Single Nucleotide Polymorphism in Patients with Moyamoya Disease

Young Seok Park, M.D., Ph.D.
Department of Neurosurgery, Chungbuk National University College of Medicine, Chungbuk National University Hospital, Cheongju, Korea

Moyamoya disease (MMD) is a chronic, progressive, cerebrovascular occlusive disorder that displays various clinical features and results in cerebral infarct or hemorrhagic stroke. Specific genes associated with the disease have not yet been identified, making identification of at-risk patients difficult before clinical manifestation. Familial MMD is not uncommon, with as many as 15% of MMD patients having a family history of the disease, suggesting a genetic etiology. Studies of single nucleotide polymorphisms (SNPs) in MMD have mostly focused on mechanical stress on vessels, endothelium, and the relationship to atherosclerosis. In this review, we discuss SNPs studies targeting the genetic etiology of MMD. Genetic analyses in familial MMD and genome-wide association studies represent promising strategies for elucidating the pathophysiology of this condition. This review also discusses future research directions, not only to offer new insights into the origin of MMD, but also to enhance our understanding of the genetic aspects of MMD. There have been several SNP studies of MMD. Current SNP studies suggest a genetic contribution to MMD, but further reliable and replicable data are needed. A large cohort or family-based design would be important. Modern SNP studies of MMD depend on novel genetic, experimental, and database methods that will hopefully hasten the arrival of a consensus conclusion.

Key Words: Moyamoya disease · Single nucleotide polymorphism · Genetic · Stroke · Cerebrovascular disease.

INTRODUCTION

Moyamoya disease (MMD) is a chronic cerebrovascular occlusive disorder that results in transient ischemia, cerebral infarcts, and hemorrhagic stroke.6-8,12-14 The disease has a bimodal age distribution of peak incidence, with peaks in children who are approximately five years of age and adults in their mid forties.6,15,16,33,70 MMD occurs higher prevalence in East Asian countries. Further, 15% of MMD cases have a family history of the disease.44 Most juvenile patients develop transient ischemic attacks or cerebral infarctions, whereas adult patients are more likely to have a hemorrhagic stroke.6,8,10,12 Although familial occurrence accounts for approximately 9–15% of MMD cases, the majority of cases are sporadic.8,12,20 This suggests some variant or impairment of genetic sequence in the same disease. Genetic associations with loci on chromosomes 3, 6, 8, 10, and 17 and a specific human leukocyte antigen (HLA) haplotype have been reported8,20,22,23,29,30, but questions about various genetic penetrations still remain. The current concept of pathogenesis of MMD is more focused on genetic factors rather than on the causes. Possible genetic variants included those of vascular endothelial growth factor, basic fibroblast growth factor, hepatocyte growth factor, transforming growth factor beta 1, granulocyte colony-stimulating factor, platelet-derived growth factor receptor beta, matrix metalloproteinase (MMP), and tissue inhibitor of metalloproteinase-2.38,59,72,73

SNP STUDIES

It has been suggested that in families, MMD may be transmitted through a polygenic or autosomal dominant mode with low penetrance.77 Linkage analyses have shown associations with loci 3p24.2–p26,22 6q25,23 8q23,62 10q23.31,14 12p12,62 and 17q25.45 SNP studies in MMD have mostly focused on mechanical stress on vessels, endothelium, and the relationship to atherosclerosis. In this review, we discuss SNP studies targeting the genetic etiology of MMD. Genetic analyses in familial MMD and genome-wide association studies represent promising strategies for elucidating the pathophysiology of this condition. This review also discusses future research directions, not only to offer new insights into the origin of MMD, but also to enhance our understanding of the genetic aspects of MMD. There have been several SNP studies of MMD. Current SNP studies suggest a genetic contribution to MMD, but further reliable and replicable data are needed. A large cohort or family-based design would be important. Modern SNP studies of MMD depend on novel genetic, experimental, and database methods that will hopefully hasten the arrival of a consensus conclusion.

