Supplementary Methods

Study design and patient selection

This retrospective study included 311 Korean patients with moyamoya disease (MMD) who had undergone *RNF213* genotyping at two tertiary university hospitals between January 2017 and August 2021. MMD was diagnosed using digital subtraction angiography or magnetic resonance angiography (MRA) combined with a review of medical records. The diagnostic criteria for MMD were based on guidelines published by the Research Committee on the Pathology and Treatment of Spontaneous Occlusion of the Circle of Willis of Japan in 2012.[1] Patients with the following underlying diseases with similar angiographic findings were excluded: (1) atherosclerosis, (2) autoimmune disease, (3) history of cranial irradiation, (4) intracranial artery dissection, (5) von Recklinghausen's disease, (6) brain tumors, and (7) sickle cell disease. Patients were classified as having pediatric MMD when they had been diagnosed before 18 years of age. A flowchart for the selection of MMD with *RNF213* genotyping is shown in Supplementary Figure 1. Analysis of the R4810K variant of the *RNF213* gene (GenBank accession number NM_001256071.1) was performed using patients' blood samples. The analysis was conducted at a commercial laboratory (Seoul Clinical Laboratories, Yongin, South Korea).

Clinical and radiologic characteristics

Information on the patients' sex, age at onset, family history of MMD, revascularization surgery, primary clinical manifestation at diagnosis, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, history of current smoking, and angiographic findings was collected via a medical record review. A family history of MMD was obtained from patients' medical records or by interviewing patients or their main caretakers. The primary clinical manifestations at diagnosis were classified as cerebral infarction, transient ischemic attack (TIA), intracranial hemorrhage/intraventricular hemorrhage (ICH/IVH), seizure, incidental findings, and others (headache, dizziness, and syncope). The most severe neurological symptom was defined as the primary clinical manifestation if two or more symptoms were present. Bilateral vasculopathy, posterior cerebral artery involvement, and Suzuki grade, which are angiographic findings of MMD that are related to disease severity, were assessed.[2] The Suzuki grade on the severe side was applied. Angiographic findings and medical records were reviewed by a neurologist who was blinded to the *RNF213* genotyping results.

Evaluation of patient outcomes and results of revascularization after bypass surgery

To evaluate the influence of the *RNF213* R4810K variant on patient outcomes, clinical outcomes including TIA, cerebral infarction, ICH/IVH, and mortality of patients with at least 3 months of follow-up were collected by retrospective medical record review. The first event was evaluated for the same recurrent events. The follow-up period was defined as the period from the date of MMD diagnosis to the date of final observation.

Evaluation of the impact of the *RNF213* R4810K variant on the development of revascularization was performed as previously described by Kawabori et al.[3] Patients who performed revascularization with preoperative MRA performed within 1 year and postoperative MRA performed between 6 and 12 months after surgery were analyzed. MRA source images were used to quantitatively evaluate collateral development by measuring the caliber of the superficial temporal artery (STA). For either direct or indirect bypass, the calibers of the STA at the level of bifurcation of the frontal and parietal branches were compared. The caliber change ratio (CCR), defined as the ratio of the postoperative caliber diameter (mm) to the preoperative caliber diameter (mm), was compared among patients with GG, GA, and AA genotypes. The caliber of the basilar artery was used as the internal control.

Statistical analysis

Differences in the clinical and radiological characteristics of MMD patients with respect to the *RNF213* R4810K variant were assessed. Continuous variables were presented as means with standard deviations and were compared using analysis of variance. Categorical variables were presented as counts (percentage) and compared using the chi-square or Fisher's exact test. Multiple comparisons for *post hoc* analysis were adjusted using Bonferroni's method. Linear to linear analysis was used for trend analysis. Statistical significance was defined as a two-sided P-value <0.05.

To evaluate the influence of *RNF213* R4810K variant on patient outcomes, the hazard ratio was evaluated using a Cox proportional regression model. The correlation between the *RNF213* R4810K variant and the CCR for STA was compared using the Mann-Whitney test. Statistical analyses were performed using SAS version 9.4 (SAS Inc., Cary, NC, USA) and the SPSS software (version 25.0; IBM Corp., Armonk, NY, USA).

Standard protocol approvals, registrations, and patient consent

This study was reviewed and approved by the Severance Hospital Yonsei University Health System Institutional Review Board (3-2021-0443). The requirement for written informed consent for participation was waived owing to this study's retrospective design.