

# A case of hereditary thrombophilia in a Chinese Han patient with both antithrombin deficiency and Factor V Leiden: A case report and literature review

Xinyuan LI<sup>1,\*</sup>, Weihong LIN<sup>1,\*</sup>, Lijun ZHU<sup>2,\*</sup>, Yonghong WANG<sup>1</sup>, Shan LIU<sup>1</sup>,  
Jing LIU<sup>1</sup>, Heqian DU<sup>1</sup>, Shaokuan FANG<sup>1</sup>

<sup>1</sup> Department of Neurology, Neuroscience Centre, the First Teaching Hospital of Jilin University, No 71 Xinmin Street, Changchun, Jilin, 130021, P.R. China.

<sup>2</sup> China-Japan Union Hospital of Jilin University, No 126 Xiantai Street, Changchun, Jilin, 130033, P.R. China.

\*These authors contributed equally to this work.

Correspondence to: Shaokuan Fang, MD., PhD.  
Department of Neurology, Neuroscience Centre  
The First Teaching Hospital of Jilin University  
No 71 Xinmin Street, Changchun, Jilin, 130021, P.R. China.  
TEL: +86431-88982396; FAX: +86431-88982378; E-MAIL: fang20063536@sina.com

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## Abstract

Hereditary thrombophilia is a blood coagulation disorder that increases the risk of venous thromboembolism, due to several genetic risk factors. Factor V Leiden(FVL) is the most common contributing factor to thrombophilia in the Caucasian population but very rare in Asian population and concurrent occurrence of antithrombin(AT) deficiency and FVL in Chinese Han population is even more rare. We report the case of a 22-year-old female who experienced recurrent intracranial venous thromboses, furthermore, color Doppler ultrasound showed multiple extracranial thromboses. Thrombophilia was suspected and screening tests indicated decreased AT activity and activated protein C sensitivity ratio, then further sequencing analysis identified missense mutations in SERPINC1 and F5. The patient's condition slightly improved after treatment with low molecular heparin during hospitalization followed by oral warfarin after discharge. The present report highlights a very rare case of thrombophilia with concurrent occurrence of AT deficiency and FVL in a Chinese Han patient, and our findings suggest that genetic testing is a reliable approach for identifying different risk factors.

## Abbreviations

VTE	- venous thromboembolism
FVL	- Factor V Leiden
AT	- antithrombin
APC-R	- activated protein C resistance
MRC	- Medical Research Council
CT	- computed tomography
MRI	- magnetic resonance imaging
MRV	- magnetic resonance venography
MRBTI	- magnetic resonance black-blood thrombus imaging
CSF	- cerebrospinal fluid

APC sr - activated protein C sensitivity ratio  
LMWH - low molecular weight heparin