Association with mechanical stress: angiogenesis and vascular repair genes (TIMP, MMP, Elastin/LIMK1 SNPs)

Dysregulation of tissue inhibitor of metalloproteinases (TIMPs)
can disrupt the balance between MMPs and TIMPs, resulting in aberrant vascular smooth muscle cell (SMC) dynamics, ultimately leading to MMD\(^\text{30}\). By degrading the neurovascular matrix, MMPs promote blood-brain barrier (BBB) damage, edema, and hemorrhage\(^\text{36,42}\). The balance between MMPs and TIMPs is known to be an important factor of BBB maintenance and vascular angiogenesis\(^\text{29}\). Several studies have demonstrated that overexpression of MMP-9 and underexpression of MMP-3, TIMP-1, and TIMP-2 are related to MMD\(^\text{31}\). Therefore, any SNPs of proteins involved in this cascade may provoke or protect against ischemic or hemorrhagic MMD.

The presence of a G/C heterozygous genotype at position -418 in the promoter of the TIMP-2 gene has been proposed as a genetic predisposing factor for MMD, but this association is debated. Park et al.\(^\text{30}\) support the data that the G/C heterozygous genotype in the TIMP-2 -418 G>C (rs8179090) promoter, MMP-2 -1575GA/-1306CC, and the dominant type (GG vs. GA+AA) of MMP 9 Q279R (rs17576) could be predisposing genetic factors for MMD development.

Vascular endothelial growth factor (VEGF) is involved in vasculogenesis in different intracranial lesions\(^\text{31}\), is an endothelial cell mitogen that induces transient vascular leakage, and is a potent angiogenic factor\(^\text{36}\). VEGF also promotes angiogenesis in cerebral ischemia\(^\text{29,41}\) and causes pathologic vessel formation\(^\text{41}\). Takekawa et al.\(^\text{41}\) reported increased VEGF expression in autopsy specimens from adults with MMD and Sakamoto et al.\(^\text{41}\) reported that the total meningeal cellularity and VEGF expression in the dura of patients with MMD was significantly higher than in the dura of controls. In ischemic disease, cerebral angiogenesis is caused by the release of VEGF\(^\text{26}\). VEGF affects vasculogenesis, endothelial cell proliferation and migration, vascular permeability, and stromal degradation through the activation of proteolytic enzymes that are involved in angiogenesis\(^\text{26,40}\). VEGF binds its receptor tyrosine kinases, VEGF receptor-1 and VEGF receptor-2 [also known as kinase insert domain containing receptor, or kinase insert domain containing receptor (KDR)] but

---

**Table 1. Reported genetic studies on Moyamoya disease**

| Target | Genetic | Author (year) |
|--------|---------|--------------|
| HLA genotyping | Type I HLA genotyping | Kihatara et al. (1982)\(^\text{27}\) |
| | Type I and II HLA genotyping | Aoyagi et al. (1995)\(^\text{30}\) |
| | HLA genotyping | Inoue et al. (1997)\(^\text{29}\) |
| | HLA-DRB1*1302 and HLA-DQB1*0609 alleles | Hong et al. (2009)\(^\text{32}\) |
| | HLA DRB1*03 and HLA DRB1*13 alleles | Kraemer et al. (2012)\(^\text{32}\) |
| Linkage analysis | Linkage to 3p24.2-26 | Ikeda et al. (1999)\(^\text{27}\) |
| | Linkage to D6S441 (6q25) | Inoue et al. (2000)\(^\text{29}\) |
| | Linkage to 17q25 | Yamauchi et al. (2000)\(^\text{37}\) |
| | 17q25.3 linkage analysis | Mineharu et al. (2008)\(^\text{43}\) |
| Hemodynamic and mechanical stress | MMP2/3/9/13 and TIMP-2 genes | Liu et al. (2010)\(^\text{39}\) |
| Endothelial nitric oxide synthase | eNOS gene (7q36) | Park et al. (2014)\(^\text{10}\) |
| Smooth Muscle cell | ACTA-2 | Guo et al. (2009)\(^\text{40}\) |
| | ACTA-2 | Roder et al. (2011)\(^\text{37}\) |
| Atherosclerosis | MTHFR 677C>T | Kim et al. (2010)\(^\text{39}\) |
| | MTHFR 677C>T | McKasson and Golomb (2011)\(^\text{40}\) |
| Cytokines and growth factors | -1575GA/-1306CC, and the dominant type in the TIMP-2-418 G>C ed. | Park et al. (2010)\(^\text{10}\) |
| | VEGF-634C allele with collateral vessel formation | Liu et al. (2012)\(^\text{39}\) |
| | MMP-2/MMP9 | Park et al. (2012)\(^\text{39}\) |
| | MMP2/3/9/13 and TIMP-2 genes | Liu et al. (2012)\(^\text{39}\) |
| | MMP-2/3/9/13 and TIMP-2 genes | Park et al. (2012)\(^\text{39}\) |
| RNF 213 | c.14576G>A RNF213 polymorphism | Kamada et al. (2011)\(^\text{32}\) |
| | RNF213 variant | Liu et al. (2011)\(^\text{40}\) |
| | RNF213 c.14576G>A polymorphism | Miyatake et al. (2012)\(^\text{38}\) |
| | RNF213 c.14576G>A | Miyawaki et al. (2012)\(^\text{38}\) |
| | p.R4810K RNF213 | Wu et al. (2012)\(^\text{38}\) |
| Others | PSRC1 | Roder et al. (2011)\(^\text{38}\) |

