

Association of *CDKN2A/CDKN2B* Gene Polymorphisms with Increased Susceptibility to Intracranial Aneurysm in a Chinese Han Population

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Objective: Several studies have reported that single-nucleotide polymorphisms (SNPs) of the *CDKN2A/CDKN2B* gene on chromosome 9p21.3 are associated with increased risk of intracranial aneurysm (IA). However, the association between IAs and SNPs of *CDKN2A/CDKN2B* in Chinese Han people is yet to be evaluated. This study examined the association of the SNPs rs10811661 and rs4977574 with IA in the Chinese Han population.

Methods: A total of 595 IA patients and 600 sex- and age-matched controls were enrolled in the study. Peripheral blood was collected and stored at -80°C until use. *CDKN2A/CDKN2B* was identified using polymerase chain reaction–ligase detection reaction. SNP genotyping was performed for rs10811661 and rs4977574 using a MassArray system. Associations between these two SNPs and IAs was tested with χ^2 or Fisher's exact tests and multivariate logistic regression.

Results: rs10811661 and rs4977574 were significantly associated with IA. The frequency of rs10811661-T in IA was higher than in controls (OR 1.26, 95% CI 1.07–1.49; $P < 0.01$). There was no significant difference in frequency of haplotype between control subjects and IA patients.

Conclusion: rs10811661 and rs4977574 on 9p21.3 were strongly associated with genetic susceptibility to IA in the Chinese Han population, which emphasizes a need for further investigation.

Keywords: intracranial aneurysm, *CDKN2A/CDKN2B* gene, Chinese Han population, SNP

Introduction

With prevalence of 1%–5% in adults, intracranial aneurysm (IA) is a complex disease with regional bulging of intracranial arteries and lesions that are usually located at the bifurcation sites.¹ It is generally reported that congenital defects and environmental risk factors can both affect the occurrence of IA. Environmental risk factors include sex, age, excessive smoking or drinking, hypertension, atherosclerosis, and diabetes.² Although a series of studies have been conducted on IA, very little information is available about its molecular pathogenesis. With regard to genetic factors, there are multiple genes associated with the etiology of IA.³

The 9p21.3 locus was first reported during a genome-wide association study of cardiovascular disease in 2007.⁴ That study demonstrated that the same variants of cardiovascular disease were associated with IA.⁵ The closest protein-coding genes are situated in a few kilobases proximal to the region of 9p21.3, which has no known protein-coding genes. These genes include *CDKN2A* and *CDKN2B*, and are

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located in a single cluster⁴ that is related to various human diseases, such as leukemia and cancer.^{6–9} One study demonstrated that the *CDKN2BAS* SNP (rs6475606) contributed to susceptibility to IA in a US population.¹⁰ Previous studies on the Chinese Han population discovered the association of rs10757278 and rs1333049 with myocardial infarction (MI), peripheral vascular disease, coronary atherosclerotic disease (CAD), and type 2 diabetes mellitus (T2DM).^{11–13} A similar study on a Japanese population revealed that rs10757272 is a new locus for susceptibility to IA while demonstrating the association between rs10757278 and IA.¹³ However, the relationship between SNPs and the pathophysiology of IA in the Han population requires further investigation.⁴

Despite these results, the mechanism of the association between 9p21 and IA remains largely unexplored. Understanding the pathophysiology of IA is the key to identify molecular markers to help identify high-risk individuals and design novel therapeutic strategies. Although the association of SNPs in 9p21 with IA has been established in the Caucasian population, these results must be corroborated in other populations. Therefore, genetic factors for IA should also be investigated in Chinese populations, owing to major differences in genetic background and environment from Caucasian cohorts.⁴ This study aimed to explore the relationship between SNPs (rs10811661 and rs4977574) and IA in the Han population.

