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CASE REPORTS

Familial moyamoya disease with bilateral presentation associated with the RNF213 c.14429G>A variant: A mother-daughter case report

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Abstract

Moyamoya disease (MMD) is a chronic idiopathic cerebrovascular disease with an undetermined etiology, characterized by stenosis or occlusion of the ends of the internal carotid arteries bilaterally and the anterior and middle cerebral arteries at their beginnings, and secondary to the formation of an abnormal vascular network at the base of the skull. We report a 12-year-old Chinese girl diagnosed with cerebral infarction and bilateral MMD. Magnetic resonance imaging (MRI) showed multiple cerebral infarctions, cerebral ischemia, and encephalomalacia. The patient's mother, a 36-year-old female, who was the biological mother of the 12-year-old girl, presented with left limb weakness 3 years prior and was diagnosed with bilateral MMD. The mother-daughter pairs with MMD were found to be due to a heterozygous variant in the RNF213 gene c.14429G> A. Clinically both had bilateral MMD, and the disease started with lesions on the left limb. After the diagnosis of MMD, mother and daughter were treated with different surgical procedures. Genetic testing for RNF213 is suggested for family member screening. *Conclusion:* Genetic testing for RNF213 is suggested for family members of MMD, and c.14429G>A variant is an important hereditary gene mutation.

Keywords: Moyamoya disease, Familial inheritance, RNF213, c.14429G>A, Genetic testing

INTRODUCTION

Moyamoya disease (MMD) was first reported by two Japanese neurosurgeons, Suzuki and Takaku. The abnormal vascular network of the skull base appears as a cloud of smoke on cerebral angiography; therefore, it was named MMD.[1] There are two peak ages of MMD onset: around 10 years of age and around 30-40 years of age. However, the age peak may occur later in women than in men. In children with MMD, the main symptoms are cerebral ischemia, especially transient ischemic attack (TIA), which is also accompanied by clinical manifestations of mental decline, seizures, and involuntary movement. Intracranial hemorrhage occurs more frequently in adult patients with MMD than in pediatric patients.[2] RNF213 encodes an unconventional E3 ubiquitin ligase and is a major susceptibility gene for MMD in East Asian populations. The Arg4810Lys mutation in this gene is most strongly associated with MMD, but its penetrance is less than 1%. The RNF213 non-Arg4810Lys mutation is more common in Caucasians, which may explain the lower prevalence of MMD in European countries and the United States than in East Asian countries.[3] Despite this established association, the phenotypic spectrum and penetrance within families carrying this variant can be heterogeneous. This report contributes to this understanding by detailing the clinical course and management in a mother-daughter pair both harboring the heterozygous c.14429G>A variant. This paper reports: Both mother-daughter pairs with MMD due to a heterozygous variant in the RNF213 gene c.14429G> A. Both the mother and her daughter had bilateral MMD, and the disease started with lesions on the left limb.

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CASE REPORT

Patient 1

A 12-year-old previously healthy girl presented with left-sided weakness consistent with a transient ischemic attack (TIA). During the episodes, she exhibited instability while holding objects and inability to walk, which lasted approximately 1–2 minutes and resolved spontaneously. A total of three such episodes occurred. Physical examination revealed no obvious neurological deficits. There was no evidence of language dysfunction, developmental delay, or other autoimmune disorders. Magnetic resonance imaging (MRI) showed multiple punctate and patchy hyperintensities in the right basal ganglia and bilateral corona radiata (Figure 1A). Cerebral MRI perfusion imaging showed reduced cerebral blood perfusion bilaterally (Figure 1B). Digital subtraction angiography (DSA) revealed bilateral occlusion of the internal carotid arteries (ICA) with moyamoya vessel formation (Figure.1C-D). After excluding surgical contraindications, she underwent an encephaloduroarteriosynangiosis (EDAS) procedure in the right hemisphere and tolerated the procedures well. After clinical improvement, follow-up cranial CTA demonstrated good intracranial blood supply (Figure 1E). The patient recovered well after surgery and received regular anticoagulation therapy with aspirin postoperatively. One year later revealed abundant filling of the right middle cerebral artery region by the external carotid artery (Figure 1F). Meanwhile, the symptoms of left-sided weakness and TIA did not recur after EDAS. Simultaneously, another EDAS revascularization procedure was performed on the left hemisphere. No postoperative complications were noted. However, the follow-up results of these patients have not yet been tracked.