**ACTA**: alpha actin 2, **HLA**: human leukocyte antigen, **PSRC1**: proline/serine-rich coiled-coil 1, **MMP**: matrix metalloproteinase, **RNF**: Ring finger protein, **TGFB1**: transforming growth factor beta-1, **TIMP**: tissue inhibitor of metalloproteinase

---

**Acta**: alpha actin 2, **HLA**: human leukocyte antigen, **PSRC1**: proline/serine-rich coiled-coil 1, **MMP**: matrix metalloproteinase, **RNF**: Ring finger protein, **TGFB1**: transforming growth factor beta-1, **HTM**: homozygous, **TIMP**: tissue inhibitor of metalloproteinase
KDR is the key receptor mediating angiogenesis and is essential for endothelial cell survival and integrity. Park et al. found the genotypes including the VEGF-634C allele had better collateral vessel formation after surgery. They suggest that VEGF or KDR polymorphisms influence MMD as well as the formation of synangiosis-induced collateral vessel after bypass surgery.

Endothelial-based molecules and genetic studies (nitric oxide, eNOS)

Endothelial nitric oxide synthase (eNOS)-derived nitric oxide (NO) is one of the principal molecules in vasoregulation. NO is responsible for endothelium-dependent vasorelaxation, inhibition of leukocyte and platelet adhesion, attenuation of inflammatory mediators, and has a key role in vasodilator regulation of vascular smooth cells. Since NO is produced by eNOS, understanding of eNOS (also known as NOS3) polymorphisms may help to explain variation in the clinical aspects of MMD.

Park et al. showed that the haplotype a-4b-G was frequently found in patients with adult-onset MMD. These genetic differences may affect age-specific clinical characteristics such as cerebral ischemia and hemorrhage.

Smooth muscle cell-based genetic studies [Alpha actin 2 (ACTA2)]

The major function of vascular smooth muscle cells (SMCs) is to contract in response to the stretch resulting from pulsatile blood flow, a process that is dependent on the cyclic interaction between thin filaments, composed of the SMC-specific isoform of α-actin (SM α-actin, encoded by ACTA2), and thick filaments, composed of SMC-specific β-myosin. ACTA2 mutations associated with MMD provide further evidence that early-onset strokes may occur via a similar pathway of excessive SMC proliferation leading to arterial occlusion.

Atherosclerosis

Thromboembolic mechanisms, as well as hemodynamic instability in patients with MMD, play roles in cerebral infarction. An autopsy study of patients with MMD showed a frequent histopathology of thrombus formation in diseased arteries. Prothrombotic disorders are associated with MMD in up to 40% of pediatric patients, and several studies have investigated the thromboembolic etiology in patients with MMD.

An association between ischemic stroke and a specific polymorphism in methylene tetrahydrofolate reductase (MTHFR; 677C>T) in children has been reported, and homozygous 677C>T in the MTHFR gene has been reported in patients with MMD. Park et al. found the recessive type of MTHFR 677C>T and the C677T/A1298C compound genotype are significantly associated with adult MMD. They also found the frequency of the CT/AA sequence of MTHFR 677/1298 is significantly higher in MMD patients than in control subjects, especially in the hemorrhagic type of MMD.

Thrombotic or thromboembolic as well as hemodynamic unbalance play roles in developing infarction in patients with MMD.