Methods

Ethics Approval and Informed Consent

All procedures complied with the Declaration of Helsinki and were approved by the Institutional Review Board and Ethics Committee of Tianjin Medical University General Hospital and the collaborating hospitals' ethics committees. All participants reported themselves to be of Han ethnicity and provided written informed consent.

Study Site and Population

To ensure the study was representative, we selected hospitals located in developed areas of China, where the patients represented a vast number of Chinese provinces. IA was confirmed by computed tomography angiography (CTA) or digital subtraction angiography (DSA). All cases underwent either surgical clipping or endovascular coiling therapy in the perioperative period to reconfirm the diagnosis of IA. Control groups were sex- and age-matched

(within 5 years), diagnosed negative for IA by DSA or CTA from the same hospital of the when they were diagnosed with subarachnoid hemorrhage, had diseases that needed to be differentiated from IAs, or other diseases, including carotid stenosis, subclavian artery stenosis, cerebral infarction, and transient ischemic attack. IA and control subjects were also matched for area of residence to reduce the effect of population heterogeneity.

Exclusion Criteria

Participants were excluded if they had active inflammatory processes or autoimmune diseases, inflammatory IA with different pathophysiology from IA, had been diagnosed with mental disorders, were pregnant, or had a family history of aneurysm. Participants in the control group were screened by interview questions, with the key criterion that they not have any IA-related diseases.

Data-Collection Procedures

Each participant consented to undergo a standardized questionnaire with in-person interview to collect data involving past medical history, family history, history of chronic diseases, and lifestyle factors of smoking habits and alcohol consumption. A standard physical examination for participants included blood pressure, pupil reflex, magnetic resonance angiography, DSA, or CTA. Two radiologists performed imaging examinations on controls to exclude IA. Biochemical parameters were obtained from samples of peripheral venous blood and analyzed at the clinical laboratory of the hospital.

Data Population

We collected clinical information, including sex, age, smoking status, alcohol usage, blood pressure, and other chronic diseases. Smokers were defined as regular smokers if they smoked one or more cigarettes per day. Former and current smokers were both as defined as smokers. Drinkers were defined as regular drinkers if they drank 20 mL of alcohol per day. Hypertension (systolic pressure >140 mmHg, diastolic blood pressure >90 mmHg, or taking hypotensive drugs) was diagnosed by physical examination procedures. Chronic disease history was recorded by in-person interview.

DNA Extraction and Genotyping

Candidate SNPs were selected on the basis of studies of epidemiological risk factors for IA. Our primary analyses examined 30 SNPs associated with established IA risk

factors, including hypertension, atherosclerotic diseases, MI, hypercholesterolemia, T2DM, and autosomal-dominant polycystic kidney disease, and SNPs were correlated with IA, with $P < 5 \times 10^{-8}$ from a published genome-wide association study. Peripheral blood (2 mL) was collected in tubes and stored at -80°C until analyzed. DNA was extracted from blood by salt fractionation. PCR was performed on an ABI Veriti 384-cell PCR thermal cycler. Genotypes were analyzed with Typer 4.0 software (MassArray compact system, Sequenom). The genotyping-success rate of all SNPs was $>99\%$. Two SNPs on 9p21.3 were studied. The primers were designed by Primer 5, and sequences were:

rs10811661: ACGTTGGATGATAAGCGTTCTTGCC CTGTC (second PCR), ACGTTGGATGAGATCAGGA GGGTAATAGAC (first PCR).

rs4977574: ACGTTGGATGGTTTGCTTTCAGGGTA CATC (second PCR), ACGTTGGATGGTTGGTGTTC AACAGGAC (first PCR).

