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CASE SERIES

Association of the Coagulation Factor V c.3865T>G Mutation with Genetic and Regional Susceptibility to Cerebral Venous and Sinus Thrombosis in Xiangyang

Jun Zhang[1,*], Qian Liu[2,*], Chenglin Sun[1], Jun Yang[1]

[1]Department of Neurology, Xiangyang No.1 People's Hospital, Hubei University of Medicine, Xiangyang, 441000, People's Republic of China; [2]Department of Oncology, Xiangyang No.1 People's Hospital, Hubei University of Medicine, Xiangyang, 441000, People's Republic of China

*These authors contributed equally to this work

Correspondence: Chenglin Sun; Jun Yang, Department of Neurology, Xiangyang No. 1 People's Hospital, Hubei University of Medicine, Jiefang Road No. 15, Xiangyang, Hubei, 441000, People's Republic of China, Email sunchenglin1813@126.com; 296051103@qq.com

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Objective: This study investigates the potential genetic and regional associations of a newly identified c.3865T>G mutation in the F5 gene (coagulation factor V) with cerebral venous and sinus thrombosis (CVST).

Methods: Two groups of CVST cases associated with hereditary thrombophilia were analyzed. Genetic sequencing was performed to identify the patients' genetic profiles. A family pedigree analysis and a review of relevant literature were conducted to assess the pathogenic significance of the mutation.

Results: Genetic analysis revealed the presence of a c.3865T>G mutation in the F5 gene in both cases. This mutation is distinct from the well-established Leiden mutation and has not been previously reported. Although the two patients' families had no direct blood relationship, both patients resided in the same geographic region, suggesting the possibility of shared environmental or genetic factors. Advances in diagnostic technologies have also facilitated the identification of hereditary thrombophilia as an increasingly recognized cause of CVST.

Conclusion: The c.3865T>G mutation in the F5 gene may represent a novel genetic contributor to CVST. Its regional clustering points to a potential genetic and geographic association. These findings provide new insights into the etiology and diagnosis of CVST and underscore the importance of investigating regional genetic predispositions further.

Keywords: CVST, F5 gene c.3865T>G mutation, hereditary thrombophilia, genetic predisposition, regional association

Introduction

Cerebral venous and sinus thrombosis (CVST) refers to a cerebrovascular condition characterized by intracranial hypertension and focal brain damage caused by thrombosis in intracranial veins or venous sinuses due to various etiologies.[1] Among the common causes of CVST are hereditary or acquired hypercoagulable states.[2] While hereditary hypercoagulable states were previously considered to be rare causes of CVST in China, advances in diagnostic technologies and increasing awareness have led to a rising rate of diagnoses in recent years.[3] This study reports two cases of CVST caused by hereditary hypercoagulable states, both of which were found to harbor the c.3865T>G mutation in the coagulation factor V (FV) gene, as confirmed by genetic sequencing. This mutation is distinct from the well-established Leiden mutation and has not been previously reported. Although the two patients had no direct familial relationship, they both resided in the same geographic region, suggesting the possibility of specific environmental or genetic factors within this area. Through case analysis and literature review, this study explores the potential genetic and regional association of the FV c.3865T>G mutation with CVST. The details of the two cases are reported as follows.

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Case Presentation

Case 1

A 59-year-old male was admitted to the neurology department on August 3, 2018, with a chief complaint of "headache for one week, worsening and accompanied by limb convulsions for one day." One week prior, the patient began experiencing intermittent, mild headaches without any clear triggering factors. Due to the relatively mild nature of the pain, he did not seek treatment initially. However, one day before admission, his headache worsened, and he began experiencing two episodes of limb convulsions with impaired consciousness. He sought medical attention at a local hospital, where a CT scan showed hemorrhage in the left frontal lobe. Initially diagnosed as intracerebral hemorrhage, he received symptomatic treatment. Unfortunately, his symptoms did not improve, and his level of consciousness progressively worsened, prompting his transfer to our neurology department. The patient denied any significant past medical history. On admission, physical examination revealed: blood pressure 130/90 mmHg, shallow coma, no verbal response or eye-opening to painful stimuli, bilaterally equal and round pupils with a diameter of approximately 2 mm, diminished light reflex, flexion response in all four limbs to painful stimuli, negative bilateral Babinski signs, and a positive Kernig sign on the right side. Relevant auxiliary examinations included: D-dimer: 9.75 μg/mL. Brain MRI (Magnetic Resonance Imaging) and MRV (Magnetic Resonance Venography): Revealed extensive hemorrhagic cerebral edema in the left frontal lobe with minor bleeding, as well as thrombosis in the superior sagittal sinus and left transverse sinus (Figure 1A–D).