Cytokines and growth factors

Several studies have found alterations in cytokines and growth factors in patients with MMD. The concentration of basic fibroblast growth factor (bFGF) in CSF has been shown to be elevated in patients with MMD compared to controls. Other studies have found increased immunoreactivity of bFGF in the dura mater, superficial temporal artery, and the circle of Willis of MMD patients. Significantly elevated expression of cellular retinoic acid-binding protein (CRABP1) was found in the CSF of MMD patients. In vitro studies of vascular smooth muscle cells (VSMCs) from MMD patients revealed alterations in the cellular response to a platelet derived growth factor (PDGF) stimulus, most probably caused by a decreased amount of PDGF receptors. Finally, higher concentrations of transforming growth factor beta 1 (TGFβ1) were found in the blood serum and VSMCs of MMD patients.

Ring finger protein 213 (RNF 213)

Three individual studies of MMD patients have revealed high frequencies of the same single base substitution (nonsynonymous mutation), the c.14576G>A (p.R4859K) variant in RNF213 (a gene located in chromosome 17q), which is present in ~2% of East Asian populations, a relatively higher rate compared with Caucasians. The RNF213 gene was further reported to correlate with the early-onset and severe forms of MMD, which indicates its value as a good biomarker for predicting prognosis.

The RNF213 gene encodes a protein with 5256 amino acids harboring a RING (Really Interesting New Gene) finger motif and an AAA (ATPase associated with a variety of cellular activities) domain, indicating the presence of both E3 ubiquitin ligase activity and an energy-dependent unfoldase. E3 ubiquitin ligase, which has several subtypes, is an enzyme that ubiquitinates specific target proteins, resulting in degradation by proteasomes.

The RNF213 variant associated with MMD prevails, but it is also found in other vascular diseases such as cerebrovascular stenosis, but not in the Caucasian MMD population. In RNF213-deficient mice, an abnormal vascular network does not develop at the base of the brain. The RNF213 variant is an important SNP, but cannot be specific to MMD only.

Genome-wide association study (GWAS) approaches are now being applied to MMD with the hope of uncovering the underlying pathogenic mechanisms. A GWAS was recently performed in Japanese MMD patients and found a strong association of MMD risk with chromosome 17q25-ter. These GWAS studies will need further investigation to solidly replicate the results using modern genetic studies based on familial or non-familial MMD.
LIMITATIONS

SNP studies have some limitations. First, most studies lack long-term follow up, which is necessary to assess clinical outcomes. The second limitation is a lack of well-defined patient and control groups. Third, genetic studies have been carried out based on a small number of case-control studies. Large population-based case-control or analyses centered on family-based designs are needed. However, SNP studies have many advantages over other genetic studies, the benefits of which depend on how SNPs will be exploited in relevant study designs and what traits and diseases will be the focus of these studies.

We have considered some of the unique aspects of SNPs and their relative advantages and disadvantages in human population-based analyses. Although progress in the search for genetic loci underlying MMD is encouraging, a relevant, specific single gene has not yet been identified. MMD appears to be a multifactorial, polygenic disorder that does not display a classic pattern of inheritance.

CONCLUSIONS

There are several studies of the association of SNPs and MMD, which focus on hemodynamic stress, the endothelium, smooth muscle, atherosclerosis, cytokines, growth factors, and RNF 213. Current SNP studies suggest a genetic contribution to MMD, but further reliable and replicable data are needed. A large cohort or family-based design will be necessary. I believe that modern MMD SNP studies depend on novel genetic, experimental, and database methods and will lead to a better understanding of MMD.

• Acknowledgements

This work was supported by the National Research Foundation of Korea (2013R1A2A2A001067990).