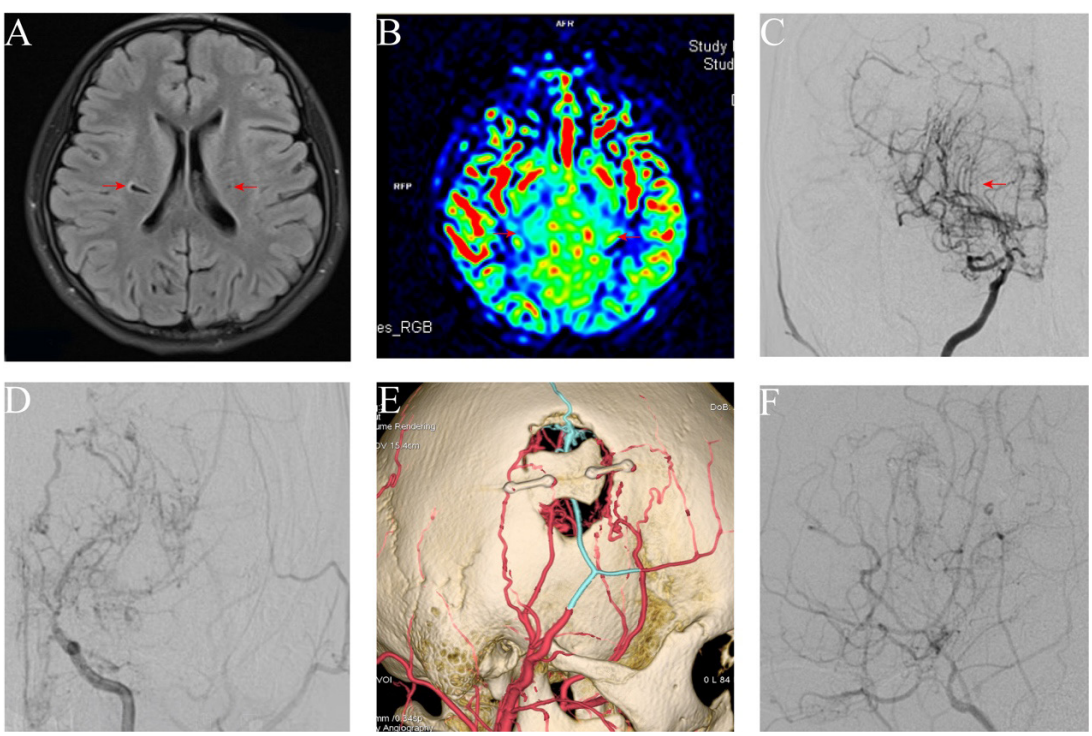

Figure 1. Image of Case 1. (A) Axial non-contrast MRI showing multiple punctate and patchy hyperintensities in the right basal ganglia and bilateral corona radiata. (B) Perfusion-weighted MRI demonstrating decreased bilateral cerebral blood flow perfusion. (C) An anteroposterior view of the right cerebral hemisphere angiogram before the procedure. (D) An anteroposterior view of the left cerebral hemisphere before the procedure. (E) Postoperative follow-up CTA. (F) Lateral view of the right cerebral hemisphere after EDAS procedure.

