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CASE REPORT

Coexistence of Hereditary Hemorrhagic Telangiectasia and Moyamoya Disease: A Case Report Highlighting a Potential Genetic Synergy

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Abstract: Hereditary hemorrhagic telangiectasia (HHT) coexisting with moyamoya disease (MMD) is exceptionally rare. We report the first case of a 45-year-old female harboring two genetic variants implicated in vascular disease: a pathogenic mutation in ACVRL1 (c.1231C>T, p.Arg411Trp) and a novel variant of uncertain significance in RNF213 (c.13685C>T, p.Pro4562Leu). This case is remarkable for the concurrent manifestation of HHT-associated peripheral telangiectasia and MMD-characteristic intracranial arterial stenosis, suggesting a possible synergistic interaction between variants affecting distinct vascular signaling pathways. These findings offer new insights into the genetic mechanisms underlying complex hereditary vascular disorders and emphasize the importance of comprehensive genetic testing in diagnosing atypical vascular phenotypes.

Keywords: hereditary hemorrhagic telangiectasia (HHT), moyamoya disease (MMD), gene variants, synergistic interaction

Background

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder characterized by localized telangiectasia and arteriovenous malformations, caused by mutations in genes such as ACVRL1 and ENG. The global prevalence of HHT is estimated to be approximately 1 in 5,000 individuals.[1] Previous research has shown that its molecular mechanisms are closely linked to the BMP9/10 signaling pathway.[2] In contrast, moyamoya disease (MMD) is a cerebrovascular disorder characterized by the progressive narrowing of intracranial arteries and the formation of abnormal collateral vessels. MMD has a higher prevalence in East Asian populations, but the prevalence in China is lower than in other East Asian countries such as Japan and South Korea, with a rate of 1.01 per 100,000 people.[3] RNF213, the major susceptibility gene for MMD, encodes an E3 ubiquitin ligase critical for angiogenesis and vascular remodeling.[4]

Although these diseases have distinct clinical manifestations, both involve abnormalities in vascular development and remodeling. Their coexistence in a single patient is exceptionally rare. This study presents the first reported case of HHT coexisting with MMD, providing insights into the potential synergistic interaction between ACVRL1 and RNF213 genetic variants and their role in complex hereditary vascular diseases.

Case Presentation

The patient, a 45-year-old female, presented with a six-year history of recurrent bilateral epistaxis that had worsened over the past year. Six years ago, she began experiencing spontaneous bilateral nosebleeds without any apparent triggers. These episodes were recurrent but resolved spontaneously. Over the past year, the frequency of epistaxis increased to 2–3 episodes per week, with poor response to repeated electrocautery treatments. Symptoms were aggravated by actions such as bending forward or exertion.

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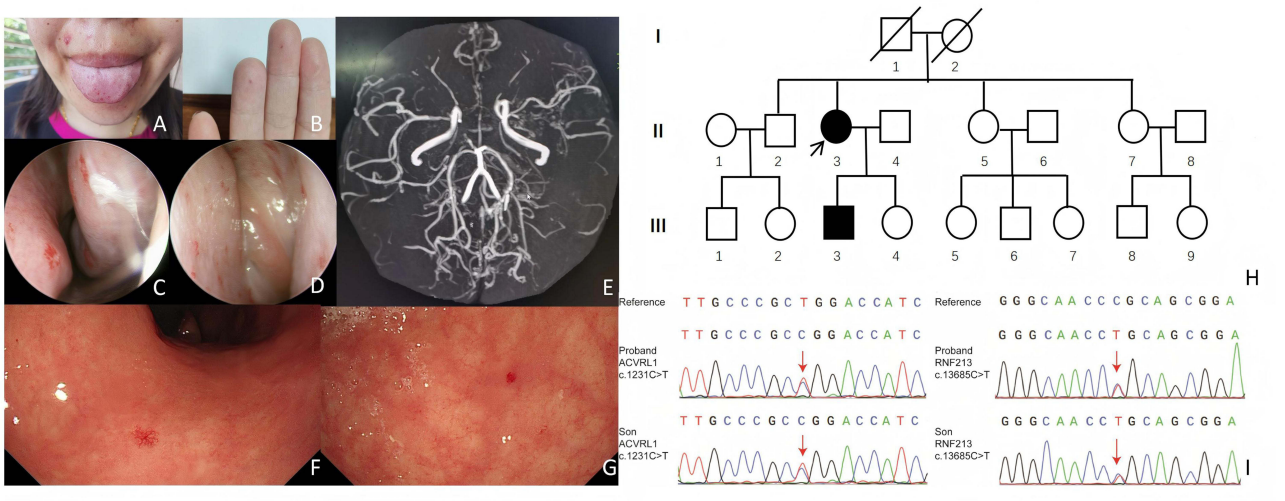