References

1. Achor SL, Gurman R, Lee M, Steinberg GK: Pathophysiology and genetic factors in moyamoya disease. Neurosurg Focus 26: E4, 2009
2. Andreoni V, Ciarmiello A, Fusco C, Ambrosiano G, Florio C, Linfante I: Moyamoya disease in Italian monozygotic twins. Neurology 53: 1332-1335, 1999
3. Asahi M, Fukui N, Sakamoto H, Shinaki T, Matsushima Y, Yamamoto M, et al.: Altered cellular responses to serum mitogens, including platelet-derived growth factor, in cultured smooth muscle cells derived from arteries of patients with moyamoya disease. J Cell Physiol 147: 191-198, 1991
4. Asahina M, Ogami K, Matsushima Y, Shimizu H, Nakagawa K, Yamamoto M, Yamamoto Y, Ikeda E, Achen MG, Breier G, Risau W: Role of transforming growth factor-beta1 in the pathogenesis of moyamoya disease. J Neurosurg 89: 623-629, 1998
5. Han H, Pyo CW, Yoo DS, Huh PW, Cho KS, Kim DS: Associations of Moyamoya patients with HLA class I and class II alleles in the Korean population. J Korean Med Sci 16: 876-880, 2001
6. Hojo M, Hoshimaru M, Miyamoto S, Taki W, Nagata I, Asahi M, et al.: Increased expression of serum Matrix Metalloproteinase-9 in patients with moyamoya disease. Surg Neurol 72: 476-480: discussion 480, 2009
7. Ikeda H, Nam DH, Oh CW: Moyamoya disease in adults: characteristics of clinical presentation and outcome after encephalo-duro-arterio-synangiosis. Clin Neurol Neurosurg 99 Suppl 2: S151-S155, 1997
8. Jin KL, Mao XJ, Nagayama T, Goldsmith PC, Greenberg DA: Induction of inheritance. J Neurol Neurosurg Psychiatry 79: 900-904, 2008
9. Burke GM, Burke AM, Sherma EA, Curley MC, Kryt HH, Bendok BR: Moyamoya disease: a summary. Neurosurg Focus 26: E11, 2009
10. Cao Y, Hong A, Schulten H, Post MJ: Update on therapeutic neurovascularization. Cardiovasc Res 65 : 639-648, 2005
11. Consensus from the MTA Initiative on Moyamoya Disease. Neurosurgery 61: 639-648, 2007
12. Han DH, Kwon OK, Byun BJ, Choi BH, Choi CW, Choi JU, et al.: A cooperative study - clinical characteristics of 334 Korean patients with moyamoya disease treated at neurological institutes (1976-1994). The Korean Society for Cerebrovascular Disease. Acta Neurochir (Wien) 142 : 1263-1273: discussion 1273-1274, 2000
13. Han DH, Nam DH, Oh CW: Moyamoya disease in adults: characteristics of clinical presentation and outcome after encephalo-duro-arterio-synangiosis. Clin Neurol Neurosurg 99 Suppl 2: S151-S155, 1997
14. Hojo M, Hoshimaru M, Miyamoto S, Taki W, Nagata I, Asahi M, et al.: Role of transforming growth factor-beta1 in the pathogenesis of moyamoya disease. J Neurosurg 89: 623-629, 1998
15. Han H, Pyo CW, Yoo DS, Huh PW, Cho KS, Kim DS: Association of Moyamoya patients with HLA class I and class II alleles in the Korean population. J Korean Med Sci 16: 876-880, 2001
16. Hojo M, Hoshimaru M, Miyamoto S, Taki W, Nagata I, Asahi M, et al.: Role of transforming growth factor-beta1 in the pathogenesis of moyamoya disease. J Neurosurg 89: 623-629, 1998
17. Hoshimaru M, Takahashi JA, Kikuchi H, Nagata I, Hatanaka M: Possible roles of fibroblast growth factor in the pathogenesis of moyamoya disease: an immunohistochemical study. J Neurosurg 75: 267-270, 1991
18. Ikeda E, Achen MG, Breier G, Risau W: Hypoxia-induced transcriptional activation and increased mRNA stability of vascular endothelial growth factor in C6 glioma cells. J Biol Chem 270: 19761-19766, 1995
19. Ikeda E, Sasaki T, Yoshimoto T, Fukui M, Arinami T: Mapping of a familial moyamoya disease gene to chromosome 3p24.2-p26. Am J Hum Genet 64: 533-537, 1999
20. Inoue TK, Ikezaki K, Sasaki T, Matsushima T, Fukui M: Linkage analysis of moyamoya disease on chromosome 6. J Child Neurol 15: 179-182, 2000
21. Inoue TK, Ikezaki K, Sasaki T, Oosumi T, Kamikawa N, Matsushima T, et al.: DNA typing of HLA in the patients with moyamoya disease. Jpn J Hum Genet 42: 507-515, 1997
22. Issa R, Krupinski J, Bujny T, Kumar S, Kaluza J, Kumar P: Vascular endothelial growth factor and its receptor, KDR, in human brain tissue after ischemic stroke. Lab Invest 79: 417-425, 1999