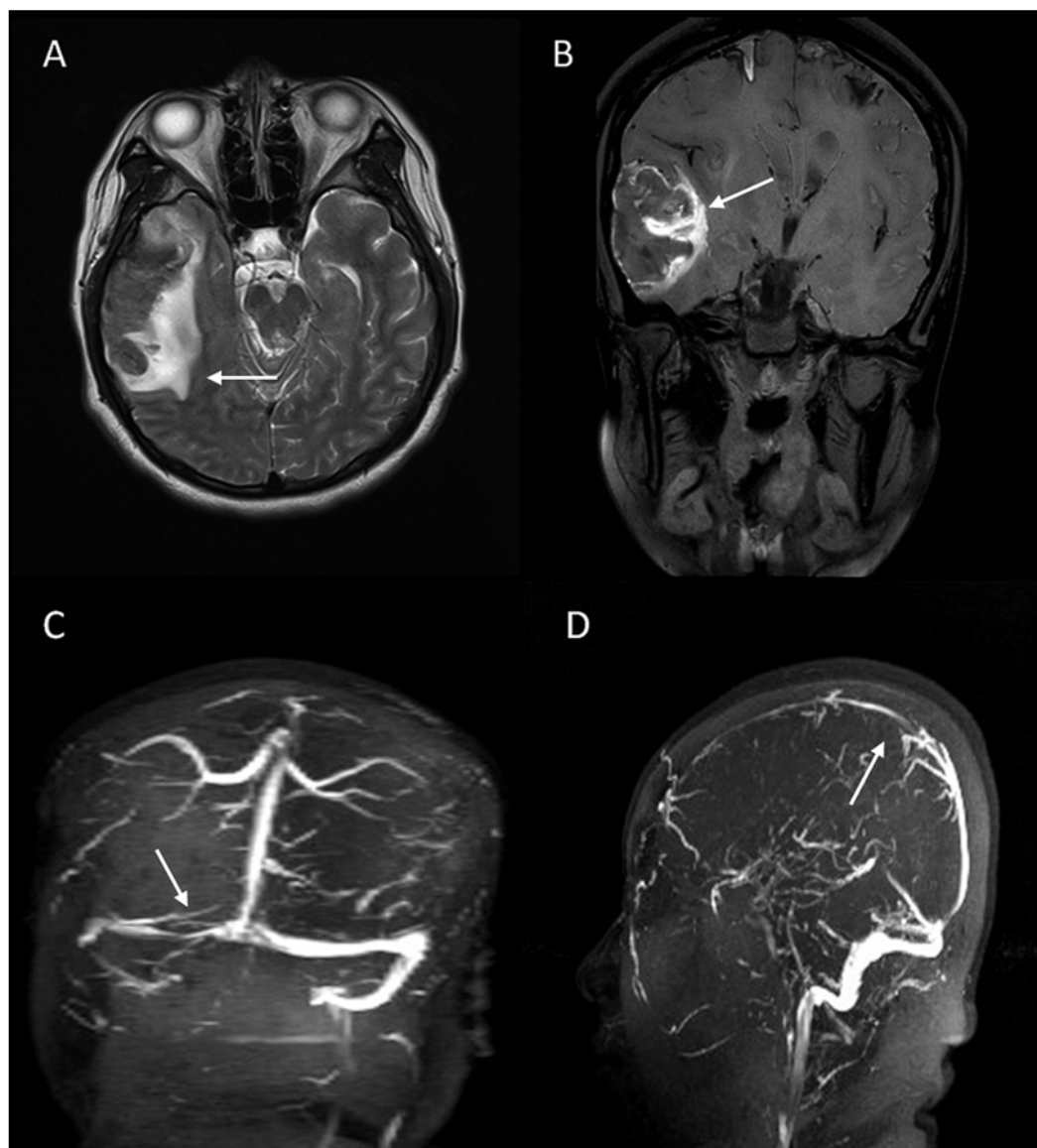
philia with concurrent occurrence of AT deficiency and FVL in a Chinese Han patient.

## INTRODUCTION

Thrombophilia involves the formation of multiple thromboses, especially venous thromboembolism (VTE), and is categorized as hereditary or acquired thrombophilia (Ekim *et al.* 2015). VTE accounts for much of the morbidity and mortality related to thromboses, with a prevalence of 56–160/100,000 people/year (Vilhena *et al.* 2016). The established inherited factors for thrombophilia include deficiencies in antithrombin (AT); protein C; and protein S; activated protein C resistance (APC-R); factor V Leiden (FVL); prothrombin G20210A mutations (Cohn *et al.* 2012) and so on. Among these, FVL is the most common contributing factor to thrombophilia in the Caucasian population (Cinier *et al.* 2016) but very rare in Asian populations. The current case highlights a very rare case of thrombo-

## CASE REPORT

A 22-year-old female patient presented to the emergency department with a 7-day history of headache and vomiting. Her medical history revealed intracranial venous thromboembolism followed by seizures with a spontaneous abortion at 6 months of gestation 2 years previously. Her blood pressure was 129/80 mmHg, and her heart rate was 106 beats/min. Her body temperature was 38.5°C. The muscle strength in her upper limbs was scored as Medical Research Council (MRC) grade 5, whereas the muscle strength in her lower limbs was scored grade 3. The muscle tone of her extremities was normal. The deep tendon reflexes of the upper limbs were increased, while those of the lower limbs were normal. There were no deficits of superficial or



**Fig. 1.** Brain MRI at admission. (A) Axial MRI T2 showed multiple abnormal signals mainly in the right temporal lobe, (B) Coronal MRBTI indicated indirect signs in the frontal and temporal lobe, (C) MRV showed thread-like signals in the sigmoid portion of the lateral sinus, (D) Abnormality in superior sagittal sinus was shown. MRI, magnetic resonance imaging; MRBTI, magnetic resonance black-blood thrombus imaging; MRV, magnetic resonance venography.