Based on the clinical history and findings, a diagnosis of cerebral venous sinus thrombosis (CVST) was considered. The patient was treated with low-molecular-weight heparin (LMWH) anticoagulation and symptomatic therapy. After one week, the patient regained consciousness, and there was no recurrence of limb convulsions. Three weeks later, his condition stabilized, and he was discharged. Follow-up brain MRI showed significant reduction in edema in the left frontal lobe (Figure 1E and F). Post-discharge, the patient received oral anticoagulation therapy with warfarin for three months. During a one-year follow-up, no recurrence was observed.

Case 2

A 50-year-old male was admitted to the neurology department on June 2, 2022, with a chief complaint of headache for three days, worsening and accompanied by unsteady gait for one day. The patient denied any past medical history. On admission, physical examination revealed: blood pressure 104/87 mmHg, clear consciousness, normal neck flexibility, bilaterally equal pupils with a diameter of 3 mm, brisk light reflexes, symmetrical oral angles, midline tongue protrusion, normal muscle strength and tone in all four limbs, negative bilateral Babinski signs, normal sensory function, and a positive cerebellar coordination test on the left side. No meningeal irritation signs were noted. Relevant auxiliary examinations included: D-dimer: 2.4 μg/mL. Brain MRI and MRV: Revealed thrombosis in the left sigmoid sinus and transverse sinus, as well as abnormal changes in the left cerebellar hemisphere, consistent with venous infarction (Figure 2A–C).

Based on the clinical history and findings, a diagnosis of CVST was made. The patient was treated with LMWH anticoagulation and neuroprotective symptomatic therapy. The headache gradually subsided, and the patient was discharged after three weeks. Follow-up brain MRI and MRV showed partial recanalization of the left sigmoid and transverse sinuses and a reduction in the size of the lesion in the left cerebellar hemisphere (Figure 2D–F). Post-discharge, the patient continued oral anticoagulation therapy with warfarin for three months. During a one-year follow-up, no recurrence was observed.

During the hospitalization of Patient 2, further inquiry revealed that he is the younger brother of Patient 1. Given the familial relationship and the clinical characteristics of both cases, a hereditary hypercoagulable condition was suspected. Blood samples were collected from seven family members for thrombophilia-related genetic testing (Shanghai BioGene Diagnostic Laboratory). The results showed that both patients carried the F5 gene mutation (c.3865T>C; p.F1289L), while no other family members tested positive for the mutation. The family diagram is presented in Figure 3.

