

Association of *HLA-DQA2* and *HLA-B* With Moyamoya Disease in the Chinese Han Population

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Abstract

Objective

An HLA imputation was conducted to explore the relationship between HLA and patients with moyamoya disease (MMD) in the Chinese Han population.

Methods

In this study, we performed an association analysis of the major histocompatibility complex region in 2,786 individuals of Chinese Han ancestry (2,031 controls and 755 patients with MMD), through a widely used HLA imputation method.

Results

We identified that the variant rs3129731 (odds ratio [OR] = 1.79, $p = 3.69 \times 10^{-16}$) located between the *MTCO3P1* and *HLA-DQA2* is a major genetic risk factor for MMD. In addition to this variant, found in the conditional association analysis, we also detected another independent signal, rs1071817 (OR = 0.62, $p = 1.20 \times 10^{-11}$), in *HLA-B*.

Conclusions

Our research suggests that the genetic polymorphism of *HLA-DQA2* and *HLA-B* could be a genetic predisposing factor for MMD in Chinese Han. This may provide some evidence for further HLA-related studies of patients with MMD of Chinese Han ethnicity and indicates that MMD is an immune-related disease.

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Glossary

GWAS = genome-wide association study; **MAF** = minor allele frequency; **MHC** = major histocompatibility complex; **MMD** = moyamoya disease; **OR** = odds ratio; **SNP** = single nucleotide polymorphism.

Moyamoya disease (MMD) is a chronic, progressive, occlusive cerebrovascular disease of unknown etiology. Its distinctive pathologic feature is the steno-occlusion of the distal internal carotid artery or its proximal branches, with the formation of fragile, small, net-like collaterals.^{1,2} It is initially described in Japan as “moya-moya” for its angiographic characteristics of “a puff of smoke.”³ Epidemiologic studies have found that the incidence of MMD is highest in East Asian countries.^{1,2} The common clinical presentations of MMD include TIA, ischemic stroke, hemorrhagic stroke, seizures, headache, and cognitive impairment. It is a common cause of stroke in children or young adults.⁴ A study has shown that MMD may be caused by genetic factors, rather than environmental factors,⁵ and genetic studies have shown that MMD-related genetic loci exist on chromosomes 3, 6, 8, and 17.⁶⁻¹¹ Our previous genome-wide association study (GWAS) also confirms the association of MMD with chromosomes 3 and 17.¹² In addition, we also find enrichment of susceptibility gene expression associated with the immune system.¹²

The *major histocompatibility complex* (MHC) encodes several key immune response genes and is also known as the HLA region in humans. It is located on chromosome 6p21 and includes a series of closely linked loci.¹³ The MHC gene can be divided into 3 regions, which are named *MHC Class I*, *MHC Class II*, and *MHC Class III*. The most important molecules of the classical human *MHC Class I* antigens are HLA-A, HLA-B, and HLA-C, whereas *MHC Class II* antigen-related molecules are HLA-DR, HLA-DQ, and HLA-DP.^{14,15} The *MHC Class III* region is located between the *Class I* and *II* regions and contains 55 protein coding genes and 5 pseudogenes.¹⁶ Many MHC gene products are involved in inflammatory responses, as part of the adaptive immune response, and interact with natural killer cell and cytokines as part of the innate immune response. They include ligands for antigen processing and expression, receptors, interacting proteins, signal transduction factors, and transcriptional regulatory factors.¹⁶ As HLA plays an important role in the immune system, it has received a lot of attention. However, studies have found that it also has important roles in other disease systems. The alleles that encode the HLA molecules have frequently been reported to be strongly associated with various diseases, such as ankylosing spondylitis, reactive arthritis,¹⁴ Takayasu arteritis,¹⁷ giant cell arteritis,¹⁸ granulomatosis with polyangiitis,¹⁹ and various other autoimmune disorders.¹⁴ Therefore, the identification of an association between *HLA* and disease susceptibility has become important to diagnose and understand the pathogenesis of the diseases.

Although some reports have suggested possible linkage with MMD on chromosomes 3p24.2-p26 and 17q25,⁶⁻⁹ a marker located on chromosome 6 is also indicated to be in linkage with MMD.⁷ Previous studies reported that some HLA alleles were associated with MMD²⁰⁻²²; however, these investigations are limited, and study cohorts are small, particularly in the Chinese Han population.