23. Jin KL, Mao XJ, Nagayama T, Goldsmith PC, Greenberg DA: Induction of inheritance. J Neurol Neurosurg Psychiatry 79: 900-904, 2008
24. King KL, Dutlo C, Kurihara T, Yamamoto M, Shikata M, Aoyagi M, Ogami K, Matsushima Y, Shikata M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Yamamoto M, Y...
of vascular endothelial growth factor and hypoxia-inducible factor-1al-
pho by global ischemia in rat brain. Neuroscience 99 : 577-585, 2000
27. Kamada F, Aoki Y, Narisawa A, Abe Y, KomatsuSaki, Kikuchi A, et al.: 
A genome-wide association study identifies RNF213 as the first Moy-
amoya disease gene. J Hum Genet 56 : 30-41, 2011
28. Kastrap A, Schulr JB, Mader I, Dichgans J, Kuker W: Diffusion-weight-
ed MRI in patients with symptomatic internal carotid artery disease. J 
Neurol 249 : 1168-1174, 2002
29. Kim SH, Hwang H, Chae JH, Kim K, Hwang YS, Lim BC: Ischemic 
stroke in a 7-month-old infant with antiphospholipid antibody and ho-
moroscopic C677T methylenetetrahydrofolate reductase (MTHFR) poly-
orphism. J Child Neurol 25 : 1047-1050, 2010
30. Kim SK, Yoo JI, Cho BK, Hong SJ, Kim YK, Moon JA, et al.: Elevation 
of CRABP-I in the cerebrospinal fluid of patients with Moyamoya dis-
ease. Stroke 34 : 2835-2841, 2003
31. Kitahara T, Okumura K, Semb a A, Yamaura A, Makino H: Genetic and 
immunological analysis on moyo-moya. J Neurol Neurosurg Psychiatry 45 : 1048-1052, 1982
32. Kraemer M, Horn FA, Roder C, Khan N, Dhall BR, Berlt R, et al.: Anal-
ysis of human lysozyme antigen genes in Caucasion patients with ide-
opathic moyamoya angiopathy. Acta Neurochir (Wien) 154 : 445-452, 2012
33. Kuroda S, Hashimoto N, Yoshimoto T, Iwasaki Y: Research Committee 
on Moyamoya Disease in Japan: Radiological findings, clinical course, 
and outcome in asymptomatic moyamoya disease: results of multicenter 
survey in Japan. Stroke 38 : 1430-1435, 2007
34. Kuroda S, Houkin K: Moyamoya disease: current concepts and future 
perspectives. Lancet Neurol 7 : 1036-1066, 2008
35. Lee CZ, Xu B, Hashimoto T, McColloeh CE, Yang GT, Young WL: Dox-
ycycline suppresses cerebral matrix metalloproteinase-9 and angiogene-
sis induced by focal hyperstimulation of vascular endothelial growth factor 
in a mouse model. Stroke 35 : 1715-1719, 2004
36. Lee SR, Lo EH: Induction of caspase-mediated cell death by matrix me-
talloproteinases in cerebral endothelial cells after hypoxia-reoxygenation. 
J Careh Blood Flow Metab 24 : 720-727, 2004
37. Li H, Zhang ZS, Liu W, Yang WZ, Dong ZN, Ma MJ, et al.: Association 
of a functional polymorphism in the MMP-5 gene with Moyamoya Dis-
ease in the Chinese Han population. Cerebrovasc Dis 30 : 618-625, 2010
38. Liu C, Roder C, Schultz C, Kasuya H, Aka gaya H, Nishizawa T, et al.: 
Analysis of TGFβ1 in European and Japanese Moyamoya disease pa-
teins. Eur J Genet Med 55 : 531-534, 2012
39. Liu W, Hashikata H, Inoue K, Matsuura N, Matsuyama Y, Kobayashi H, 
et al.: A rare Asian founder polymorphism of Raptor may explain the 
high prevalence of moyamoya disease among East Asians and its low 
prevalence among Caucasians. Environ Health Prev Med 15 : 94-104, 
2010
40. Liu W, Morito D, Takashima S, Minehara Y, Kobayashi H, Hitomi T, et 
al.: Identification of RNF213 as a susceptibility gene for moyamoya dis-
ease and its possible role in vascular development. Pediatr Neurosurg 27 : 182-
189, 1997
41. McKassen MJ, Kolomb MR: Two children with both arm ischemia and 
arterial ischemic stroke during the perinatal period. J Child Neurol 26 : 
1548-1554, 2011
42. Lo EH, Dallara T, Moskowitz MA: Mechanisms, challenges and oppor-
tunities in stroke. Nat Rev Neurosci 4 : 399-415, 2003
43. Malek AM, Connors S, Roberton RL, Folkman J, Scott RM: Evaluation of 
cerebrospinal fluid levels of basic fibroblast growth factor in moyama-
yoa and central nervous system disorders. Pediatr Neurosurg 27 : 182-
189, 1997
44. Michalski C, Golomb MR: Two children with both arm ischemia and 