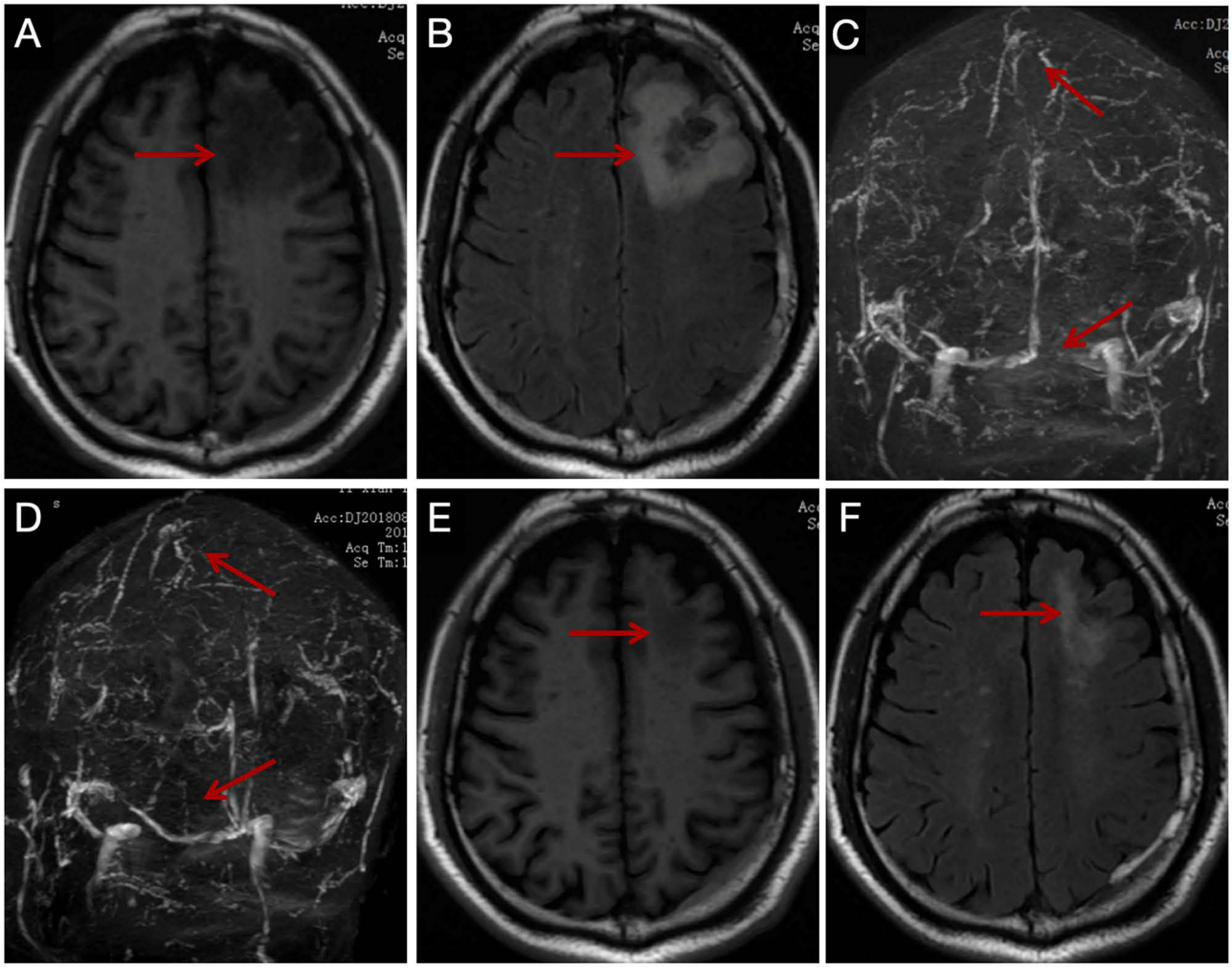

Figure 1 (**A**–**D**) 2018.8.09 Head MR suggested large area of cerebral edema in the left frontal lobe, minimal hemorrhage, thrombosis in the upper sagittal sinus and left transverse sinus (**A**) T1 Flair: The red arrow represents a large area of low signal with mixed signals in the left frontal lobe. (**B**). T2 Flair: The red arrow represents a large area of high signal with mixed signals in the left frontal lobe. (**C** and **D**). MRV: The red arrow represents thrombosis formation in the superior sagittal sinus and the left transverse sinus. (**E** and **F**), August 30, 2018: Significant reduction in edema in the left frontal lobe. (**C**). T1 Flair: The red arrow represents a large area of low signal with mixed signals in the left frontal lobe, with a smaller extent than before. (**F**). T2 Flair: The red arrow represents a large area of high signal with mixed signals in the left frontal lobe, with a smaller extent than before.

Case 3

A 60-year-old female was admitted to the neurology department on April 12, 2024, with complaints of "headache for 2 days and right-sided limb weakness for 7 hours." In 2016, the patient experienced deep vein thrombosis (DVT) in the right lower limb. Blood pressure was 127/88 mmHg, the patient was conscious, and speech was clear. Pupils were bilaterally equal and round, with brisk light reflexes. The right nasolabial fold was shallow, tongue protrusion deviated to the right, and neck flexibility was normal. Muscle strength was Grade 3 in the right limbs and Grade 5 in the left limbs. Muscle tone was normal, and bilateral pathological reflexes were negative. Relevant auxiliary examinations: D-dimer: 7.17 mg/L. Brain MRI and MRV: Showed thrombosis in the superior sagittal sinus and hemorrhagic cerebral edema in the right frontal lobe (Figure 4A–C).

Based on the clinical history and findings, a diagnosis of cerebral venous sinus thrombosis (CVST) was considered. The patient was treated with low-molecular-weight heparin (LMWH) anticoagulation, neuroprotective therapy, and symptomatic management. Her headache resolved, and the right-sided limb weakness returned to normal. A follow-up D-dimer level was 3.94 mg/L. Two weeks later, the patient was discharged. Follow-up brain MRI and MRV revealed

