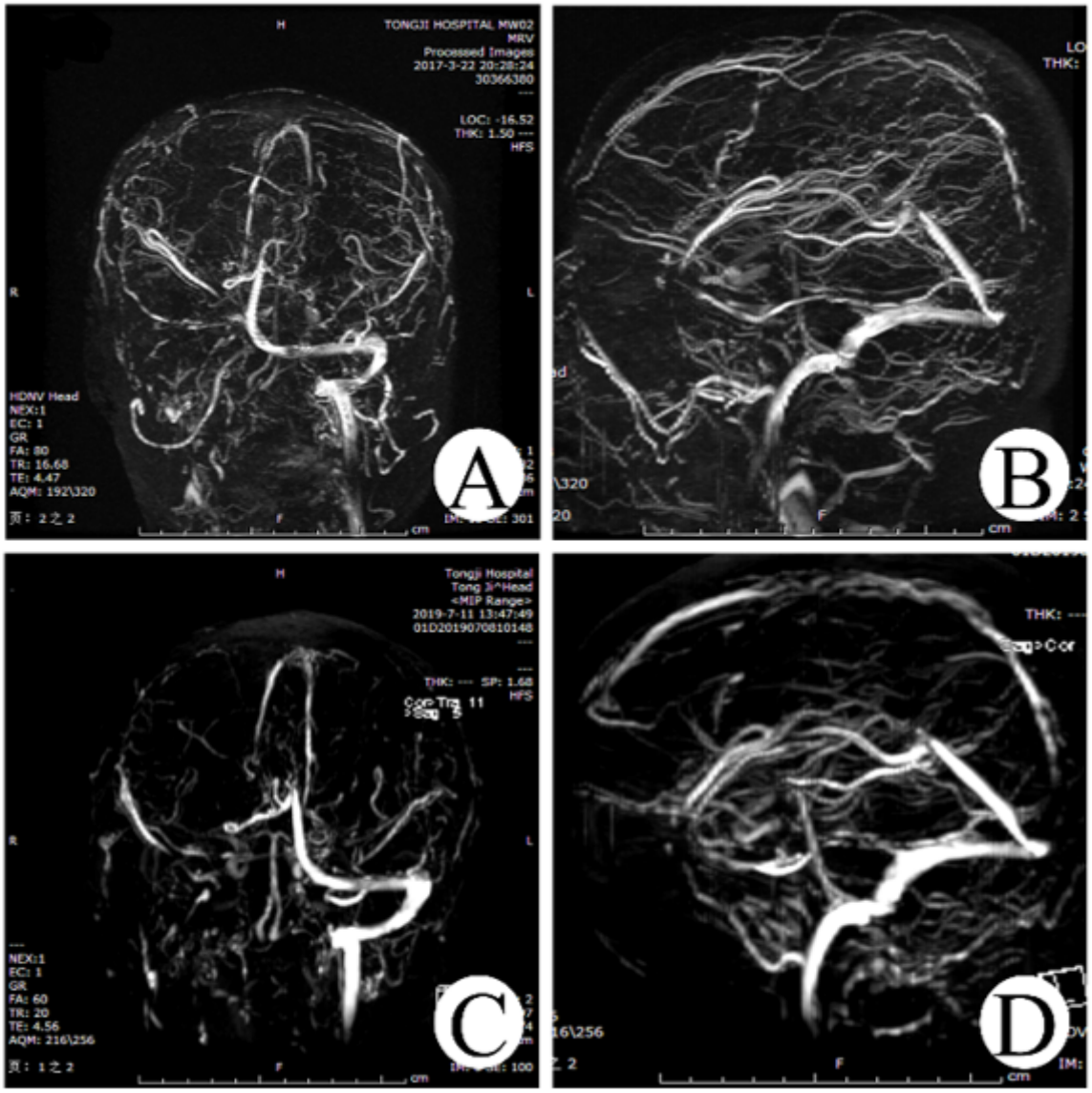

Figure 3

The brain magnetic resonance venography in 2017 reveals thrombosis involving right transverse sinus, right sigmoid sinus, superior sagittal sinus (A, B). The repeated magnetic resonance venography in 2019 demonstrates partial recanalization of right transverse sinus, right sigmoid sinus, superior sagittal sinus and the formation of aberrant collateral vessels (C, D).

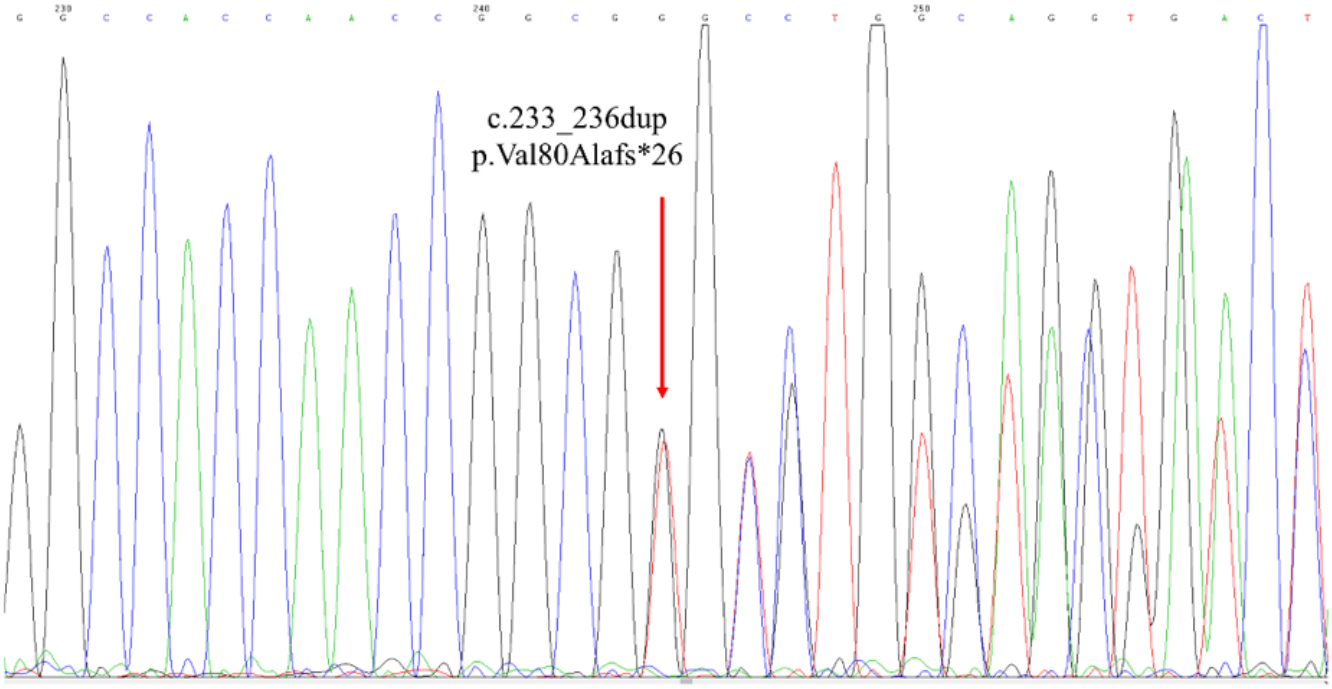

Figure 4

The heterozygous mutation in the SERPINC1 gene (c.233_236dup, p.Val80Alafs*26) was identified in the patient. The red arrow indicates the start of the frameshift duplication in the SERPINC1 gene.