Patient 2

A 36-year-old female, who was the biological mother of Patient 1, presented with left limb weakness 3 years prior and was diagnosed with MMD. One month after discharge from her initial hospitalization, she developed slurred speech. Approximately 1 year ago, she experienced left hand weakness with impaired grasping and left lower extremity weakness resulting in inability to walk, without paresthesia or abnormal cutaneous sensation. She was diagnosed with MMD at a local hospital and achieved symptomatic relief after conservative treatment, followed by oral aspirin administration for 3 months. One month before the current evaluation, she suffered from dysarthria again and was readmitted to a local hospital, with improvement after treatment. Oral aspirin was continued thereafter. At the current admission, she was conscious and alert with fluent speech. Physical examination revealed equal and round bilateral pupils with a diameter of 2.5 mm and brisk light reflex. Muscle strength of all limbs was grade 5, and muscle tone was normal. Abdominal wall reflexes and tendon reflexes were preserved, and pathological reflexes were absent. Routine cranial MRI demonstrated multiple hypointense on T1WI and hyperintense on T2WI lesions in the left frontal lobe, left basal ganglia and corona radiata, right corona radiata (Figure. 2A), and right genu of the corpus callosum (Figure. 2B). MRI perfusion imaging showed decreased cerebral blood flow and cerebral blood volume in the left cerebral hemisphere relative to the contralateral side (Figure 2C). DSA demonstrated formation of moyamoya vessels in the right cerebral hemisphere (Figure 2D). Although DSA revealed bilateral moyamoya-like vascular changes, the left middle cerebral artery was not completely occluded, and the left superficial temporal artery was anatomically small and unfavorable for immediate bypass surgery. Meanwhile, the patient's clinical symptoms were relatively mild at that time. For these reasons, we elected to perform prophylactic right-sided superficial temporal artery-middle cerebral artery (STA-MCA) bypass first. Cranial CTA shows intracranial blood supply from the right superficial temporal artery (Figure 2E). The patient recovered well after surgery and received regular anticoagulation therapy with aspirin postoperatively. The patient recovered well after surgery. Approximately 6 months after the procedure, follow-up angiography

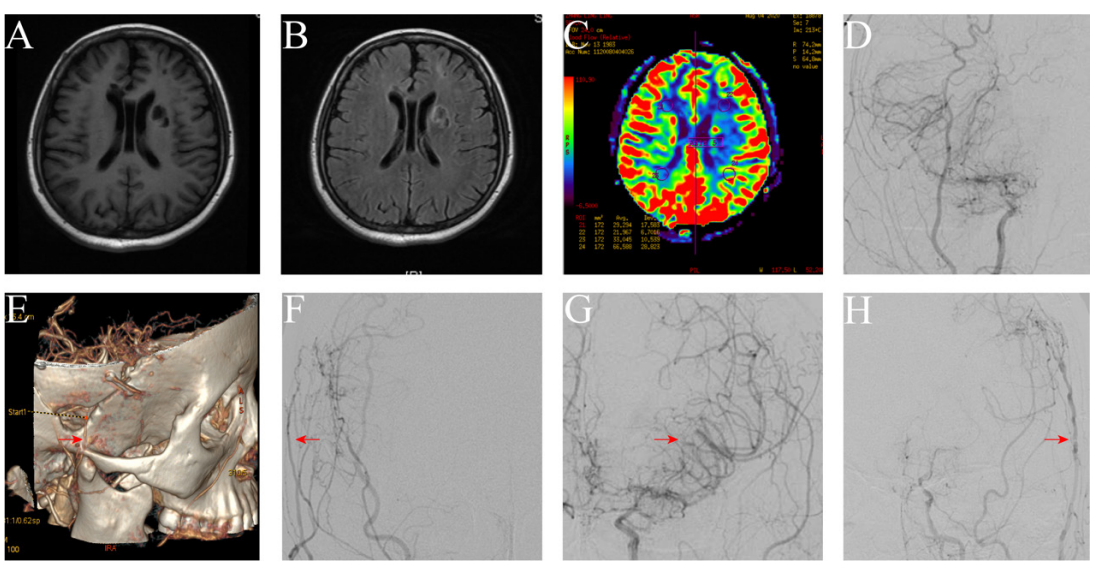

Figure 2. Image of Case 2. (A, B) Multiple hypointense on T1WI and hyperintense on T2WI lesions in the left frontal lobe, left basal ganglia, bilateral corona radiata, and right genu of the corpus callosum. (C) MRI shows decreased cerebral perfusion in the left cerebral hemisphere. (D) An anteroposterior view of the right cerebral hemisphere before the procedure. (E) Postoperative CTA showing the right superficial temporal artery (arrow). (F) Anteroposterior view of the right cerebral hemisphere after the STA-MCA bypass surgery. (G) An anteroposterior view of the left cerebral hemisphere before the procedure. (H) Lateral view of the left cerebral hemisphere after EMS procedure.

revealed that the external carotid artery provided good circulatory supply to the right cerebral hemisphere (Figure 2F). For the left hemisphere, the left superficial temporal artery was hypoplastic and thus not suitable for direct bypass. We initially planned to perform middle meningeal artery (MMA) bypass. However, intraoperative observation revealed low blood flow in the MMA, so we instead performed dural inversion combined with temporal muscle transplantation (EMS). One year later, the DSA result showed extensive collateral vascularization from the external carotid artery in the left cerebral hemisphere, but she did not experience further new neurologic symptoms (Figure 2G). She was maintained on regular aspirin and antiepileptic medications and scheduled for long-term follow-up.