We investigated the distributions of HLA genes in Chinese Han patients with MMD to identify *HLA* markers that may contribute to genetic susceptibility.

Methods

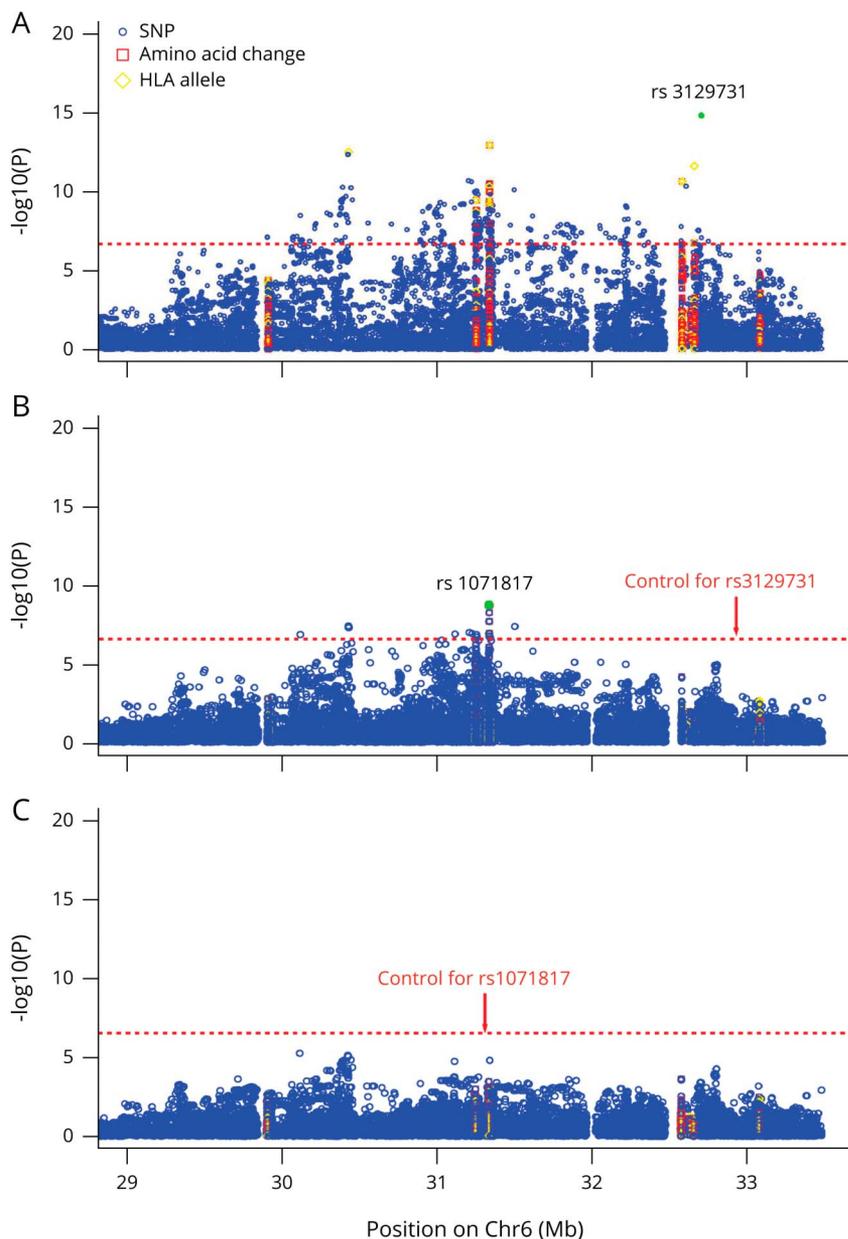
MMD GWAS Data

The study data were obtained from our previous MMD GWAS for 755 cases and 2031 controls that were genotyped by HumanOmniZhongHua-8 BeadChip, which was previously described in our early studies.¹² All of the cases fulfilled the diagnosis guideline established by the Research Committee on Spontaneous Occlusion of the Circle of Willis (MMD) of the Ministry of Health and Welfare of Japan.^{1,23,24} All the cases were diagnosed by digital subtraction angiography or MR angiography, with stenosis of the bilateral internal carotid artery system. According to the guideline, moyamoya syndrome and patients with vasculopathy caused by atherosclerosis, irradiation, meningitis, brain neoplasm, head trauma, Recklinghausen disease, Down syndrome, and autoimmune disease to the head were excluded. The health control groups were recruited such that they matched cases in terms of age, sex, and geographical distribution (birthplace), and controls with a medical history of any cerebrovascular diseases or myocardial infarction were excluded. All the study subjects and single nucleotide polymorphisms (SNPs) were extracted via a standard quality control criteria, exclusion of closely related relative and outliers in terms of ancestry, SNP, and sample call rate (<90%), SNP minor allele frequency (MAF) (<1%), and Hardy-Weinberg equilibrium ($p \leq 10^{-4}$) cutoffs. The study subjects were homogeneous and it showed no evidence of systemic bias or potential population substructure which after the principal component analysis runs to exclude the occurrence of the above.

Standard Protocol Approvals, Registrations, and Patient Consents

Written informed consent was obtained from all participants. The study was approved by the Ethics Committee of Anhui Medical University and implemented according to the Declaration of Helsinki.

Figure 1 Stepwise Conditional Association Plots of the Variants for Moyamoya Disease in the HLA Region