arterial ischemic stroke during the perinatal period. J Child Neurol 26 : 
1548-1554, 2011
45. Minehara Y, Liu W, Inoue K, Matsura N, Inoue S, Takenaka K, et al.: 
Autosomal dominant moyamoya disease maps to chromosome 17q23.3. 
Neurology 70 (24 Pt 2) : 2357-2363, 2008
46. Miyatake S, Miyake N, Touho H, Nishihara-Tadaki A, Konoyo Y, Okada I, et 
al.: Homozygous c.1457G>A variant of RNF213 predicts early-on-
set and severe form of moyamoya disease. Neurology 78 : 803-810, 2012
47. Miyatake S, Touho H, Miyake N, Obha C, Doi H, Sai tsu H, et al.: Sib-
ling cases of moyamoya disease having homozygous and heterozygous 
c.1457G>A variant in RNF213 showed varying clinical course and se-
verity. J Hum Genet 57 : 804-806, 2012
48. Miyovski S, Imai H, Takeyanagi S, Mukasa A, Nakatomi H, Saito N: 
Identification of a genetic variant common to moyamoya disease and 
intracranial major artery stenosis/occlusion. Stroke 43 : 3371-3374, 2012
49. Moncada S, Higgs A: The L-arginine-nitric oxide pathway. N Engl J Med 
329 : 2002-2012, 1993
50. Mukhopadhyay D, Ti oskas L, Zhou XM, Foster D, Brugge JS, Suhkhatme 
VP: Hypoxic induction of human vascular endothelial growth factor 
expression through e-Src activation. Nature 375 : 577-581, 1995
51. Nanba R, Kuroda S, Tada M, Ishikawa T, Houkin K, Iwasaki Y: Clinical 
features of familial moyamoya disease. Child Nerv Syst 22 : 258-262, 
2006
52. Nanba R, Tada M, Kuroda S, Houkin K, Iwasaki Y: Sequence analysis 
and bioinformatics analysis of chromosome 17q25 in familial moyamo-
yoa disease. Child Nerv Syst 21 : 62-68, 2005
53. Park YS, Jeon YI, Kim HS, Chae KY, Oh SH, Han IB, et al.: The role of 
VEGF and KDR polymorphisms in moyamoya disease and collateral 
recanalization. PloS One 7 : e7158, 2012
54. Park YS, Jeon YI, Kim HS, Han IB, Choi JU, Kim DS, et al.: The roles of 
the methylenetetrahydrofolate reductase 677C>T and 1298A>C polymor-
phisms in moyamoya disease patients. Child Nerv Syst 30 : 1687-1695, 
2014
55. Park YS, Jeon YI, Kim HS, Han IB, Oh SH, Kim DS, et al.: The GC+CC 
genotype at position 418 in TIMP-2 promoter and the -1575GA/-
1573GC genotype in MMP-2 is genetic predisposing factors for preva-
ience of moyamoya disease. BMC Neurol 14 : 180, 2014
56. Park YS, Min KT, Kim YG, Lee YH, Cheong HJ, Yeon IS, et al.: Age-
specific eNOS polymorphism diseases. Child Nerv Syst 27 : 1919-1926, 
2011
57. Roder C, Peters V, Kasuya H, Nishizawa T, Wakita S, Berg D, et al.: Anal-
ysis of ACTA2 in European Moyamoya disease patients. Eur J Paediatr 
Neurosci 15 : 117-122, 2011
58. Roder C, Peters V, Kasuya H, Nishizawa T, Takehara Y, Berg D, et al.: 
Common genetic polymorphisms in moyamoya and atherosclerotic dis-
ease in Europeans. Child Nerv Syst 27 : 245-252, 2011
59. Roder C, Peters V, Kasuya H, Nishizawa T, Takehara Y, Berg D, et al.: 
Polymorphisms in TGFβ1 and PDGFβR are associated with Moyama-
yoa disease in European patients. Acta Neurochir (Wien) 152 : 2153-2160, 
2010
60. Ruel M, Khan TA, Voisine P, Bianchi C, Sellek FW: Vasomotor dysfunc-
tion after cardiac surgery. Eur J Cardiothorac Surg 26 : 1002-1014, 2004
61. Sakamoto S, Kidani Y, Yamasaki E, Shibakawa M, Obha S, Shrestha R, et al.: 
Expression of vascular endothelial growth factor in dura mater of 
patients with moyamoya disease. Neurosurg Rev 31 : 77-81, discussion 
81, 2008
62. Sakurai K, Horisuchi Y, Ikeda H, Ikizaki K, Yoshimoto T, Fukui M, et al.: 
A novel susceptibility locus for moyamoya disease on chromosome 
8q23. J Hum Genet 49 : 278-281, 2004
63. Schork NJ, Fallin D, Lanchbury JS: Single nucleotide polymorphisms 
and the future of genetic epidemiology. Clin Genet 58 : 250-264, 2000
64. Scott RM: Arteriovenous malformation and moyamoya disease. Child 
Nerv Syst 13 : 357, 1997
65. Skardoulas A, Youdakis KA, Mastroyiannis S, Vagias E, Magoufis G,
Koukoutsakis P: Moyamoya syndrome in a child with pyruvate kinase deficiency and combined prothrombotic factors. J Child Neurol 22: 474-478, 2007

