Nonatherosclerotic Isolated Middle Cerebral Artery Disease May Be Early Manifestation of Moyamoya Disease

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**Background and Purpose**—Middle cerebral artery steno-occlusive disease (MCAD) is not an uncommon cause of ischemic stroke in young Asians. Aside from atherosclerosis, the pathogenesis of MCAD include various nonatherosclerotic vasculopathies, most of which are yet to be defined. This study investigated the pathogenesis of symptomatic isolated MCAD in young Asian patients using high-resolution magnetic resonance imaging (HR-MRI) and mutation analysis of RNF213.

**Methods**—Patients aged <60 years with stroke or transient ischemic attack caused by MCAD were prospectively enrolled. Patients with a confirmed diagnosis of moyamoya disease, dissection, and vasculitis; with significant steno-occlusion in cerebral arteries other than the MCA; or with high-risk cardioembolic source were excluded. Using high-resolution MRI, patients were classified into an atherosclerosis group and a nonatherosclerosis group.

**Results**—Eighty-one patients were enrolled, 45 (56.6%) in the atherosclerosis and 36 (44.4%) in the nonatherosclerosis group. The nonatherosclerosis group was significantly younger (P=0.013), had a smaller number of vascular risk factors (P=0.001), showed a lower homocysteine level (P<0.001), thinner intima-media thickness (P=0.006), and had more frequent heterozygotes at RNF213 (P=0.045) than the atherosclerosis group. Diffusion-weighted image lesion pattern showed no significant differences in assumed stroke mechanisms between the 2 groups.

**Conclusions**—Nonatherosclerotic pathogenesis are common in young Asians with symptomatic isolated MCAD. Clinical findings, high-resolution MRI features, and results of RNF213 mutation analysis suggest that moyamoya disease is responsible etiologically for a significant portion of nonatherosclerotic lesions. Symptomatic isolated MCAD may be an early manifestation of moyamoya disease in young Asian adults. (Stroke. 2016;47:2229-2235. DOI: 10.1161/STROKEAHA.116.012751.)

**Key Words:** atherosclerosis ■ cerebral arterial diseases ■ intracranial atherosclerosis ■ magnetic resonance imaging ■ moyamoya disease

The middle cerebral artery steno-occlusive disease (MCAD) is the most important vascular lesion causing ischemic stroke, especially in Asian population. Although atherosclerosis is the most frequent cause of MCAD, the latter can also be caused by nonatherosclerotic vasculopathies, such as moyamoya disease (MMD), arterial wall dissection, and vasculitis, with nonatherosclerotic etiology being an important cause of stroke, especially in younger aged individuals. Therefore, the differential etiologic diagnosis of acute infarction involving the MCA in younger adults should include atherosclerosis and nonatherosclerotic vasculopathies.

Despite of the extensive evaluation for differential diagnosis, the exact pathomechanism of MCAD is not clarified in a large portion of patients. Moreover, conventional imaging techniques, such as magnetic resonance angiography (MRA) and cerebral angiography, show only the vascular lumen. These difficulties in determining the pathogenesis of MCAD in clinical practice often result in an underestimation of nonatherosclerotic vasculopathies. The misinclusion of nonatherosclerotic diseases as intracranial atherosclerosis has constantly been raised as a problem in assessing intracranial artery stenosis, with MMD frequently misclassified etiologically.

Unlike conventional arterial imaging, high-resolution MRI (HR-MRI) can visualize the arterial wall itself. Although the MCA is a small, deep-seated intracranial vessel, HR-MRI has shown diagnostic value in differentiating vascular wall pathologies because of atherosclerosis from those because of nonatherosclerotic vasculopathies, including MMD. Recent genome-wide and locus-specific association studies found...
that the gene encoding ring finger protein 213 (RNF213) conferred susceptibility to MMD among East Asian populations.\textsuperscript{11-13} Both HR-MRI and gene tests are useful tools in evaluating MCAD.

This study was designed to identify the clinical characteristics of young Asian patients with symptomatic isolated MCAD using HR-MRI. Clinical features, as determined by HR-MRI and RNF213 mutation analysis, were compared in patients with atherosclerotic and nonatherosclerotic MCAD.