The association of each locus used for conditioning (rs3129731 and rs1071817) is shown in the green dot in each panel. In each plot, the horizontal axis shows the chromosomal position (based on University of California Santa Cruz hg19 assembly) and the vertical axis shows $-\log_{10}(p)$ value for association with MMD in the logistic regression model. The horizontal dashed line corresponds to the meaning threshold $p = 5 \times 10^{-8}$.

Imputation of the HLA Region

We extracted SNP genotypes located in the MHC region (29–34 Mb at chromosome 6) and then imputed 2- and 4-digit classical alleles for *HLA-A* (MIM 142800), *HLA-B* (MIM 142830), *HLA-C* (MIM 142840), *HLA-DRB1* (MIM 142857), *HLA-DQB1* (MIM 604305), *HLA-DQA1* (MIM 146880), *HLA-DPB1* (MIM 142858), and *HLA-DPA1* (MIM 142880), their corresponding amino acid polymorphisms, and SNPs, on the basis of 2 reference panels: the HLA and SNP genotypes from the 1000 Genomes Project reference data (only the Chinese Han population)²⁵ and the Han-MHC database ($n = 10,689$).²⁶ For the postimputed data, the variants, with low imputation quality ($r^2 < 0.10$), or MAF below 0.01 or significant deviation from HardyWeinberg

equilibrium ($p < 1.00 \times 10^{-4}$, software PLINK version 1.07) had been removed. All information about the SNPs, amino acid residues, and 2-digit and 4-digit HLA alleles were encoded as binary variables and phased by the Beagle 3.0.4 imputation program powered by the SNP2HLA method with some modifications.

Association Analysis

After imputation, we did an association analysis and set a genome-wide significance threshold ($p = 5.0 \times 10^{-8}$) to find sites with significant association. We determined the top independent associations using a stepwise logistic regression model to explore MMD independent loci, controlling for the most significant sites of p value as covariates in raw date of

Table 1 Association of HLA Alleles, Amino Acid Polymorphisms, and Single Nucleotide Polymorphisms With Moyamoya Disease Susceptibility

Variants	A1/A2	Frequency of A1		OR (95% CI)	p Value	
		Cases	Control			
HLA allele	<i>HLA-B*46</i>	P/A	0.07	0.14	0.49 (0.40–0.61)	4.12×10^{-11}
Amino acid polymorphism	HLA-B amino acid Ala24	A/P	0.57	0.45	1.58 (1.41–1.78)	3.48×10^{-14}
SNPs	rs3129731	T/G	0.26	0.17	1.79 (1.55–2.06)	3.69×10^{-16}
	rs1071817	T/G	0.21	0.3	0.62 (0.54–0.71)	1.20×10^{-11}

Abbreviations: A1/A2 = effective allele/alternative allele; A/P = absent/present; OR = estimated odds ratio; p = statistical logistic p value of each variant; 95% CI: 95% confidence interval for OR.