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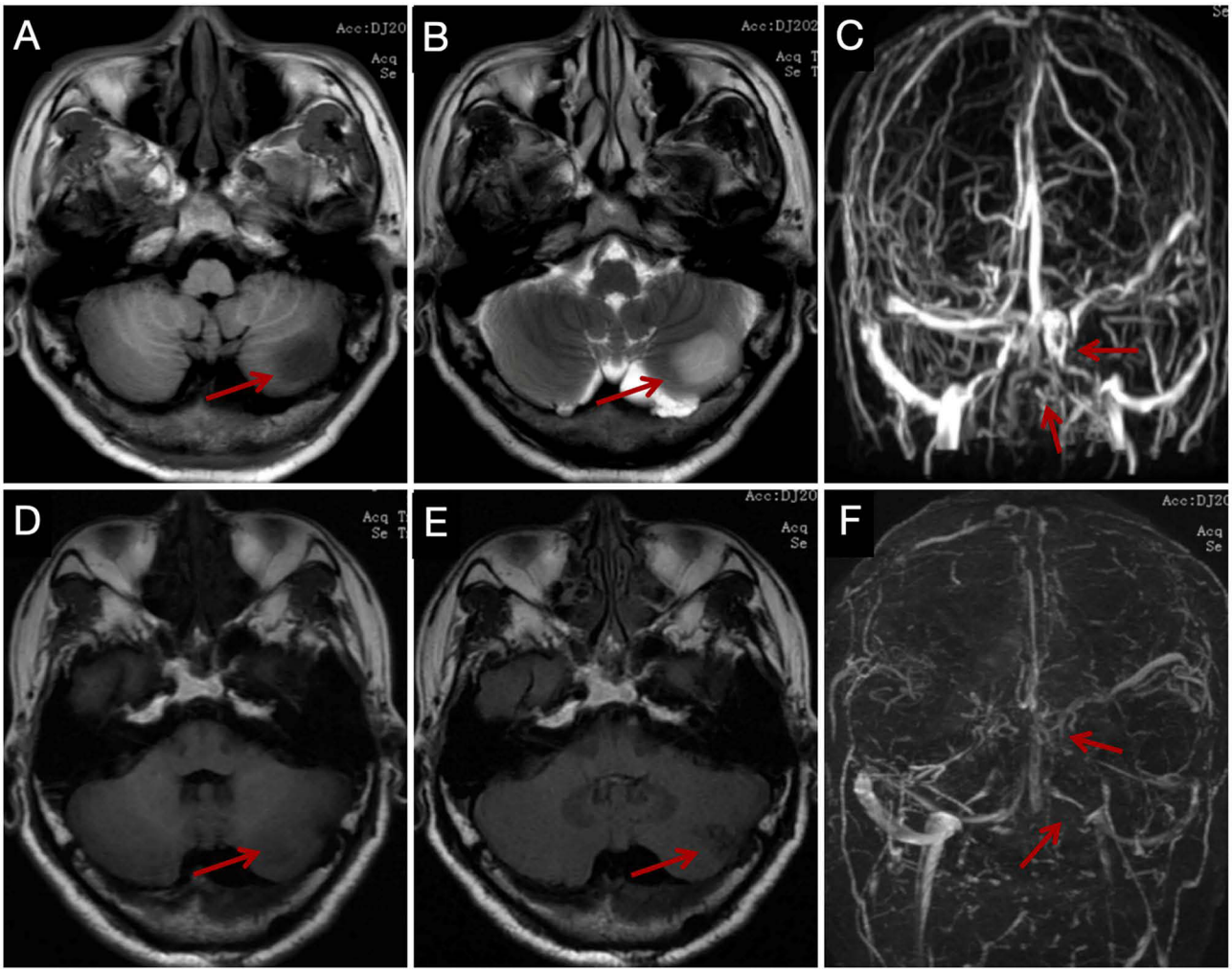

Figure 2 (**A–C**) 2022.06.02 Head MR indicated abnormal changes in the left cerebellar hemisphere, venous sinus thrombosis in the left sigmoid sinus and transverse sinus (**A**). T1W The red arrow represents a low signal in the left cerebellar hemisphere. (**B**). T2W: The red arrow represents a high signal in the left cerebellar hemisphere. (**C**). MRV The red arrow represents the formation of venous sinus thrombosis in the left sigmoid sinus and transverse sinus; (**D–F**) 2022.06.27 Head MR indicated that the left cerebellar hemisphere around the left sigmoid sinus and transverse sinus showed (**D**) T1Flair The red arrow represents a decrease in the low signal lesion around the left cerebellar hemisphere, with a smaller extent than before. (**E**). T2Flair The red arrow represents a reduction in the signal lesion around the left cerebellar hemisphere, with a smaller extent than before. (**F**). MRV The red arrow represents faint enhancement observed in the left sigmoid sinus and transverse sinus.

reduced cerebral edema in the right frontal lobe compared to the previous imaging, with no changes in the superior sagittal sinus thrombosis (Figure 4D–F).