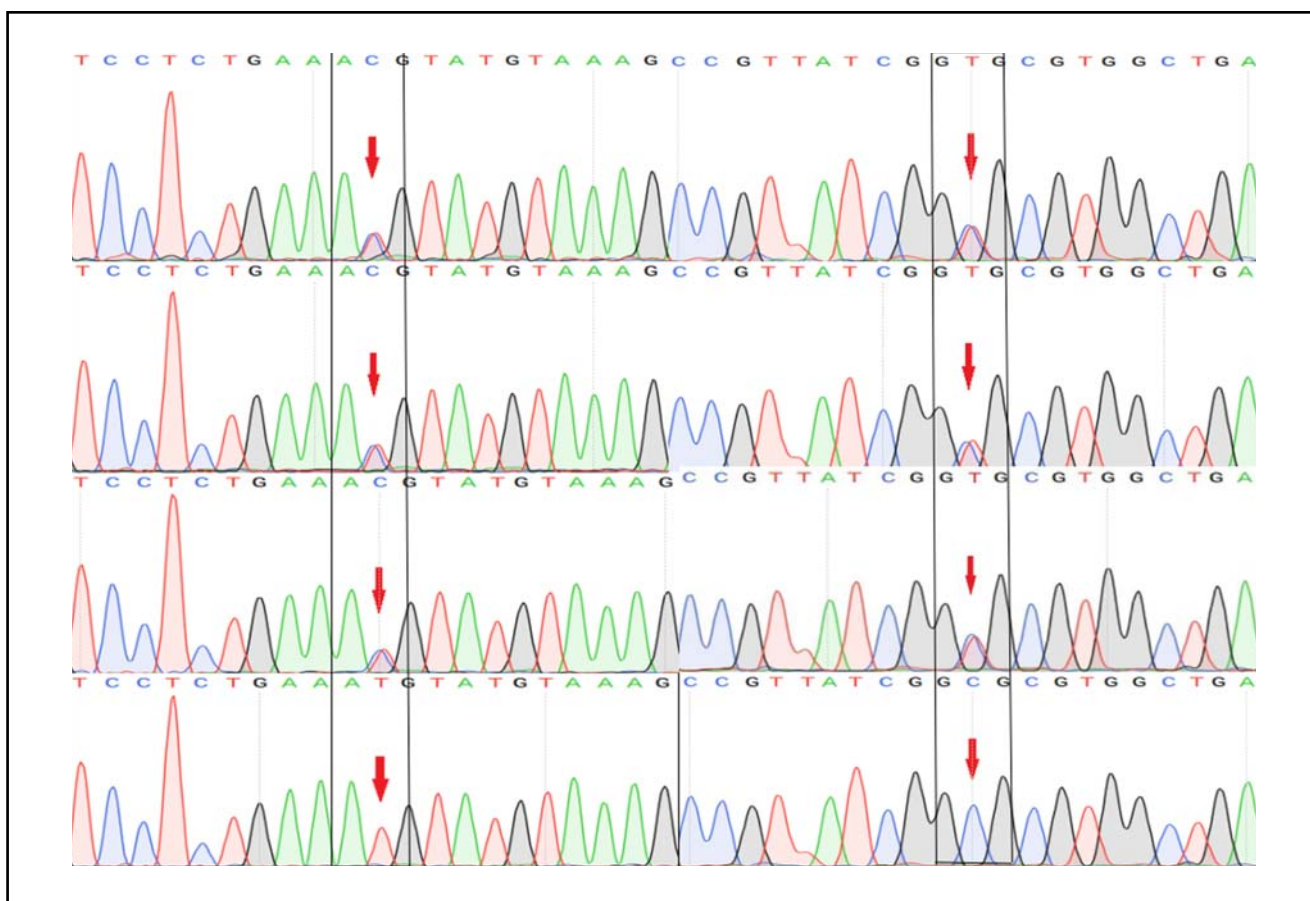
deep sensation, and cranial nerve examination was normal. Babinski and Chaddock signs were bilaterally positive. Computed tomography (CT) showed intracerebral hemorrhage in the right temporal lobe. Cranial magnetic resonance imaging (MRI) showed multiple abnormal signals mainly in the right temporal lobe. Cranial magnetic resonance venography (MRV) indicated thread-like signals in the sigmoid portion of the lateral sinus and superior sagittal sinus. Magnetic resonance black-blood thrombus imaging (MRBTI) further confirmed the abnormalities in the right frontal and temporal lobes (Figure 1). Blood tests revealed a D-dimer concentration of 629  $\mu\text{g/l}$ , serum homocysteine concentration of 12.4  $\mu\text{mol/l}$  (normal range: 0–15  $\mu\text{mol/l}$ ), AT activity of 51% (normal range: 80–120%), serum AT concentration of 8.4 mg/dl (normal range: 15–31 mg/dl), plasma protein S level of 39.6% (normal range: 60–130%), and protein C level of 80% (normal range: 70–140%). Tests for the anticardiolipin and  $\beta$ -2 glycoprotein antibodies were negative. Lumbar puncture showed a cerebrospinal fluid (CSF) pressure of 400 mmH<sub>2</sub>O. The results of biochemical and cytological examinations of the CSF were normal. Tests for thyroid function, rheumatic antineutrophil cytoplasmic antibodies, erythrocyte sedimentation rate, creatine