Here, we just show the most significant variants; one can refer to others in table e-3, links.lww.com/NXG/A424.

imputation; then, the results were analyzed, and the p value was found to be significant. The most significant loci was then used as the new control signal and it was taken as the most significant point of the p value as a new signal after control. Then, we selected the most significant point after control as covariates to control, and so on, until no site reaches the significant level ($p < 5.0 \times 10^{-8}$).

Construction of Protein Spatial Structure

We queried the target amino acid sequence on GenBank (ncbi.nlm.nih.gov) and used protein homology modeling with the SWISS-MODEL online website (swissmodel.expasy.org). The image was prepared using VMD 1.9.3.

Data Availability

Anonymized data will be shared by request from any qualified investigator.

Results

HLA Imputation Result

From our previous MMD GWAS data, we chose 8,245 SNPs in 755 MMD cases and 2031 controls using an optimized target capture array. After quality control, we finally obtained 6,789 SNPs. Then, using the imputation method, we successfully inferred the 2-digit and 4-digit genotypes of 8 HLA genes, their corresponding amino acid polymorphisms, and the SNPs in the MHC region of the 2,786 subjects. We obtained 29,948 variants. After strict quality control of all variants obtained from imputation, we finally obtained 25,729 variants to further assess their association with the risk of MMD (table e-1, links.lww.com/NXG/A422).

rs3129731 Has the Strongest Association With MMD Risk

As shown in figure 1, the top association signal was given by rs3129731 (odds ratio [OR] = 1.79, $p = 3.69 \times 10^{-16}$; table 1), an intergenic SNP located between the *MTCO3P1* and *HLA-DQA2*, when the variants in the MHC region were tested for overall risk of MMD (patients vs control individuals). We also

found an HLA allele in *HLA-B* (*HLA-B*46*, OR = 0.49, $p = 4.12 \times 10^{-11}$; table 1).

HLA-B Associations With MMD in the Chinese Han Population

We then investigated additional *HLA* variants that were associated with the risk of MMD but were independent of rs3129731. When conditioning on rs3129731, we observed a significant independent SNP at *HLA-B* amino acid position 94 (rs1071817, OR = 0.62, $p = 1.20 \times 10^{-11}$) and a most significant amino acid polymorphism (*HLA-B* amino acid 24, OR = 1.58, $p = 3.48 \times 10^{-14}$). We then conditioned on rs3129731 and rs1071817 but observed no other significant associations ($p < 5.0 \times 10^{-8}$) (table e-2, links.lww.com/NXG/A423). These results indicate that MMD, associated with the MHC region, can be explained by combinations of multiple *HLA-B* genes.

The 3D Ribbon Model of the HLA Protein

The *HLA-B* structure was based on Protein Data Bank entry 6at5.²⁷ The *HLA-B* amino acid 94 residue is located in a α -helix structure, within a peptide-binding groove, and the *HLA-B* amino acid 24 residue is located in a β -strand structure at the beginning of the protein peptide chain (figure 2).

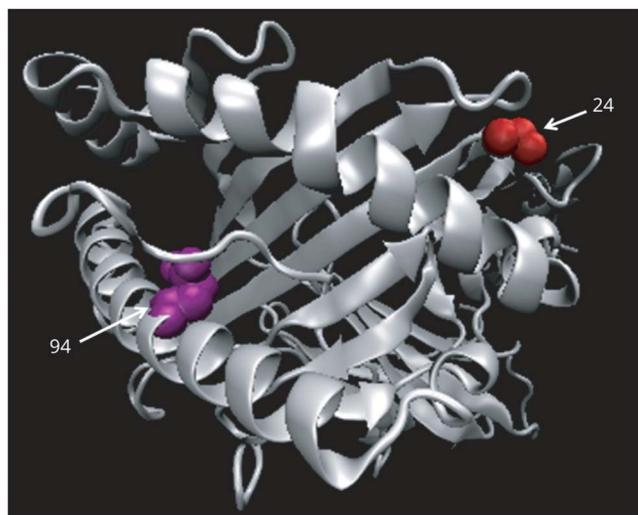
The flowchart of the research process can be found in the appendix (figure e-1, links.lww.com/NXG/A421).