After discharge, the patient was prescribed oral dabigatran for anticoagulation therapy. One month later, follow-up brain MRI and MRV revealed resolution of cerebral edema in the right frontal lobe and small vascular signals in the superior sagittal sinus (Figure 4G–I). Based on the patient's medical history, including a DVT in 2016 and the current CVST with no clear provoking factors, a hereditary hypercoagulable condition was suspected. Family history revealed that both parents were deceased, but the exact causes of death were unclear. The patient's brother had died of pulmonary embolism, while her sister was in good health. The patient's children reside out of town and were unavailable for sample collection. Blood samples were collected from the patient and her sister for thrombophilia-related genetic testing, conducted by Shanghai BioGene Diagnostic Laboratory. Results showed that both individuals carried the F5 gene mutation (c.3865T>C; p.F1289L). Figure 5 presents the family diagram.

Discussion

Stroke has become the leading cause of health problems in the world today, with CVST accounting for 0.5%–1.0% of all stroke cases.[4] CVST is caused by various factors and results in blood flow obstruction or impairment of cerebrospinal

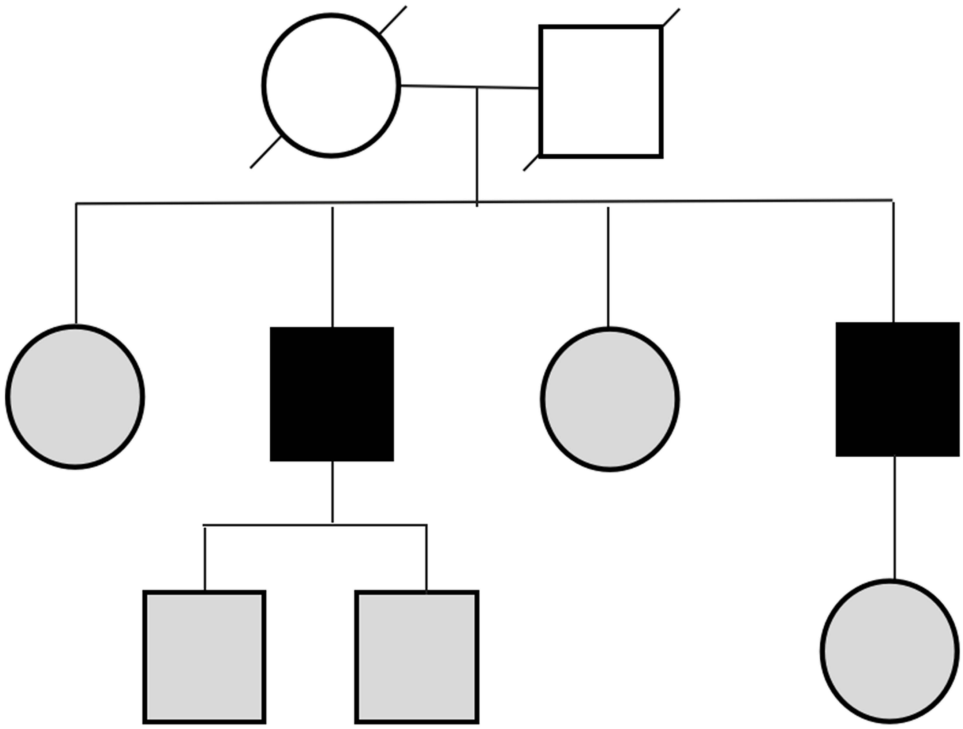

Figure 3 Family diagram of case 1 and 2. Family diagram of case 3. Black fill represents a family member with F5 (c.3865T and gt; C: p F1289L) mutation; grey fill represents family member with no detected genetic mutation; Slant line fill represents family member with F5 (c.3865T and gt; C: p F1289L) mutation but no CVST; diagonal line represents deceased family member; white fill represents family member without FV testing or CVST; square represents male; circle represents female.

