Pediatric Issue

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 strokes[6,34,64,67,70]. 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[34].

Most juvenile patients develop transient ischemic attacks or cerebral infarctions[12], whereas adult patients are more likely to have a hemorrhagic stroke[33,45,51]. Although familial occurrence accounts for approximately 9–15% of MMD cases, the majority of cases are sporadic[8,43]. This suggests some variant or impairment of genetic sequence in the same disease. Genetic associations with loci on chromosome 3, 6, 8, 10, and 17 and a specific human leukocyte antigen (HLA) haplotype have been reported[14,17,22,23,52,62], 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]. Current single nucleotide polymorphism (SNP) studies suggest a genetic contribution to MMD. Here, we discuss current single nucleotide genetic studies in MMD.

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 on the relationship to atherosclerosis (Table 1).

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

Dysregulation of tissue inhibitor of metalloproteinases (TIMPs)

Table 1. Reported genetic studies on Moyamoya disease

Target	Genetic	Author (year)
HLA genotyping	Type1 HLA genotyping	Kihatara et al. (1982)[31]
	Type I and IIHLA genotyping	Aoyagi et al. (1995)[4]
	HLA genotyping	Inoue et al. (1997)[24]
	HLA-DRB1*1302 and HLA-DQB1*0609 alleles	Hong et al. (2009)[19]
	HLA DRB1*03 and HLA DRB1*13 alleles	Kraemer et al. (2012)[32]
Linkage analysis	Linkage to 3p24.2-26	Ikeda et al. (1999)[22]
	Linkage to D6S441 (6q25)	Inoue et al. (2000)[23]
	Linkage to 17q25	Yamauchi et al. (2000)[77]
	17q25.3 linkage analysis	Mineharu et al. (2008)[45]
	17q25.3 linkage analysis	Liu et al. (2010)[39]
Hemodynamic and mechanical stress	MMP2/3/9/13 and TIMP2 genes	Li et al. (2010)[37]
	MMP2/MMP9	Park et al. (2014)[55]
Endothelial nitric oxide synthase	eNOS gene (7q36)	Park et al. (2011)[56]
Smooth Muscle cell	ACTA-2	Guo et al. (2009)[14]
	ACTA-2	Roder et al. (2011)[57]
Atherosclerosis	MTHFR; 677C>T	Kim et al. (2010)[29]
	MTHFR; 677C>T	McKasson and Golomb (2011)[44]
	CT/AA sequence of MTHFR 677/1298	Park et al. (2014)[54]
Cytokines and growth factors	B-FGF, CRABP1, PDGFRB, TGFB1, located in 5q31-q32 and 19q13.1	Roder et al. (2010)[59]
	TGFB1	Liu et al. (2012)[38]
	VEGF-634C allele with collateral vessel formation	Park et al. (2012)[53]
RNF 213	c.14576G>A RNF213 polymorphism	Kamada et al. (2011)[27]
	RNF213 variant	Liu et al. (2011)[40]
	RNF213 c.14576G>A polymorphism	Miyatake et al. (2012)[46]
	RNF213 c.14576G>A	Miyawaki et al. (2012)[48]
	Earlier onset and more severe course in patients HMZ for c.14576G>A RNF213 variant	Miyatake et al. (2012)[47]
	p.R4810K RNF213	Wu et al. (2012)[74]
Others	PSRC-1	Roder et al. (2011)[58]

ACTA : alpha actin 2, HLA : human leukocyte antigen, PSRC1 : proline/serine-rich coiled-coil 1, MMP : matrix metalloproteinase, RNF : Ring finger protein, TFGB1 : transforming growth factor beta-1, HMZ : homozygous, TIMP : tissue inhibitor of metalloproteinase

can disrupt the balance between MMPs and TIMPs, resulting in aberrant vascular smooth muscle cell (SMC) dynamics, ultimately leading to MMD[55]. By degrading the neurovascular matrix, MMPs promote blood-brain barrier (BBB) damage, edema, and hemorrhage[5,36,42]. The balance between MMPs and TIMPs is known to be an important factor of BBB maintenance and vascular angiogenesis[35]. Several studies have demonstrated that overexpression of MMP-9 and underexpression of MMP-3, TIMP-1, and TIMP-2 are related to MMD[11]. 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.[55] 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[61], is an endothelial cell mitogen that induces transient vascular leakage, and is a potent angiogenic factor[69]. VEGF also promotes angiogenesis in cerebral ischemia[25,61] and causes pathologic vessel formation[9]. Takekawa et al.[68] reported increased VEGF expression in autopsy specimens from adults with MMD and Sakamoto et al.[61] 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[9,26]. VEGF affects vasculogenesis, endothelial cell proliferation and migration, vascular permeability, and stromal degradation through the activation of proteolytic enzymes that are involved in angiogenesis[21,50]. 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 contaning receptor (KDR)] but

KDR is the key receptor mediating angiogenesis[71] and is essential for endothelial cell survival and integrity[13]. Park et al.[53] 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[56]. Endothelial NO is responsible for endothelium-dependent vasorelaxation, inhibition of leukocyte and platelet adhesion, attenuation of inflammatory mediators, and has a key role in vasodilatory regulation of vascular smooth cells[49,60]. Since NO is produced by eNOS, an understanding of eNOS (also known as NOS3) polymorphisms may help to explain variation in the clinical aspects of MMD.

Park et al.[56] show that the haplotype a-4b-G was frequently found in patients with adult-onset MMD. These genetic differences can affect age-specific clinical characteristics such as cerebral ischemia and hemorrhage[56].

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[14]. 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[14,57].

Atherosclerosis

Thromboembolic mechanisms, as well as hemodynamic instability in patients with MMD, play roles in cerebral infarction[54]. An autopsy study of patients with MMD showed a frequent histopathology of thrombus formation in the diseased arteries[77]. Prothrombotic disorders are associated with MMD in up to 40% of pediatric patients[7], and several studies have investigated the thromboembolic etiology in patients with MMD[2,54,65].

An association between ischemic stroke and a specific polymorphism in methylene tetrahydrofolate reductase (MTHFR; 677C>T) in children has been reported[29,44], and homozygous 677C>T in the MTHFR gene has been reported in patients with MMD[2,65]. Park et al.[54] 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[54].

Thrombotic or thromboembolic as well as hemodynamic unbalance play roles in developing infarction in patients with MMD[10,28,76].

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[43,78]. Other studies have found increased immunoreactivity of bFGF in the dura mater[20], superficial temporal artery[18,20], and the circle of Willis[14] of MMD patients. Significantly elevated expression of cellular retinoic acid-binding protein (CRABP1) was found in the CSF of MMD patients[30]. *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[3,22,75]. Finally, higher concentrations of transforming growth factor beta 1 (TGFB1) were found in the blood serum and VSMCs of MMD patients[18,78].

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 *RFP213* (a gene located in chromosome 17q)[27,40,46]. The c.14576G>A in RNF213 is present in ~2% of East Asian populations, a relatively higher rate compared with Caucasians[27,40,46]. 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[46].

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[48]. The RNF213 variant associated with MMD prevails, but it is also found in other vascular diseases such as cerebrovascular stenosis[48], but not in the Caucasian MMD population[41]. In RNF213-deficient mice, an abnormal vascular network does not develop at the base of the brain[66]. 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[1]. A GWAS was recently performed in Japanese MMD patients and found a strong association of MMD risk with chromosome 17q25-ter[27]. 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, SNPs 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[63].

We have considered some of the unique aspects of SNPs and their relative advantages and disadvantages in human population-based analyses[63]. 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.

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