**Methods**

**Patients**

Patients aged <60 years with stroke or transient ischemic attack caused by MCAD who visited the Department of Neurology at Asan Medical Center from October 2010 to September 2013 and underwent HR-MRI to evaluate the diseased segment of index MCA were prospectively recruited.

Patients were excluded if contrast-enhanced MRA showed significant steno-occlusion in extracranial cerebral arteries and intracranial arteries other than the MCAs; if they had high-risk cardioembolic source according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification; if there was recanalization of the occluded MCA in follow-up MRA; or if they were diagnosed with nonatherosclerotic vasculopathy, angiographically confirmed MMD because of bilateral narrowing of the internal carotid arteries or MCAs with moyamoya vessel formation, vasculitis as shown by clear laboratory evidence or active central nervous system infection associated with multiple cerebral arterial narrowing, or dissection associated with the presence of a double lumen or aneurysmal formation. In addition, patients with poor image quality preventing further analysis of the vessel wall or lumen were excluded from this study.

Patients were classified as atherosclerosis and nonatherosclerosis groups according to the characteristics of the diseased segment of the MCA on HR-MRI. Patients were assigned to the atherosclerosis group if they had atherosclerotic plaque, eccentric stenosis with or without enhancement suggesting atherosclerotic plaque,\textsuperscript{6,8,14,15} or relatively large diameter vessels (cutoff value \(\geq 2.4\) mm).\textsuperscript{9,16} Patients who did not meet these conditions were included in the nonatherosclerosis group. They had relatively smaller diameter (<2.4 mm) vessels and concentric stenosis without atherosclerotic plaque. MMD showed concentric narrowing or blunted obliteration of the vessel lumen without plaque.\textsuperscript{9,14,16-18} Vasculitis was diffuse, with concentric vessel wall enhancement and possible multifocal stenosis or a beaded pattern.\textsuperscript{14} Dissection may have shown a pattern similar to that of atherosclerosis, including eccentric wall thickening with enhancement; however, distinguishing features such as bright signals on T1-weighted image, suggesting a hemorrhagic component, or a flap or dual lumen were considered dissection.\textsuperscript{14,15} (Figure).

**Ethical Considerations**

The study protocol, including systematic chart and imaging review, was approved by the institutional review board of the Asan Medical Center. Informed consent was obtained from patients or members of their families.

**MR Protocol**

MR imaging was performed as described in our previous study\textsuperscript{6} using an Achieva 3.0T TX scanner (Philips, Eindhoven, The Netherlands) with a standard 8-channel head coil. Conventional 3-dimensional (3D) time-of-flight MRA was performed in an axial plane, followed by HR-MRI on the stenotic side determined on the 3D time-of-flight MRA. Sagittal T1-weighted, T2-weighted, and proton density-weighted images using megluminegadoterate were obtained if there were no contraindications.

**HR-MRI Analysis**

HR-MRI images of the MCA trunk were analyzed by 2 reviewers (Y.-I. K., J.-K. L.) blinded to the clinical information. Characteristics analyzed included concentricity, the presence of plaque, outer diameter, enhancement patterns, and location of the stenotic segment of the MCA on sagittal images perpendicular to M1. Any discrepancies were resolved by a third investigator (S.-H. A.).

Abnormalities were evaluated using the following parameters: (1) If the stenotic portion of the vessel wall was found to be evenly thickened in a circumferential manner on the cross-sectional image of the vessel, the wall abnormality was considered concentric; if not, it was considered as eccentric stenosis. (2) Plaques were identified based on the presence of eccentric wall thickening; thin sections were defined as those <50% of the thickness of the thickest point by visual inspection. (3) The diameter of the outer vessel wall was measured on proton density-weighted images generated using HR-MRI. The smallest lumen on cross-sectional images of the stenotic MCA was selected and measured; the measurements taken by the 2 reviewers were averaged. (4) Enhancement of the stenotic vessel wall was determined by comparing pre-enhancement and post-enhancement sagittal proton density-weighted images. (5) The distribution of the stenotic portion in the MCA was assessed. The M1 segment of the MCA was subdivided into proximal, middle, and distal segments, and the segment containing the stenotic portion was assessed. Narrowing of the three segments was considered as diffuse stenosis of the MCA, whereas other narrowings were considered focal stenosis.