fluid circulation, which then leads to intracranial hypertension and localized brain damage.[5] Diagnosis of CVST is often incorrect or missed. CVST is associated with various pathogenic factors, different clinical manifestations, and high disability and mortality rates, and poses a heavy burden to the family and society.[6] The incidence of CVST in European and American countries is approximately (0.5–2.0)/100,000 and that in developing countries such as the Middle East and Latin America can reach 7/100,000.[7] CVST is primarily caused by hereditary or acquired hypercoagulability, infection, inflammatory responses, autoimmune diseases, tumors, blood diseases, and drugs.[8,9] The incidence of intracranial venous vein and venous sinus thrombosis caused by genetic hypercoagulability states such as factor V Leiden mutation, thrombin G20210A mutation, and protein C, protein S, or antithrombin defects, is lower in China than in other countries, and these states are not the primary cause of CVST in China. However, as the domestic attention to CVST and the detection level has increased, the diagnosis rate of CVST has also increased each year. The recently published Chinese guidelines for the diagnosis and treatment of CVST highlight that hereditary and acquired thrombophilia ranks as the second most common cause of CVST.[10] This study is the first to report the FV c.3865T>G mutation in two CVST patients, suggesting that this mutation may represent a potential pathogenic variant in Asian populations.

In the hereditary thrombosis state, the genetic coagulation factor deficiency is among the key causes of CVST, and FV is a crucial member.[11] FV is located on chromosome 1q23. The prothrombin complex requires this protein co-factor to catalyze rapid thrombin generation, thereby increasing the thrombin activation rate by more than 1000 times. It also exerts an important influence on thrombin production.[12] The hereditary coagulation FV deficiency (HFVD) is a rare autosomal recessive hemorrhagic disease first described by Norwegian scholar Paul Owren in the 1940s. In this deficiency, a point G1691A mutation in the FV gene causes the replacement of arginine at position 506 of FV (Arg506Gln, FV Leiden).[13] Ethnic and regional differences are observed in the occurrence of this mutation. The incidence of FV Leiden carriers in the Caucasian healthy population is 2%–10%. FV Leiden mutations the most common genetic susceptibility factor in this race, which increases the risk of thrombosis by 5- to 10-fold.[14] This mutation is extremely rare in Asian populations including in Chinese people. In 1998, WP Chen et al first identified the FV R306G (FV Hong Kong) mutation in Chinese VTE patients in Hong Kong, China.[15] In the same year, a research team at the

