Title	Reversible Cerebral Angiopathy after Viral Infection in a Pediatric Patient with Genetic Variant of RNF213
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Reversible Cerebral Angiopathy after Viral Infection in a Pediatric Patient with Genetic

Variant of RNF213

**Abstract** 

Ring finger protein (RNF)213 is known as a susceptibility gene for moyamoya disease (MMD),

which is characterized by bilateral carotid folk stenosis. Cerebral angiopathy after viral infection

has been known to present angiographical appearance resembling MMD, however its pathogenesis

and genetic background are not well known. We report a case of reversible cerebral angiopathy

after viral infection in a pediatric patient with genetic variant of RNF213 mutation. The patient had

developed a severe headache after hand, foot, and mouth disease. Magnetic resonance imaging and

magnetic resonance angiography (MRA) performed 2-3 weeks after disease onset revealed

bilateral carotid folk stenosis and an old cerebral infarction in the left putamen. The patient's

headache spontaneously resolved and the follow-up MRA showed a complete spontaneous

resolution of the arterial stenosis after 9 months. We were able to determine genetic predisposition

to angiopathy by identifying the RNF213 c.14576G>A (rs112735431, p.R4859K) mutation. Based

on the present case, we hypothesize that an RNF213 variant might play an important role for the

onset of post-viral cerebral angiopathy.

**Keywords:** cerebral angiopathy; moyamoya disease; *RNF213*; hand, foot, and mouth disease;

enterovirus; viral infection.

1

## **Case Description**

A 6-year-old Japanese boy without prior health problems or family history of stroke or moyamoya disease (MMD) visited a pediatric clinic due to severe headache. He had been diagnosed with hand, foot, and mouth disease (HFMD) 2–3 weeks prior and has had a persistent severe headache since. Magnetic resonance imaging (MRI) revealed an old cerebral infarction in the left putamen and magnetic resonance angiography (MRA) showed bilateral stenosis of the terminal portion of the internal carotid arteries (ICAs), middle cerebral arteries (MCAs), and anterior cerebral arteries (ACAs) (Fig. 1A, B).

The patient was referred to our hospital for further examination. However, the headache resolved and the follow-up MRA after 2 months revealed resolution of the bilateral ICA and MCA stenosis, with residual stenosis in the left proximal ACA (Fig. 1C). The follow-up MRA after 9 months showed no apparent cerebral artery stenosis, including the left ACA (Fig. 1D). Genotyping by Sanger sequencing revealed a heterozygous allele of the variant ring finger protein (*RNF*)213 c.14576G>A (rs112735431, p.R4859K).

# **Discussion**

Cerebral angiopathy, including ischemic stroke, has been reported after some viral infections such as herpesviruses, varicella zoster virus, adenovirus, parvovirus B19, rhinovirus, and influenza virus (1-5). HFMD is typically caused by enterovirus 71 or coxsackie virus, but is usually diagnosed based only on the clinical features, without serological viral detection, as in the present case. Piccolo et al. reported a case of cerebral angiopathy after enterovirus infection, but the diagnosis was not HFMD and further virus subtype determination was not performed (6). To the best of our knowledge, this is the first report of cerebral angiopathy after HFMD. We speculate

that progressive cerebral artery stenosis during the disease acme induced the severe headache and

cerebral infarction in the present case.

Interestingly, the patient was found to have genetic variant of RNF213, which is associated with

susceptibility to cerebral angiopathy, such as MMD or atherosclerotic stenosis (7-10). This is also

the first report that associates post-viral angiopathy to genetic variant of RNF213. It is speculated

that pediatric patients with this variant could harbor covert cerebral arteriopathy after viral

infections. The present case suggests that genetic variant of RNF213 is potentially common

pathological pathway in both viral-induced cerebral angiopathy and MMD regarding their similar

angiographical appearance of bilateral carotid folk stenosis. Therefore, identifying an RNF213

variant may have a crucial role in detecting patients who could develop angiopathy or MMD after

viral infections.

### **Conflicts of interest**

None.

### **Funding**

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3

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# Figure legends

**Figure 1.** Chronologic presentation of the MRI and MRA findings. (A) Fluid-attenuated inversion recovery image performed 2–3 weeks after headache onset revealed an old cerebral infarction in the left putamen (arrow). The lesion did not present a high-intensity signal on diffusion weighted

imaging, indicating acute cerebral infarction, nor a low-intensity signal in T2 star-weighted images, suggesting a hemorrhagic change (these are not shown). (B) Initial MRA performed at the same time revealed bilateral stenotic changes in the distal ICAs and in the proximal portions of the ACAs and MCAs (solid arrowheads). (C) MRA performed after 2 months showed spontaneous resolution of the bilateral ICA and MCA and the right ACA stenosis, with a residual left ACA stenosis (open white arrowhead). (D) MRA performed after 9 months showed complete disappearance of the arterial stenosis.