Lesion patterns were also analyzed on diffusion-weighted images (DWI) to determine stroke mechanism. Ischemic lesions on DWI were classified into three groups: (1) single subcortical lesions were considered as local branch occlusions; (2) cortical or multiple images using high-resolution magnetic resonance imaging findings. 

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**Figure.** Patient categorization according to high-resolution magnetic resonance imaging findings.
scattered lesions in the MCA territory were defined as artery-to-artery embolisms; and (3) ischemic lesions in the watershed zone were considered hypoperfusion. Any differences in the assessments by the 2 reviewers were resolved by consensus.

**Mutation Analysis of the RNF213 Gene**

Genomic DNA was extracted from peripheral blood using a Puregene Blood Kit (Qiagen, Hilden, Germany). To identify the major single nucleotide polymorphisms of RNF213 in East Asian patients (ie, p.D4013N, p.P4608S, p.R4810K, p.R4853K, p.D4836N, and p.E4950D), three exons (ie, exons 44, 60, and 62) and the appropriate exon–intron boundaries of RNF213 were amplified by polymerase chain reaction and directly sequenced using an ABI3130xl Genetic analyzer (Applied Biosystems, Foster City, CA), according to the manufacturer’s instructions. The sequencing results were compared with established human RNF213 sequences (GenBank Accession No. NM_001256071.1). The investigators involved in genotyping were blinded to phenotypic information.

**Statistical Analysis**

All statistical analyses were performed using SPSS 21.0 software. Categorical variables were compared using the χ² test or Fisher exact test, and continuous variables were compared using Student t-tests. A P-value <0.05 was considered statistically significant.

**Results**

During the study period, 2939 patients visited Asan Medical Center due to ischemic stroke and 640 (21.8%) patients were <60 years. Among them, 199 (31%) patients were classified as large artery atherosclerosis according to TOAST classification. Finally, 81 (40.7%) patients with symptomatic isolated MCAD were enrolled. HR-MRI findings classified 45 (55.6%) patients into the atherosclerosis group and 36 (44.4%) into the nonatherosclerosis group (Table 1). The nonatherosclerosis group was significantly younger (40.1±10.5 versus 45.7±8.9 years, P=0.013) and included a higher percentage of women (58.3% [21/36] versus 44.4% [20/45]; P=0.214) than the atherosclerosis group.

The median number of vascular risk factors per patient (1 [1–2.75] versus 2 [1–3]; P=0.001) and the level of homocysteine (12.4±5.0 versus 18.5±7.0, P=0.001) was significantly lower in the nonatherosclerosis than in the atherosclerosis group. The level of low density lipoprotein was lower in the nonatherosclerosis than in the atherosclerosis group. Although we have excluded patients with angiographically confirmed MMD or dissection, patients in the nonatherosclerosis group were still younger, more frequently female, had fewer vascular risk factors and demonstrated a thinner IMT comparing to those in the atherosclerosis group. Mutation analysis showed that RNF213 heterozygotes were more frequent in the nonatherosclerosis group than in the atherosclerosis group. Among the various single nucleotide polymorphisms of RNF213 gene, only the heterozygote of p.R4810K was more frequent in the nonatherosclerosis group than the atherosclerosis group (62.5% [10/16] versus 26.7% [4/15], respectively; P=0.045).

HR-MRI findings of the MCAD were also reviewed (Table 2). MCAD diameter was significantly smaller (P<0.0001), enhancement was less frequent (P<0.0001), and diffuse stenosis (P<0.0001) of symptomatic MCA was more common in the nonatherosclerosis group than in the atherosclerosis group. In the further analysis of nonatherosclerotic group, 28 patients who showed concentric stenosis with smaller diameter were considered as MMD. These suspected MMD cases showed female dominance with younger age and lower homocysteine than atherosclerosis group. Three cases (10.7%) had family history of MMD and 9 of 13 cases (69.2%) showed the heterozygote of RNF 213 (Table 1). Two patients who showed diffuse concentric enhancement and multifocal stenosis were considered as vasculitis, and the other 4 patients who showed intimal flap were considered as dissection. However, 2 patients did not meet any of the above-mentioned findings and were also classified into nonatherosclerosis group.