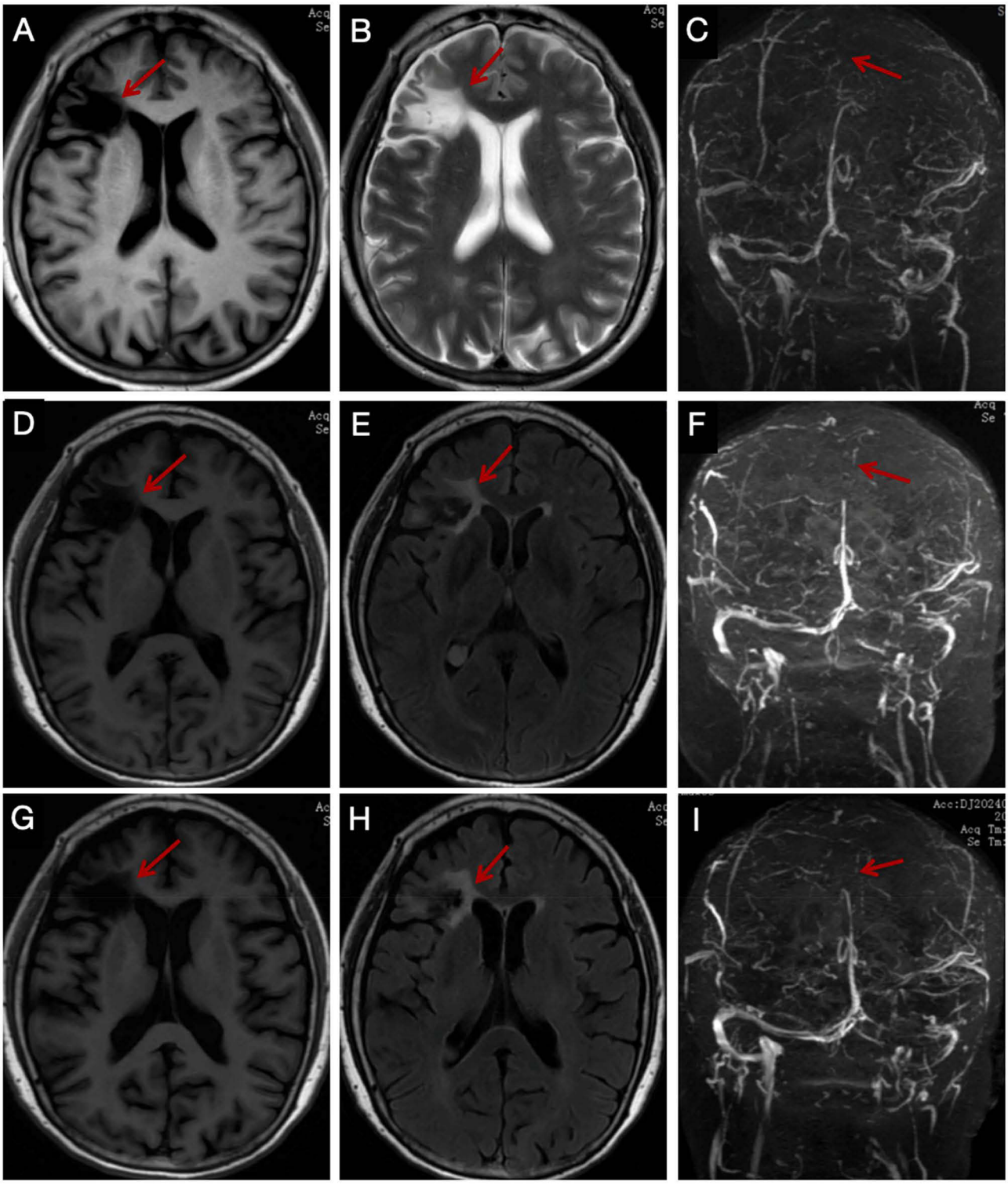

Figure 4 (**A**–**C**) 2024.4.13 Head MR suggested congestion of cerebral edema of right frontal lobe, thrombosis of superior sagittal sinus (**A**). T1W The red arrow represents a low signal in the right frontal lobe. (**B**). T2W The red arrow represents a high signal in the right frontal lobe. (**C**). MRV The red arrow represents thrombosis formation in the superior sagittal sinus.(**D–F**) 2024.4.28 Head MR indicates decreased right frontal lobe brain edema than anterior, superior sagittal sinus thrombosis compared with anterior (**D**). T1Flair The red arrow represents a reduction in the low signal lesion in the right frontal lobe, with a smaller extent than before. (**E**). T2Flair The red arrow represents a reduction in the high signal lesion in the right frontal lobe, with a smaller extent than before. (**F**). MRV The red arrow points to the same thrombosis in the superior sagittal sinus as before. (**G–I**) 2024.5.28 Head MR suggested the absorption period of cerebral edema in the right frontal lobe and the upper sagittal sinus with (**G**). T1Flair The red arrow represents the absorption phase of brain edema in the right frontal lobe. (**H**). T2Flair The red arrow represents the absorption phase of brain edema in the right frontal lobe. (**I**). MRV A fine vascular shadow is seen locally in the superior sagittal sinus (red arrow).