kinase level, and rheumatoid factors were unremarkable. Ultrasound of the neck revealed a circumfluence obstacle of the jugular vein and slow blood in the J2 segments of the bilateral internal jugular veins. Furthermore, thrombosis was observed in the bilateral cephalic veins by color Doppler ultrasound, and therefore, the patient was diagnosed with thrombophilia. Genetic testing identified two missense mutations in the F5 [c.6443T>C(p.Met2120Thr)] and SERPINC1 [c.880C>T(p.Arg294Cys)] genes, which encode factor V and AT, respectively. The same genetic mutations were identified in her mother and younger brother (Figure 2), but not in her father. Furthermore, they

**Tab. 1.** Clinical phenotype and laboratory data for the family.

Subjects	Age	Clinical phenotype	AT activity	APCs <sub>r</sub>
Patient	22	Two episodes	51%	1.5
Father	53	No thrombotic events	92%	2.3
Mother	54	DVT(lower limbs)	70%	1.7
Younger brother	12	No thrombotic events	87%	2.1

APCs<sub>r</sub>, activated protein C sensitivity ratio; DVT, deep venous thrombosis; AT, antithrombin; NA, not applicable.



**Fig. 2.** Sequence chromatograms of F5 and SERPINC1 gene for the family (the patient, mother, younger brother, and father). The missense C to T transitions (marked with red arrow) of p.Met2120Thr in F5 and p.Arg294Cys in SERPINC1 were present concurrently in the patient, her mother, and her younger brother but not in her father.

were screened for activated protein C sensitivity ratio (APCsr) and AT (Table 1). The patient's condition improved after treatment with low molecular weight heparin (LMWH) during hospitalization followed by oral warfarin after discharge. She had an international normalized ratio (INR) of 2.6 at the 6-month follow-up, and repeat laboratory tests were performed with AT activity of 62% and an APCsr of 1.7, which further confirmed the diagnosis.

## DISCUSSION

AT deficiency is categorized into two types based on quality and quantity: type I is defined as a parallel reduction in AT antigen and activity, and type II is characterized by decreased functional activity but a normal antigen level. Type II is further subdivided into three subtypes according to the defect in the functional domain: impairment of the heparin-binding site (type IIBS), impairment of the reactive site (type IIRS), and pleiotropic effects of multiple defects (type IIPE) (Bayston & Lane 1997). Inherited AT deficiency, caused by mutations in the SERPINC1 gene, consisting of seven exons and six introns and spanning 13.477 bp (Perry & Carrell 1996), is transmitted in an autosomal dominant manner (David *et al.* 2004) and is a well-known risk factor predisposing patients to a first VTE episode and dramatically increasing their risk of recurrent VTE. The prevalence of inherited AT deficiency is estimated to be 0.02–0.25% among the general population and type I AT deficiency is 2-times more prevalent than type II (Sekiya *et al.* 2017). More than 200 different AT mutations have been identified, mainly involving heterozygous mutations (Fischer *et al.* 2013). In addition, SERPINC1 nonsynonymous mutations in AT have been reported in a Chinese Han population, including nonsense, missense, frameshift, splice-site mutations, etc. Variant genotypes may manifest as different phenotypes. It was reported that carriers of nonsense mutations, which mainly cause type I AT deficiency, have a higher risk of VTE, younger age at first onset of VTE, and lower AT activities than do missense mutation carriers, leading to type I or II deficiency. However, there are no differences in the thrombus sites between patients with the two mutations (Wang *et al.* 2016).