Clinical symptom presentation was not significantly different between the 2 groups (P=0.125) and symptomatic ischemia was more frequently observed. Suspected MMD cases of nonatherosclerosis group showed more transient ischemic attack than symptomatic ischemia. Acute stage DWI images of 51 of the 81 patients were analyzed to define lesion patterns. In both groups, artery-to-artery embolism was the most common apparent stroke mechanism. There was no statistically significant difference in lesion patterns between the 2 groups (P=0.166; Table 2).

**Discussion**

The HR-MRI findings presented here indicate that nonatherosclerotic pathogenesis account for a significant proportion of symptomatic isolated MCAD in young adult subjects. Although we have excluded patients with angiographically confirmed MMD or dissection, patients in the nonatherosclerosis group were still younger, more frequently female, had fewer vascular risk factors and demonstrated a thinner IMT in the atherosclerosis group. The prevalence of nonatherosclerotic etiology was higher than expected and was similar to the prevalence of atherosclerotic etiology in young patients with symptomatic isolated MCAD. A previous study from our center, using HR-MRI to assess patients with isolated MCAD, found that 69 of the 95 patients (72.6%) could be classified into the nonatherosclerosis group, a much higher percentage than in this study. The difference may have been because of the inclusion in the present study of patients with symptomatic MCAD. The younger age at stroke onset and the higher percentage of females observed in the nonatherosclerosis group may have resulted from the higher prevalence of MMD in this group. HR-MRI of
The nonatherosclerotic group showed that 28 of these patients had concentric stenosis with smaller diameter, characteristics of MMD. Symptom onset of adult MMD usually occurs from the mid-30s to the mid-40s, much younger than in patients with atherosclerotic disease. Moreover, about two third of patients with MMD are female. The mean number of vascular risk factors was lower in the nonatherosclerosis than in the atherosclerosis group. Because this study excluded patients >60 years of age, the prevalence of each individual vascular risk factor, including hypertension, hyperlipidemia, and diabetes mellitus, was similar in between the 2 groups. Homocysteine level was significantly lower in the nonatherosclerosis group than in atherosclerosis group. Hyperhomocysteinemia is associated with ischemic stroke and atherosclerosis. Endothelial dysfunction, subsequent thrombosis, and an abnormality in coagulation system caused by homocysteine have been suggested as the mechanism of atherosclerosis. The association between homocysteine and MMD has not been suggested yet. Considering the results of the present study, homocysteine is associated with atherosclerosis, and it could be a good independent discriminator between atherosclerosis and nonatherosclerosis. Mean carotid IMT, a reliable indicator of systemic atherosclerosis, was significantly thinner in the nonatherosclerosis than in the atherosclerosis group, with all patients having an IMT >1.0 mm showing a typical atherosclerotic pattern on HR-MRI. The difference in clinical characteristics of these 2 groups suggests that HR-MRI can reflect differences in vascular pathologies and can reproducibly evaluate MCAD.

Clinical symptom presentation and stroke mechanism according to DWI lesion pattern were similar in the nonatherosclerosis and atherosclerosis groups. The most common stroke mechanism in both groups was artery-to-artery embolism, an interesting finding, inasmuch as the 2 groups have different vascular pathologies. Generally, advanced MMD presents with infarction in the watershed territories among the anterior, middle, and posterior cerebral arteries. However, the stroke mechanism of unilateral adult MMD is still unknown. In unilateral MMD, the MCA may not be narrow enough to cause hemodynamic insufficiency, and collateral flows from other vessels may function better than advanced MMD. In a previous histopathologic study of patients with MMD, thrombi were frequently detected in the cervical and intracranial extracerebral arteries, and fibrous thickening of the intima and edema in the innermost luminal surface were the most common vascular alterations associated with the thrombus formation. This mechanism may explain the frequent artery-to-artery embolism observed in the nonatherosclerosis group. Demographic and HR-MRI findings, such as younger age at stroke onset, higher percentage of females, and concentric MCA stenosis with smaller vessel diameter, would suggest a higher prevalence of MMD among nonatherosclerotic patients. Recent genome-wide and locus-specific association studies found that the RNF213 gene was associated with