Discussion

We have applied an *HLA* imputation approach to our previous MMD GWAS data, which was of a well-characterized cohort of 755 Chinese Han patients with MMD and 2031 healthy controls. After correlation analysis, we identified the common variant rs3129731, within the *HLA* locus, as a main genetic risk factor for acquiring MMD. We also found another independent signal, rs1071817 in *HLA-B*, by condition analysis.

SNP rs3129731 is located in the intergenic region between the *MTCO3P1* and *HLA-DQA2*. *MTCO3P1* (mitochondrially encoded cytochrome C oxidase III pseudogene 1) is a

Figure 2 Three-Dimensional Ribbon Models for HLA-B



HLA-B amino acid residues 94 and 24 are highlighted in purple and red, respectively (for interpretation of the references to colors in this figure legend, the reader is suggested to refer to the web version of this article).

pseudogene and was affiliated with the lncRNA class. *HLA-DQA2* belongs to the HLA Class II alpha chain family. This variant showed a strong association with the expression of *HLA-DQA2* in the artery (gtexportal.org/home/). *HLA-DQA2* is believed to play a central role in peptide loading of MHC-II molecules. Class II molecules are expressed in antigen-presenting cells (APCs) (B lymphocytes, dendritic cells, and macrophages) and are used to present antigenic peptides to the cell surface, to be recognized by CD4⁺ T cells. Dimer formation with *HLA-DQB2* and *HLA-DQA2* plays an importance role in immunology.²⁸ Studies have found that *HLA-DQA2* is associated with some autoimmune diseases, such as systemic lupus erythematosus²⁹ and rheumatoid arthritis.³⁰

In addition, there is an enrichment of amino acid mutations and alleles in the *HLA-DRB* region. The most significant mutation is at *HLA-DRB1* amino acid position 9, which is located on the N-terminal signal peptide. *HLA-DRB1* can bind peptides that are derived from antigens, which access the endocytic route of APCs. The peptides are presented on the cell surface for recognition by CD4⁺ T cells. Studies have found that some CD4⁺ T cells are unique because they are strongly cytotoxic and have the ability to directly kill cells infected with virus. This HLA Class II molecule is known to be involved, which provides insights into how specific CD4⁺ T cells may participate in vascular immunopathology.³¹

In Japanese patients, a significant association of *HLA-DR1* with MMD is reported ($p < 0.05$).³² It is also reported that *HLA-DRB1*1501* and *HLA-DQB1*0502* are associated with MMD.^{22,33} In Korean patients, *HLA-DRB1*1302* and *HLA-DQB1*0609* showed an association in familial patients (Unpublished data).¹⁴ We also found some significant association

in both *HLA-DQB* and *HLA-DRB*, and we observed that amino acid mutations and allele frequencies were enriched in the *HLA-DRB1* gene region. These results suggest that although there are differences between *HLA* and MMD in Japanese, Korean, and Han patients, there are some similarities.

We also found another significant variant, rs1071817, when comparing patients with controls. This variant maps to the *HLA-B* gene and encodes amino acid 94 of HLA-B. We found 1 nonsense variant, with a gain of stop signal, and 2 missense variants at this site. Amino acid 94 of HLA-B is located in the alpha 1 chain of the MHC-I molecule and is located outside the cell membrane. This chain may be responsible for binding to peptides. In addition to amino acid 94 of HLA-B, we found other amino acid polymorphisms in HLA-B such as amino acid 24 of HLA-B, which is located in a β -strand structure (table e-3, links.lww.com/NXG/A424). Those variations may lead to changes in the function of the alpha 1 chain of the MHC-I molecule by affecting the normal synthesis. Associations of *HLA-B46* and *B54* ($p < 0.05$ or < 0.025) with the risk of MMD in Japanese patients with MMD were reported in the early 1980s.²⁰ A significant association with *HLA-B67* was found in an investigation of 32 unrelated Japanese patients with MMD.²¹ It revealed the association of *HLA-B35* with females in the late-onset group of individuals with MMD in the Korean population.³² In our study, we observed that amino acid mutations and allele frequencies were significantly enriched in the HLA-B gene region, and we also found some of the HLA alleles described above. However, only *HLA-B46* showed a significant difference between case and control ($p = 4.12 \times 10^{-11}$). Several studies showed that *HLA-B46* may also be associated with Graves disease.^{34,35}

