Rapid Progression of Unilateral Moyamoya Disease in a Patient with a Family History and an RNF213 Risk Variant

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Introduction
Moyamoya disease (MMD) is a progressive steno-occlusive vasculopathy that involves large intracranial arteries accompanied by moyamoya collaterals [1, 2]. It was demonstrated that the p. R4810K missense variant in the RNF213 gene on 17q25.3 locus [3–5] increases susceptibility to MMD in East Asian populations [6]. Genetic diagnosis enabled us to find presymptomatic patients with MMD.

Case Report
A 36-year-old woman, who had no past medical history, received MRI screening examination to check for MMD because her mother and her aunt had the disease. The initial examination in August 2005 showed no apparent intracranial arterial stenosis (fig. 1a). One year later, she received the second MRI scan, which showed proximal right middle cerebral artery (MCA) occlusion (fig. 1b). Conventional angiography confirmed MCA occlusion with minor moyamoya collaterals at the base of the brain (fig. 1c). No stenosis was observed on the contralateral side. Despite rapid progression of the arterial occlusion, the patient did not develop any neurological symptoms or ischemic brain lesions on MRI. She was conservatively followed up by annual MRI examinations without surgical intervention. The occlusive lesion has remained stable for 6 years without any progression.

The patient and her family members, including unaffected members, received both genetic testing for RNF213 and MRI examination in 2005; the family is pedigree 18 in our previous paper [6]. Sequencing of RNF213 in the patient’s mother and aunt revealed two haplotypes carrying p.R4810K: allele A₂, which is common among patients with MMD, and allele A₁, which is rare among patients with MMD [6]. The patient inherited an A₂ allele for p.R4810K (fig. 1d). On the other hand, her elder and younger sisters inherited an A₂ allele from their mother for p.R4810K, and no arterial stenosis was identified in either the initial or annual follow-up MRI examinations.

Ethical approval for this study was given by the Institutional Review Board and Ethics Committee of the Kyoto University School of Medicine, Kyoto University, Japan.

Discussion
Due to incomplete penetrance of the p.R4810K variant, RNF213 is considered to be a susceptibility gene and other genetic or environmental factors may be associated with MMD. However, the genome-wide linkage and association analysis only showed a significant signal in RNF213 on 17q25.3, indicating that other genetic factors have a much lower effect as compared with RNF213 [3, 6]. p.R4810K or other mutations in RNF213 were observed in all familial cases of MMD including Japanese, Korean and European populations and p.R4810K was associated with an increased risk of MMD with an odds ratio of as much as 338.9 for a Japanese population [6], which was confirmed in independent studies [5, 7]. These results indicate that p.R4810K screening would be a most appropriate approach to identify asymptomatic patients, especially those who have a family history of MMD.

In the present study, a 36-year-old woman, who was positive for RNF213, had de novo progression of unilateral MMD within only a year. In the past reports, a 59-year-old woman showed de novo progression of bilateral MMD within a 5-year interval and a 46-year-old woman developed unilateral MMD between 2004 and 2009 [8, 9]. Albeit not adult cases, Amlie-Lefond et al. [10] reported a 3-month-old patient with MMD and reviewed other 8 cases of early infancy before the age of 1 year, suggesting that MMD can develop very rapidly. Therefore, frequent follow-ups by MRI should be recommended for those who were diagnosed as having genetic risk factors for MMD.

Although the elder and younger sisters of the patient had the p.R4810K variant, they have not developed MMD. Since they may develop MMD several years later, a close follow-up is necessary. Alternatively, the discordant phenotype of the sisters may represent allelic differences between A₁ and A₂ [6]. The patient and the affected mother and aunt share p.R4810K on the same allele (A₂), whereas the unaffected sisters have A₁, suggesting a possibility that the 5’ portion of RNF213 may have a modifier effect on the steno-occlusive phenotype. Still another possibility includes environmental factors, which may affect the pene...
trance, although we could not identify any environmental differences between the affected patient and the unaffected sisters. The patient had one A allele (heterozygote) and developed unilateral MMD, whereas her mother and aunt had two A alleles (homozygote) and developed bilateral MMD. Miyatake et al. [7] reported that the number of risk alleles in RNF213 is associated with earlier age at onset and a severe form of the disease. Bilateral progression may also be associated with the number of risk alleles. Further follow-ups and investigations are warranted for this family.

Fig. 1. a Initial magnetic resonance angiography (MRA; 1.5 tesla) of the patient. No arterial stenosis was observed. b Second MRA (1.5 tesla) study 1 year after the initial examination showed disruption of the right MCA. c Digital subtraction angiography following the second MRA examination revealed right MCA occlusion and the formation of collateral circulation at the base of the brain. Distant MCA was filled with contrast media via collaterals. d The family with familial MMD. Filled symbols indicate patients with MMD; half-filled symbols, patients with unilateral MMD; circles, women; squares, men; crossed symbols, deceased people. The half-filled symbol in the third generation represents the 36-year-old patient in this report. Genotypes of the risk allele of RNF213 are shown. GG represents wild type; GA, homozygote for the risk variant, AA heterozygote for the risk variant. Numbers are attached to the variant ’A’ to discriminate the two different alleles. The patient and her affected mother and aunt share the risk variant on the same allele (∆).

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Disclosure Statement
None.
References