66. Sonobe S, Fujimura M, Niiyama K, Nishijima Y, Ito A, Shimizu H, et al.: Temporal profile of the vascular anatomy evaluated by 9.4-T magnetic resonance angiography and histopathological analysis in mice lacking RNF213: a susceptibility gene for moyamoya disease. Brain Res 1552: 64-71, 2014

67. Starke RM, Komotar RJ, Connolly ES: Optimal surgical treatment for moyamoya disease in adults: direct versus indirect bypass. Neurosurg Focus 26: E8, 2009

68. Takekawa Y, Umezawa T, Ueno Y, Sawada T, Kobayashi M: Pathological and immunohistochemical findings of an autopsy case of adult moyamoya disease. Neuropathology 24: 236-242, 2004

69. Thomas KA: Vascular endothelial growth factor, a potent and selective angiogenic agent. J Biol Chem 271: 603-606, 1996

70. Wakai K, Tamakoshi A, Ikezaki K, Fukui M, Kawamura T, Aoki R, et al.: Epidemiological features of moyamoya disease in Japan: findings from a nationwide survey. Clin Neurol Neurosurg 99 Suppl 2: S1-S5, 1997

71. Waltenberger J, Claesson-Welsh L, Sieghahn A, Shibuya M, Heldin CH: Different signal transduction properties of KDR and Flt1, two receptors for vascular endothelial growth factor. J Biol Chem 269: 26988-26995, 1994

72. Wang X, Zhang Z, Liu W, Xiong Y, Sun W, Huang X, et al.: Impacts and interactions of PDGFRB, MMP-3, TIMP-2, and RNF213 polymorphisms on the risk of Moyamoya disease in Han Chinese human subjects. Gene 526: 437-442, 2013

73. Weinberg DG, Arnaout OM, Rahme RJ, Assou SG, Batjer HH, Bendok BR: Moyamoya disease: a review of histopathology, biochemistry, and genetics. Neurosurg Focus 30: E20, 2011

74. Wu Z, Jiang H, Zhang L, Xu X, Zhang X, Kang Z, et al.: Molecular analysis of RNF213 gene for moyamoya disease in the Chinese Han population. PLoS One 7: e48179, 2012

75. Yamamoto M, Aoyagi M, Fukui N, Matsushima Y, Yamamoto K: Differences in cellular responses to mitogens in arterial smooth muscle cells derived from patients with moyamoya disease. Stroke 29: 1188-1193, 1998

76. Yamashita M, Oka K, Tanaka K: Histopathology of the brain vascular network in moyamoya disease. Stroke 14: 50-58, 1983

77. Yamauchi T, Tada M, Houkin K, Tanaka T, Nakamura Y, Kuroda S, et al.: Linkage of familial moyamoya disease (spontaneous occlusion of the circle of Willis) to chromosome 17q25. Stroke 31: 930-935, 2000

78. Yoshimoto T, Houkin K, Takahashi A, Abe H: Angiogenic factors in moyamoya disease. Stroke 27: 2160-2165, 1996