### Table 1. Baseline Demographic and Clinical Characteristics of Patients

<table>
<thead>
<tr>
<th></th>
<th>Atherosclerosis Group</th>
<th>Nonatherosclerosis Group</th>
<th>P Value</th>
<th>Nonatherosclerosis Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Suspected MMD</td>
</tr>
<tr>
<td>No. of subjects, %</td>
<td>45 (55.6%)</td>
<td>36 (44.4%)</td>
<td>…</td>
<td>28 (77.8%)</td>
</tr>
<tr>
<td>Age of onset, y</td>
<td>45.7±8.9</td>
<td>40.1±10.5</td>
<td>0.013</td>
<td>41.3±10.0</td>
</tr>
<tr>
<td>Female</td>
<td>20 (44.4%)</td>
<td>21 (58.3%)</td>
<td>0.214</td>
<td>17 (60.7%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>16 (35.6%)</td>
<td>8 (22.2%)</td>
<td>0.192</td>
<td>7 (25%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10 (22.2%)</td>
<td>3 (8.3%)</td>
<td>0.091</td>
<td>2 (7.1%)</td>
</tr>
<tr>
<td>Hb A1C</td>
<td>6.5±1.5</td>
<td>5.9±1.3</td>
<td>0.089</td>
<td>5.8±1.3</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>20 (44.4%)</td>
<td>9 (25.0%)</td>
<td>0.070</td>
<td>4 (14.3%)</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>122.6±45.7</td>
<td>103.6±39.3</td>
<td>0.053</td>
<td>100.3±24.9</td>
</tr>
<tr>
<td>Homocysteine, µmol/L</td>
<td>18.5±7.0</td>
<td>12.4±5.0</td>
<td>0.090</td>
<td>11.6±4.4</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1 (2.2%)</td>
<td>1 (2.8%)</td>
<td>0.873</td>
<td>1 (3.6%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>17 (37.8%)</td>
<td>10 (27.8%)</td>
<td>0.343</td>
<td>8 (28.6%)</td>
</tr>
<tr>
<td>Family history of stroke</td>
<td>14 (31.1%)</td>
<td>11 (30.6%)</td>
<td>0.957</td>
<td>9 (32.1%)</td>
</tr>
<tr>
<td>Family history of MMD</td>
<td>1 (2.2%)</td>
<td>3 (8.3%)</td>
<td>0.207</td>
<td>3 (10.7%)</td>
</tr>
<tr>
<td>Number of risk factors</td>
<td>2 (1–3)</td>
<td>1 (1–2.75)</td>
<td>0.001</td>
<td>1 (0.25–2)</td>
</tr>
<tr>
<td>≥1.0 mm, n (%)</td>
<td>8/30 (26.7%)</td>
<td>0/17 (0%)</td>
<td>0.089</td>
<td>0/12 (0%)</td>
</tr>
<tr>
<td>Heterozygote of RNF 213†</td>
<td>4/15 (26.7%)</td>
<td>10/16 (62.5%)</td>
<td>0.045</td>
<td>9/13 (69.2%)</td>
</tr>
</tbody>
</table>

Results are expressed as number (column %), mean±SD or median (interquartile range). IMT indicates intima-media thickness; LDL, low density lipoprotein; MMD, Moyamoya disease; and RNF, ring finger protein.

*Carotid duplex sonography was performed in 47 of the 81 patients, 35 in the atherosclerosis group and 12 in the nonatherosclerosis group.
†RNF mutation analysis was performed in 31 of the 81 patients, 15 in the atherosclerosis group and 16 in the nonatherosclerosis group.

P value between atherosclerosis group and nonatherosclerosis group.
sustainability to MMD among East Asian populations. The exact mechanism by which RNF213 mutations are related to MMD remains unknown. The finding, that RNF213 mutations are more frequent in the nonatherosclerosis group, provides further evidence that MMD could be more prevalent in the nonatherosclerosis group. Definitive MMD is usually diagnosed by the presence of bilateral stenosis or occlusion of the terminal portion of the intracranial internal carotid artery or the proximal portion of the anterior cerebral artery and/or MCA with the development of moyamoya vessels. However, whether these criteria can be applied to adult-onset MMD is unclear. Adult-onset MMD can present with unilateral MCAD and/or MCA with the development of moyamoya vessels.