Figure 1 Clinical, Radiological, and Genetic Findings in a Patient with Hereditary Hemorrhagic Telangiectasia and Moyamoya Disease. (**A**) Telangiectasia on the tongue mucosa. (**B**) Telangiectasia on the skin of the fingertips. (**C** and **D**) Nasal endoscopy showing characteristic telangiectasia ("rose petal-like" appearance) on the nasal mucosa. (**E**) Brain magnetic resonance angiography (MRA) revealing reduced distal branches of the bilateral anterior and middle cerebral arteries, with abnormal small collateral vessels, consistent with moyamoya disease. (**F** and **G**). Telangiectasia observed on the gastric mucosa during endoscopy. (**H**) Pedigree of the proband's family. The arrow indicates the proband (the patient), black symbols represent HHT-positive individuals, and slashed symbols indicate deceased family members. (**I**) Sanger sequencing results of the proband and her son. Red arrows indicate the identified genetic variants: ACVRL1 c.1231C>T in the proband and RNF213 c.13685C>T in both the proband and her son.

Physical examination revealed scattered red, pinpoint telangiectasia on the face, oral mucosa, and fingertips. Nasal endoscopy showed classic "rose petal-like" vascular telangiectasia in the nasal mucosa bilaterally (Figure 1A–D). The patient denied neurological symptoms such as headache or dizziness and had no history of trauma or surgery. Family history was notable for her son having occasional nosebleeds, while her parents were healthy. She reported no history of hypertension, diabetes, or other chronic illnesses.

Auxiliary Examinations

Laboratory tests revealed a hemoglobin level of 83 g/L and an elevated reticulocyte count (85.9 × 10^9/L), indicating moderate anemia with compensatory bone marrow hyperplasia. Coagulation parameters and biochemical markers were within normal limits. Gastrointestinal endoscopy identified multiple sites of Telangiectasia (Figure 1F and G). Brain MRI and MRA (Figure 1E) showed a marked reduction in distal branches of the bilateral anterior and middle cerebral arteries, along with scattered small vascular networks, consistent with the typical imaging features of MMD.

Whole-exome sequencing identified a heterozygous pathogenic mutation in the ACVRL1 gene (c.1231C>T, p.Arg411Trp) and a heterozygous variant of uncertain significance in the RNF213 gene (c.13685C>T, p.Pro4562Leu) (Figure 1I). Bioinformatic analysis suggested a high likelihood of pathogenicity for the RNF213 variant, with a CADD_phred score of 18.2 and a REVEL score of 0.146 (Table 1). Based on clinical manifestations, imaging findings, and genetic testing, the patient was diagnosed with HHT 2 coexisting with moyamoya disease.

Table 1 Bioinformatic Analysis of ACVRL1 and RNF213 Variants Identified in the Patient

Gene	Variant	REVEL	SIFT	M-CAP	PolyPhen-2	PROVEAN	Mutation Taster	FATHMM	DANN	GERP++
ACVRL1	c.1231C>T p.Arg411Trp	0.824	D	D	D	D	A	D	0.999	4.98
RNF213	c.13685C>T p.Pro4562Leu	0.146	T	D	/	D	N	T	0.979	5.26

Notes: DANN, scores closer to 1 are more deleterious; GERP++, higher scores are more deleterious.
Abbreviations: A, disease causing automatic; D, Deleterious; T, Tolerated; N, polymorphism.

Genetic testing of the patient's 21-year-old son revealed inheritance of both the ACVRL1 and RNF213 variants. While the son experienced occasional episodes of epistaxis, brain MRI did not show any features indicative of moyamoya disease.

