p.R4810K

Ito et al. aimed to investigate the association between RNF213 founder polymorphism (p.R4810K) and each direct and indirect collateral development. By qualitative and quantitative evaluations of direct and indirect surgical collaterals using time-of-flight MR angiography, the postoperative development of each type of bypass was evaluated independently into two categories. Multivariate logistic regression analysis was performed to study the contributing factors for the development of each surgical collateral. Excellent development of postoperative direct and indirect bypass was observed in 65 hemispheres (70%) by qualitative evaluation, which was confirmed by quantitative evaluation. Multivariate logistic regression analysis of excellent indirect bypass development revealed a significant positive correlation with the p.R4810K (odds ratio, OR4.0; 95%-confidence interval, CI 1.2-16), advanced MR angiographic stage (OR9.5; 95%CI 1.7-73), and preoperative middle meningeal artery caliber (OR6.8; 95%CI 1.8-35), but a significant negative correlation was found with the excellent direct bypass development (OR0.17; 95%CI 0.03-0.75). No significant correlation was observed between excellent direct bypass development and the p.R4810K (OR0.95; 95%CI 0.37-2.4).In conclusion, excellent development of indirect collaterals after STA-MCA anastomosis combined with indirect pial synangiosis occurs more frequently in adult Moyamoya disease (MMD) with the RNF213 founder polymorphism, suggesting a role of the p.R4810K variant for marked in-growth of indirect collaterals and the utility of preoperative genetic analysis [1)].

The p.R4810K variant was detected in 254 Chinese moyamoya patients. Surgically treated 273 hemispheres with preoperative and postoperative digital subtraction angiography were included. Postoperative collateral formation (PCF) was evaluated on lateral and anteroposterior views using angiography. Univariate and multivariate logistic regression analyses were performed to determine the influence factors for PCF.

Among 254 patients, 191 (75.2%) patients carried wild-type p.R4810K variant (GG) and 63 patients (24.8%) carried the heterozygous p.R4810K variant (GA). PCF was better in patients with GA than in patients with GG both on lateral views and anteroposterior views ($p < 0.001$ and $p < 0.001$). Over the median 7 months follow-up after discharge, good PCF was observed in 201 hemispheres (73.6%), and poor PCF was observed in 72 hemispheres (26.4%). The univariable logistic regression showed that patients with GA (OR 4.681; 95% CI 1.925-11.383; $p = 0.001$) was associated with good PCF. On the other hand, the increasing age (OR 0.971; 95% CI 0.952-0.989; $p = 0.002$) and the presence of hemorrhage (OR 0.189; 95% CI 0.096-0.374; $p = 0.000$) were associated with poor PCF. Multivariate logistic regression analyses of p.R4810K variant and clinical variables showed that GA (OR 3.671; 95% CI 1.452-9.283; $p = 0.006$) was associated with a good PCF, while the presence of hemorrhage (OR 0.258; 95% CI 0.065-0.362; $p = 0.000$) was identified as a predictor of poor PCF.

The heterozygous p.R4810K variant was associated with better PCF [2)].

The c.14429G>A (p.R4810K) variant was identified in 125 (75.8%) of 165 MMD patients. Most patients (112) were heterozygous, and 13 patients had 2 copies of the c.14429G>A variant. A novel heterozygous variant, c.12086A>G (p.Q4029R), was found in 1 additional patient. The minor allele frequency of the c.14429G>A variant was significantly higher in the MMD group (138 [41.8%] of 330 patients) than in the control group (8 [1.36%] of 588 subjects; $p < 0.001$). The c.14429G>A

(p.R4810K) variant significantly increased the risk of MMD in Korean patients, with an OR of 52.11 ($p < 0.001$) compared with controls. Moreover, c.14429G>A (p.R4810K) genotypes occurred more frequently in patients with a family history of MMD. The homozygous variant was highly associated with early-onset MMD (age at onset < 5 years), cerebral infarction at diagnosis, and cognitive impairment in long-term outcome.

The findings indicate that the c.14429G>A (p.R4810K) allele of RNF213 is strongly associated with Korean patients with MMD. The homozygous c.14429G>A (p.R4810K) variant is particularly related to early-onset MMD, severe symptomatic manifestations at diagnosis, and poor prognosis. This genotypic variant may be a useful biomarker for early-onset MMD or unstable MMD with cerebral infarction, which requires early diagnosis and revascularization treatment [3].

1)
Ito M, Kawabori M, Sugiyama T, Tokairin K, Tatezawa R, Uchino H, Kazumata K, Houkin K, Fujimura M. Impact of RNF213 founder polymorphism (p.R4810K) on the postoperative development of indirect pial synangiosis after direct/indirect combined revascularization surgery for adult Moyamoya disease. Neurosurg Rev. 2022 Feb 7. doi: 10.1007/s10143-022-01749-9. Epub ahead of print. PMID: 35128622.
2)
Ge P, Ye X, Liu X, Deng X, Wang J, Wang R, Zhang Y, Zhang D, Zhang Q, Zhao J. Association between p.R4810K Variant and Postoperative Collateral Formation in Patients with Moyamoya Disease. Cerebrovasc Dis. 2019 Oct 2:1-8. doi: 10.1159/000503250. [Epub ahead of print] PubMed PMID: 31578010.
3)
Kim EH, Yum MS, Ra YS, Park JB, Ahn JS, Kim GH, Goo HW, Ko TS, Yoo HW. Importance of RNF213 polymorphism on clinical features and long-term outcome in moyamoya disease. J Neurosurg. 2015 Oct 2:1-7. [Epub ahead of print] PubMed PMID: 26430847.