FVL is the most common contributing factor for VTE, especially DVT in the legs (Cinier *et al.* 2016). Heterozygous carriers of FVL have a 3–8-fold increased risk of VTE, while homozygous carriers have a 90-fold increased risk (Boroumand *et al.* 2014). The prevalence of heterozygous carriers is about 3–5% in the Caucasian population and 18% among unselected Caucasian patients with a first episode of VTE. However, there is a very low incidence in African and Asian populations (Ekim *et al.* 2015). Previous studies have confirmed that the F5 missense mutation G1691A (Arg506Gln) polymorphism in exon 10 is responsible for APC-R (Pezeshkpoor *et al.* 2016), leading to a hypercoagulable state

as the result of less anticoagulation function of APC. Under normal conditions, Factor V plays a pivotal role as a coagulant factor and APC serves as an anticoagulant protein in the elimination of activated coagulation factors V, VIII, and X to maintain the balance of the procoagulant, anticoagulant, and fibrinolytic pathways. The mutant factor V cannot be inactivated by APC and increases thrombotic risk. In the current case, a reduced factor V level in Met2120Thr carriers was associated with increased APC-R, further increasing the risk for thrombophilia (Scanavini *et al.* 2004).

In the current case, the patient experienced the onset symptom of intracranial venous thrombosis and was diagnosed with thrombophilia along with AT deficiency and FVL mutation. AT deficiency and activated protein C resistance arising from FVL are both autosomal dominant genetic disorders due to SERPINC1 and F5 gene mutations, respectively. Because of the rarity of these two conditions, their combined occurrence in the same patient, especially in a Chinese Han family, is even more highly unlikely. DNA sequencing identified missense mutations in F5 and SERPINC1: a p.Met2120Thr mutation in the code for factor V and a p.Arg294Cys mutation in the code for AT. The Met2120Thr mutation was reported as a FVL polymorphism in the C2 domain, causing a reduced level of factor V and resulting in a significantly increased APC-R (Scanavini *et al.* 2004). The Arg294Cys mutation was found to be a nonsynonymous mutation in SERPINC1 exon 5 that is related tightly to AT in 173 Japanese DVT patients (Miyata *et al.* 2009). We hypothesized that her younger brother's asymptomatic status was either due to incomplete penetrance or type II AT deficiency and that he had a lower risk of VTE and older predicted age at onset of first event (Sekiya *et al.* 2017).

Once thrombophilia is suspected, we should conduct well-designed screening tests and further genetic testing in order to identify the cause of thrombophilia, to choose the most appropriate treatment, and to decide whether long-term prophylaxis is needed to prevent a thrombotic recurrence. To accurately test for thrombophilia, the patient was switched to LMWH 2 weeks before testing because LMWH can reduce the level of AT. The patient had low AT activity, and clotting assay detected reduced APCsr. However, these assays if performed during an acute thrombotic episode can be misleading; thus, repeat assays were performed at 6-month follow-up after the thrombotic episode to confirm the diagnosis (Korovin *et al.* 2016).

For a first episode of unprovoked thromboembolism, LMWH, which is a first-line therapy, particularly for AT deficiency, that can improve the anticoagulant effect by least 1000-fold when AT interacts with heparin sulphate (Wang D *et al.* 2016), should be given for at least 5 days, followed by oral anticoagulants for 6 months according to standard guidelines, with the recommendation that the INR should be controlled between 2 and 3 (Campello *et al.* 2016). Lifelong prophylactic antico-

agulant therapy is recommended for recurrent thrombosis in which the INR can be higher. Our patient received treatment with LMWH for 5 days during hospitalization, which was followed by oral warfarin from an initial dosage of 3 mg up to 4.5 mg after discharge. The patient had an INR of 2.6 at the 6-month follow-up. However, oral anticoagulants should be avoided by patients who are pregnant and those who have active cancer, antiphospholipid antibody syndrome, severe renal insufficiency, or prosthetic heart valves. LMWH can benefit women with recurrent pregnancy loss. In addition, there are additional new anticoagulants like edoxaban, apixaban, and rivaroxaban (Shen *et al.* 2016). The use of these new oral anticoagulants may be an option, especially for FVL heterozygous carriers. It is worth mentioning that edoxaban requires an initial treatment with heparin whereas apixaban and rivaroxaban do not (Campello *et al.* 2016).

In conclusion, FVL in Chinese patients is seldom reported and the concurrence of AT deficiency and FVL is even more rare. This is the first case report with two combinations of thrombophilia risk factors in a Chinese Han patient, and our findings suggest that genetic testing is a reliable approach for distinguishing different risk factors. More studies are warranted to explore the incidence of FVL and the co-existence of risk factors in Chinese people.

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