Differential Diagnosis

This case necessitates differentiation from the following conditions:

Von Willebrand Disease (vWD): While vWD is characterized by mucosal bleeding, it lacks the hallmark telangiectasia observed in this patient. Moreover, vWD is typically associated with abnormal coagulation parameters, which were not present in this case.

Systemic Vasculitis: Although systemic vasculitis can involve cerebral vessels, it does not exhibit the characteristic imaging features of moyamoya disease. Additionally, systemic vasculitis is often accompanied by signs of systemic inflammation, which were absent in this patient.

The coexistence of a pathogenic ACVRL1 mutation and an RNF213 variant, along with the clinical features, confirms the diagnosis of HHT combined with moyamoya disease.

Treatment and Follow-Up

The patient underwent local hemostatic treatment for HHT-related bleeding and anemia correction therapy. Regular follow-up was arranged to monitor the progression of cerebrovascular abnormalities and assess the potential risks associated with moyamoya disease.

Discussion

This study provides significant insights into the first reported case of HHT coexisting with MMD, identifying the rare co-occurrence of ACVRL1 and RNF213 gene variants through genetic testing.

Previous research has shown that loss-of-function mutations in ACVRL1 disrupt the BMP9/10 signaling pathway, leading to endothelial dysfunction and compromised vascular integrity. The ACVRL1 c.1231C>T (p.Arg411Trp) mutation identified in this patient is a known pathogenic variant for HHT. However, its association with cerebrovascular malformations has rarely been reported, suggesting possible phenotypic variability.[5] Furthermore, RNF213 is recognized as the major susceptibility gene for MMD in East Asian populations, encoding an E3 ubiquitin ligase essential for endothelial function and angiogenesis.[6] The RNF213 c.13685C>T (p.Pro4562Leu) variant detected in this study is a novel finding. Although its pathogenicity remains uncertain, imaging findings and bioinformatic analysis suggest a potential role in MMD development.

Notably, the co-occurrence of ACVRL1 and RNF213 variants implies a potential synergistic effect. Previous studies have shown that RNF213 influences vascular remodeling through tumor necrosis factor-alpha (TNF-α)-mediated inflammatory signaling.[7] Meanwhile, vascular wall abnormalities caused by ACVRL1 mutations may create a predisposed environment for RNF213-related vascular anomalies. This gene-gene interaction may account for the unique phenotype observed in this patient, characterized by peripheral telangiectasia and intracranial arterial stenosis. Moreover, knockout studies in zebrafish demonstrating abnormal cranial and ocular vasculature development due to RNF213 deficiency further support its critical role in angiogenesis regulation.[8] However, current evidence suggests that RNF213 variants require a "second hit" to trigger a dominant phenotype, highlighting the importance of interactions with other genetic or environmental factors.[8] This may explain the phenotypic differences observed in the patient's son, who carried both variants but exhibited milder clinical features.

Although these findings hold significant potential, we acknowledge that this study is based on a single case report. A single case cannot provide conclusive evidence for the gene-gene interaction mechanisms. Future studies involving larger sample sizes and experimental models are needed to validate these findings.

This case is significant as the first to identify this specific genetic variant combination, offering a novel perspective on gene-gene interactions across distinct vascular signaling pathways. These findings underscore the importance of comprehensive genetic testing in diagnosing complex hereditary vascular diseases, particularly in

patients with atypical or mixed phenotypes. Further foundational research is essential to unravel the precise roles of these genes in vascular pathophysiology. Such studies could pave the way for innovative, gene-targeted therapies, offering personalized solutions for complex hereditary vascular diseases.

Ethics Approval and Patient Consent

This study was conducted in strict accordance with the ethical principles outlined in the Declaration of Helsinki. Approval for this study was obtained from the Ethics Committee of Shandong Provincial ENT Hospital (Approval Number: XYK20200805). Since no identifiable patient information was disclosed, additional institutional approval for case publication was not required. Written informed consent was obtained from all patients prior to their participation in the study, including consent to publish case details and any accompanying images. All patient data were anonymized to protect their privacy in accordance with data protection regulations.

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Liu S and Meng L contributed equally and are co-first authors for this work.

Author Contributions

All authors made a significant contribution to the work reported, whether in the study conception, design, or execution; data acquisition, analysis, or interpretation; or in all of these areas. All authors 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 report has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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