Formal written informed consent for genetic testing was obtained from family members. Genetic testing was approved by the Ethics Committee of the Second Hospital of Shandong University. Genetic testing showed that the RNF213 mutations were all heterozygous for c.14429G>A, and the p. Arg4810Lys mutation was caused by c.14429G>A in the RNF213 gene (Figure 3A). At the same time, the mother was found to have a mutation in the AP4S1 gene for Hereditary spastic paraplegia type 52 (SPG52): c.289C>T (p. Arg97) (Figure 3B).

DISCUSSION

Currently, the etiology of MMD is not completely clear, and genetic, infectious, and autoimmune diseases may be potential treatment factors for MMD. Studies have found that RNF213 gene mutations played a pivotal role in the genetic basis of MMD in 2011.[4] The RNF213 gene is responsible for encoding a substantial protein comprising 5207 amino acids. Electron microscopic observations in rat experiments revealed a distinct protein structure: one end extending into a long arm, the center harboring an ATPase motor within a looped section, and the other end housing an E3 enzyme module. These insights indicate that mutations within the RNF213 gene result in a diminished E3 enzyme and motor protein, subsequently influencing hypoxia, fat metabolism, NF-kB signaling, and angiogenesis. Consequently, the RNF213 gene mutation does not affect only cerebral vessels; it may influence systemic vessels, predisposing individuals to diverse vascular ailments. The c.14429G>A mutation rate in patients with a family history of MMD; The mutation rate of

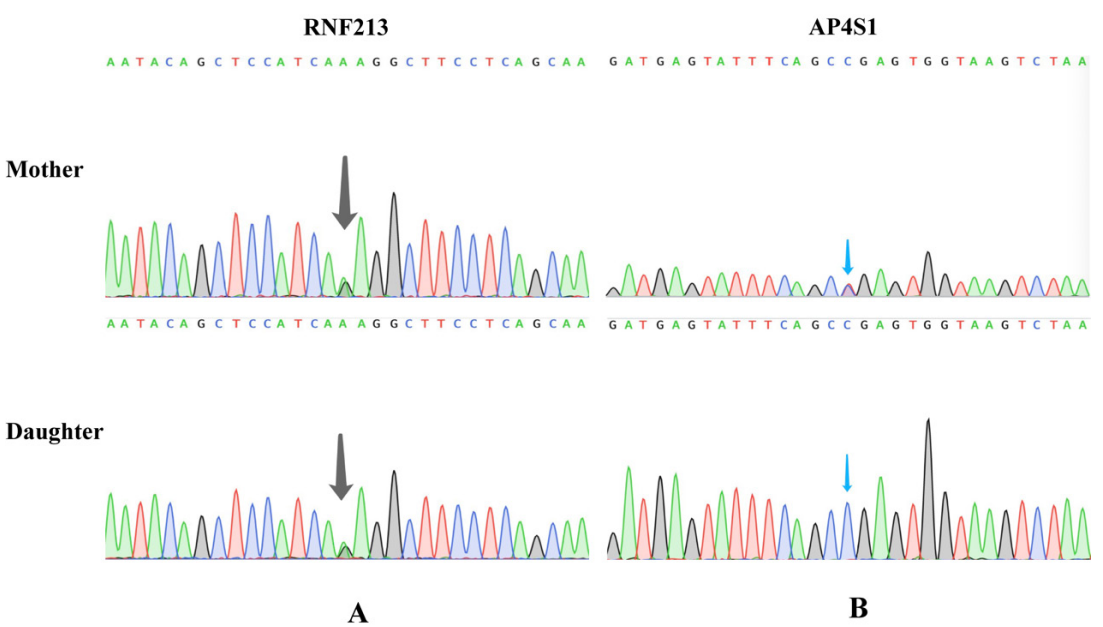

Figure 3. Sequence chromatography of the identified gene variants. (A) The arrows indicate that the mother and her daughter shared a heterozygous c.14429G>A variant. (B) The arrow indicates that the mother has c.289C>T (p. Arg97) heterozygous mutant, but her daughter did not have the disease-causing gene.