During early stages of adult-onset MMD, patients may present with focal MCA stenosis without sufficient development of moyamoya collaterals. Moreover, although rare, initial stenotic changes could occur at the mid-M1 portion of the MCA. Recent studies showed that many patients with intracranial arterial stenosis who did not meet all the diagnostic criteria of MMD also showed RNF213 abnormality, suggesting that adult-onset MMD may be misclassified as intracranial atherosclerosis. This is supported by the results presented here, suggesting that symptomatic isolated MCAD in young Asian adults may be an early manifestation of adult MMD.

This study had several limitations. First, HR-MRI findings were not correlated with the histopathologic findings, with final confirmative diagnosis requiring long-term follow-up. Rather, we correlated HR-MRI findings, which can help diagnose intracranial arterial stenosis, with a genetic analysis of RNF213. Second, there are some missing data. Some subjects did not agree to the genetic test, so mutation analysis was not performed in all subjects. Some cases referred from other centers and those with transient ischemic attack had no DWI images. Third, by excluding the patients showing significant steno-occlusion in the extracranial cervical arteries, characteristics of nonatherosclerosis group could be magnified. Nevertheless, we excluded patients who have cervical artery stenosis, who may have a high atherosclerotic burden, and can cause artery-to-artery embolism. Because we aimed to identify the characteristics of isolated MCAD, we excluded those patients. Fourth, the present study enrolled only Korean subjects, and variants in RNF213 are associated with susceptibility to MMD only in East Asian populations. Therefore, these results may not be applicable to other populations. Nevertheless, our data are valuable because the inclusion of patients with nonatherosclerotic disease, including MMD, in epidemiological studies of intracranial artery stenosis may confuse results in Asian populations. Our findings suggest that symptomatic isolated MCAD in young Asian adults may be an early manifestation of adult MMD. Fifth, partially recanalized embolic occlusion may also look like a stenosis of MCA. We did our best effort to exclude those patients. Patients, who were suspicious of embolic source, received an extensive evaluation to detect cardioembolic source. In addition, patients were also excluded if the angiography image in the HR-MRI taken 4 to 5 days after initial work-up revealed a recanalized MCAD, suggesting an embolic occlusion. Although there is still a possibility of embolic stroke of undetermined source, the effect of these patients may be insignificant as the prevalence of RNF213 in cervical carotid stenosis or cardioembolic stroke was rare. Sixth, there are limitations stemming from the classification based on HR-MRI findings. Although a previous study suggested the threshold value of the stenotic MCA...
outer diameter as 2.4 mm, it could be influenced by sex or severity of stenosis. However, the sex difference of outer vessel diameter in the previous studies\textsuperscript{37,38} was small and it could have limited effect on the results of our study. Classification of 4 patients was controversial whether atherosclerosis or dissection of nonatherosclerotic group. Differential diagnosis of dissection and atherosclerosis is often challenging because of their similar characteristics of HR-MRI. Atherosclerotic feature such as eccentric wall thickening with enhancement can be seen in dissection, and increased T1 signal of dissection can also be seen in intraplaque hemorrhage of atherosclerosis. This gray zone is the limitation of HR-MRI, and further development of imaging quality can help to solve this problem.

**Summary and Conclusions**

Nonatherosclerotic pathogenesis are common in young Asians with symptomatic isolated MCAD. The clinical findings, HR-MRI features, and RNF213 mutation results suggest that MMD is responsible for a significant proportion of patients with nonatherosclerotic pathogenesis. Symptomatic isolated MCAD in young Asian adults may be an early manifestation of adult MMD.

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**Disclosures**

None.

**References**


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Supplemental table I. Result of the RNF213 gene analysis according to the subgroup.

<table>
<thead>
<tr>
<th></th>
<th>Atherosclerosis group (n=15)</th>
<th>Non-atherosclerosis group (n=16)</th>
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<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Moyamoya disease type</td>
</tr>
<tr>
<td>Heterozygote of p.R4810K</td>
<td>4/15</td>
<td>10/16</td>
</tr>
<tr>
<td></td>
<td>(26.7%)</td>
<td>(62.5%)</td>
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</tbody>
</table>