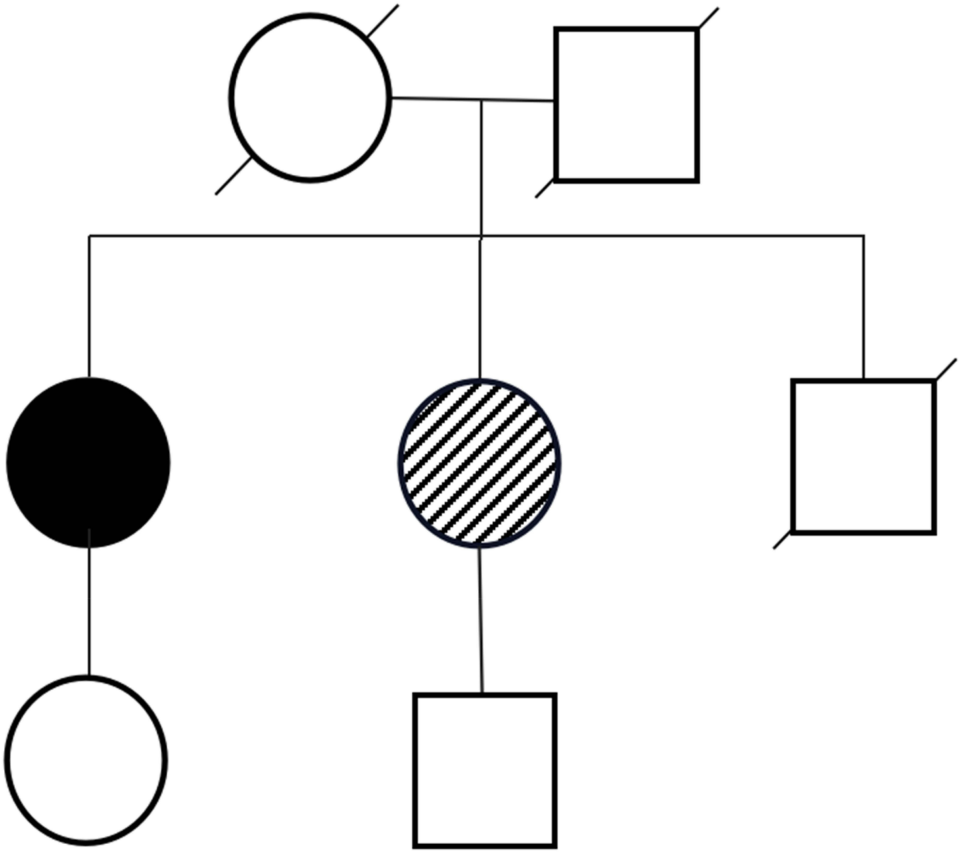

Figure 5 Family diagram of case 3. Black fill represents a family member with F5 (c.3865T and gt; C: p F1289L) mutation; grey fill represents family member with no detected genetic mutation; Slant line fill represents family member with F5 (c.3865T and gt; C: p F1289L) mutation but no CVST; diagonal line represents deceased family member; white fill represents family member without FV testing or CVST; square represents male; circle represents female.

University of Cambridge reported about the FV R306T (FV Cambridge) mutation.[16] In the early 2000s, Thompson J et al first reported the FV A1079T (FV Liverpool) mutation. Sara Sacchetti et al further discovered the molecular mechanism underlying the role of coagulation FV in thrombosis and reported its significance as a potential therapeutic target.[17] In this study, both patients were found to carry the FV c.3865T>G mutation, while the FV Leiden mutation, commonly observed in Caucasian populations, was not detected. This finding aligns with previous research suggesting that the FV Leiden mutation is rare in Asian populations. Moreover, it indicates that the FV c.3865T>G mutation may represent a rare hereditary thrombophilic factor specific to certain Chinese populations. Based on family pedigree analysis and genetic sequencing results, we hypothesize that this mutation is associated with hereditary hypercoagul ability. However, the molecular mechanisms of the c.3865T>G mutation and its role in promoting hypercoagul ability remain unclear and warrant further investigation to confirm its pathogenicity.

Notably, this study found that while the two families had no direct familial relationship, they both resided long-term within the jurisdiction of Xiangyang City, Hubei Province, specifically in Gucheng County and Fancheng District. These two locations are situated along the Han River, with a straight-line distance of approximately 70 kilometers. This finding suggests that the FV c.3865T>G mutation may have a certain regional genetic characteristic, akin to the concentrated distribution of specific genetic mutations observed in other geographic areas. For example, a 2022 study on FV deficiency patients in Keelung City, Taiwan, identified a specific FV gene mutation, the homozygous Met1736Val mutation, which was found at a higher frequency in this region compared to other areas of Taiwan.[18] In light of these findings, the possibility that environmental or geographic factors contribute to the increased prevalence of certain hereditary mutations in specific regions warrants further attention. This hypothesis requires validation through larger-scale, multi-center clinical studies.

This study has certain limitations, such as the small sample size and the inability to conduct comprehensive molecular genetic analyses of the patients' family members. Additionally, functional experiments and mechanistic studies of the mutation have not yet been performed, meaning the conclusions of this study require further evidence for validation. In future research, we plan to collaborate with other medical institutions in the Xiangyang region to conduct multi-center, large-sample genetic studies. These efforts aim to determine whether the FV c.3865T>G mutation is a pathogenic variant and to further investigate its potential regional and genetic mechanisms. Such studies would not only enhance our understanding of the genetic causes of CVST but also provide valuable insights for personalized treatment and genetic counseling for affected families.

Data Sharing Statement

The medical records of the patients contains all the necessary data that was used for this case report. Given the privacy concerns, regulations and informed consent provided by the patient and their guardian, this record cannot be made publicly available. Further information can be obtained upon contacting the corresponding author.

Ethics Approval

This study was approved by the Ethics and Scientific Committee of Hubei University of Medicine. Approval was obtained from Hubei University of Medicine to publish the case details. Written informed consent was obtained from both patients to publish their clinical history. Copies of approval and written consents are available upon reasonable request from the authors.

Consent for Publication

We confirm that the patients provided written informed consent for their case details and images to be published.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors have no conflicts of interest to declare for this work.

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