p.R4810K was significantly higher than that in those without a family history of MMD. The results of one study showed that patients with heterozygous variants of RNF213 c.14429G > A (p. Arg4810Lys) were more likely to have bilateral symptoms and progressive status compared to RNF213 variant purebreds (Suzuki grade≥4).[5] Scholars in Japan have reported the case of a 5-year-old Japanese boy diagnosed with cerebral infarction and unilateral MMD. Genetic testing confirmed the presence of a c.14429G>A heterozygous variant in RNF213. However, the boy's mother, who had no corresponding symptoms of MMD, was shown to have the same mutation as the RNF213 sequencing results.[6] Another study reported on a family with hereditary MMD. Both the boy and the girl were diagnosed with severe bilateral MMD, but the boy presented with numbness of the left hand accompanied by language and movement disorders, while the girl presented with complex symptoms such as language disorders, movement disorders, and limb fatigue. The patient's mother was diagnosed with asymptomatic bilateral MMD by using MRA.[7] In contrast to the reported case of unilateral MMD in a child with an asymptomatic carrier mother, both affected individuals in our pedigree presented with bilateral disease. Like the Chinese familial case, our patients exhibited phenotypic concordance (left limb onset), underscoring a potential genotype-phenotype correlation within this specific variant.

SPG52 is caused by biallelic mutations in AP4S1 which encodes a subunit of the adaptor protein complex 4 (AP-4).[8] SPG52 are clinically classified into pure and complex subtypes.The pure form presents with isolated progressive spastic weakness of the lower extremities, hypertonic bladder dysfunction, and mild reduced vibration sensation. By contrast, the complex form is accompanied by additional neurological or non-neurological features, including seizures, dementia, muscle atrophy, ataxia, intellectual disability, peripheral neuropathy, extrapyramidal disorders, gastroesophageal reflux, Dupuytren's disease, and varicose veins. SPG52 may present from infancy to adulthood, with approximately 40% of cases being sporadic.[9] An incidental finding was a heterozygous AP4S1 variant in the mother, associated with autosomal recessive spastic paraplegia. While its contribution to her MMD phenotype is unlikely given the recessive inheritance pattern and the daughter's unaffected status for this variant, it highlights the complexity of genetic counseling in such cases.

Variants in RNF213 are closely associated with MMD, with a founder effect. Several studies have confirmed that RNF213 is a susceptibility gene with a dose-dependent clinical phenotype.[10] Knocking out RNF213 in brain endothelial cells resulted in significant morphological changes and enhanced blood-brain barrier permeability. The expression of endothelial cell junction proteins essential for blood-brain barrier maintenance, such as platelet endothelial cell adhesion molecule-1, was downregulated. Studies have also found that brain endothelial cells show abnormal leukocyte transport potential and secrete many proinflammatory cytokines.[11] MMD cases with the heterozygous RNF213 variant manifest as a severe disease phenotype. Revascularization is effective in MMD patients. Early surgical intervention should be considered to prevent symptom progression later in life.

Genetic testing was performed in the mother and daughter only. Other relatives were not tested due to long distance and high cost, resulting in an incomplete pedigree. Further follow-up will be included in our ongoing study of RNF213 p.Arg4810Lys.

In conclusion, RNF213 screening represents a reasonable strategy for the surveillance and early detection of moyamoya disease in at-risk family members. This case report provides valuable insights into the molecular diagnosis of MMD, and we suggest that RNF213 may serve as the first-line gene for the genetic diagnosis of MMD. Notably, when a mother is affected by MMD and her first child is diagnosed with the disease, targeted genetic screening for MMD susceptibility genes should be strongly recommended for the second child. We hope this case report will assist clinicians in the diagnosis and clinical decision-making for patients with familial moyamoya disease.

DISCLOSURE

Ethics: Informed consent was obtained from each participant included in the study.

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Conflict of interest: None

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