By applying autoimmunity and inflammation classification gene chips, a study found differential expression in 32 genes in the peripheral blood of patients with MMD, compared with healthy controls. After searching the gene pool, 23 of the genes were related to cellular immunity and 9 were related to humoral immunity.³⁶ In our study, significant association was found between HLA Class I and II genes and the risk of MMD. Both these genes are important components of humoral immunity and cellular immunity, which suggests that both types of immunity are involved in MMD. Another epidemiologic study found that 8.5% of patients with MMD had type I diabetes, which is significantly higher than in the average US population (8.5% vs 0.4%, $p < 0.001$).^{37,38} The prevalence of autoimmune thyroid disease (Graves disease and thyroiditis) in the moyamoya cohort was 17%, which is also significantly higher than that of the general population in the United States (17% vs 8.0%, $p < 0.01$).³⁸ Previous reports suggest that viral and bacterial infection may be involved in the pathogenesis of MMD^{39,40} and the autoimmune antibody is recognized more frequently in patients with MMD.^{41,42} Through the imputation approach, our data also indicate that MMD may be an immune-related disease and comorbid with autoimmune diseases.

Although this study provides interesting insights about HLA variants of MMD, it still has some limitations. First, the imputation will be some deviations; to reduce deviations, we referenced the most comprehensive panel of Chinese population at present²⁶ and carried strict quality controls. Second, because of extensive linkage disequilibrium, high polymorphism, and strong genetic heterogeneity in the MHC region,^{43,44} the genetic variation that we could capture was limited, and we excluded the rare variations with an MAF of less than 1% in the MHC region. Therefore, we may show association only between part of the MHC region and MMD. Further functional studies are required to reveal the exact role of the identified variants.

We have shown by imputation that the genetic predisposition to MMD in Chinese Han is associated with HLA. The variants rs3129731 and rs1071817 were significantly associated with the disease in this population. Our findings suggest that the genetic polymorphisms of HLA-DQA2 and HLA-B could be genetic predisposing factors for MMD in Chinese Han. This may provide some evidence for further HLA-related studies of patients with MMD with Chinese Han ethnicity and further suggests that MMD is an immune-related disease.

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Disclosure

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Name	Location	Contribution
Jiang Wan, MD	Department of Neurology, the First Affiliated Hospital of Anhui Medical University, the School of Mental Health and Psychological Sciences, Anhui Medical University, Hefei, Anhui Province, China	Acquisition of data, drafting the article, reviewed the submitted version of the manuscript, approved the final version of the manuscript on behalf of all authors, statistical analysis, and critically revising the article

Appendix (continued)

Name	Location	Contribution
Wei Ling, PhD	Institute of Artificial Intelligence, Hefei Comprehensive National Science Center, China	Acquisition of data, drafting the article, reviewed the submitted version of the manuscript, approved the final version of the manuscript on behalf of all authors, statistical analysis, and critically revising the article
Zhang Zhengshan, MD	Department of Neurosurgery, the Fifth Medical Centre, Chinese PLA General Hospital (Former 307th Hospital of PLA), Beijing, China	Acquisition of data, drafting the article, reviewed the submitted version of the manuscript, approved the final version of the manuscript on behalf of all authors, statistical analysis, and critically revising the article
Zuo Xianbo, PhD	Department of Dermatology, the First Affiliated Hospital, Anhui Medical University, Hefei, Anhui Province, China	Conception and design, analysis and interpretation of data, study supervision, and critically revising the article
Duan Lian, PhD	Department of Neurosurgery, the Fifth Medical Centre, Chinese PLA General Hospital (Former 307th Hospital of PLA), Beijing, China	Conception and design, administrative/technical/material support, and critically revising the article
Wang Kai, PhD	School of Mental Health and Psychological Sciences, Anhui Medical University, Anhui Province, China	Conception and design, study supervision, and critically revising the article

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