Statistical Analysis

Continuous variables were analyzed using nonparametric Mann–Whitney tests. Hardy–Weinberg equilibrium for each SNP was tested with Pearson's χ^2 tests. These tests were used to examine any differences in allelic and genotypic frequencies between patients and controls. The 95% CIs and ORs for the impact of heterozygous and homozygous genotypes on the risk of IA were analyzed with multivariate logistic regression analysis. Two-sided P -values were applied, with $P < 0.05$ considered statistically significant. All statistical analyses were performed by SPSS 17.0. Haplotypes and haplotype frequencies between patients and controls for the two SNPs in 9p21 were also compared. Linkage disequilibrium (LD) haplotypes of SNPs was examined by Haploview software. Adjusted ORs of haplotype were calculated by logistic regression analysis via Plink.

Results

Patient Characteristics

The study included a total of 1,195 subjects between July 2014 and December 2018 in China (Table 1). IA patients were diagnosed in the neurosurgery departments of the hospitals participating. Of the 595 IA patients enrolled, 251 were men (42.2%), 1.4 times the number of female patients. Sex distribution was consistent with previous studies. All participants were aged 18–80 years.

Table 1 Characteristics of Sporadic and Control Cases

Cases (n=595)	Controls (n=600)	P	
Age (years), mean (SD)	55.5 (13.20)	55.4 (15.32)	0.87
Male sex, n (%)	251 (42.2)	260 (43.3)	0.688
Smoking, n (%)	170 (28.6)	191 (31.8)	0.219
Drinking, n (%)	82 (13.8)	115 (19.2)	0.515
Hypertension, n (%)	206 (34.6)	184 (30.7)	0.145
Type 2 diabetes, n (%)	50 (8.4)	46 (7.7)	0.639
Dyslipidemia, n (%)	62 (10.4)	81 (13.5)	0.101
IAs, n (%)			
SIA	530 (89.1)	NA	NA
MIAs	65 (10.9)	NA	NA
IA location, n (%)			
MCA	109 (16.1)	NA	NA
ACA	27 (4.0)	NA	NA
ACoA	111 (16.4)	NA	NA
PCoA	214 (31.7)	NA	NA
ICA	130 (19.2)	NA	NA
VBA	55 (8.1)	NA	NA
IA condition, n (%)			
Ruptured	521 (87.6)	NA	NA
Unruptured	74 (12.4)	NA	NA

Abbreviations: SIA, single intracranial aneurysm; MIAs, multiple intracranial aneurysms; NA, not available; PCoA, posterior communicating artery; VBA, vertebralbasilar artery; ACoA, anterior communicating artery; MCA, middle cerebral artery; ACA, anterior CA; ICA, internal CA.

A total of 676 IAs were detected, including 530 single IAs and 65 multiple IAs. More details are shown in Table 1.

SNP Analysis

Minor-allele frequency for both SNPs was >0.05 , and we hypothesized that they were prime targets for the HapMap project. As shown in Table 2, neither IA patients nor control subjects showed significant deviation from the Hardy–Weinberg equilibrium for either SNP. Associations between the two SNPs and IAs and differences among the seven genotype sites and allele frequency were assessed with χ^2 or Fisher's exact tests (Table 3). There were significant differences for genotype frequency of rs10811661 between the IA cases and controls ($\chi^2 = 7.584$, $P = 0.005$). Genotype distribution of the two polymorphisms and ORs, 95% CIs, and P -values of the SNPs were estimated using logistic regression analysis between IA cases and controls (Table 4). Risk-allele frequencies of rs10811661 were significantly different

Table 2 Hardy–Weinberg Equilibrium SNP Analysis

	Test	A ₁	A ₂	Genotype ^d	O (Het)	E (Het)	P
rs4977574	All ^a	G	A	251/574/315	0.5035	0.4984	0.7664
rs4977574	Aff ^b	G	A	139/261/155	0.4703	0.4996	0.1741
rs4977574	Unaff ^c	G	A	112/313/160	0.535	0.4966	0.06738
rs10811661	All	C	T	262/557/300	0.4978	0.4994	0.9048
rs10811661	Aff	C	T	147/266/133	0.4872	0.4997	0.5499
rs10811661	Unaff	C	T	115/291/167	0.5079	0.4959	0.6133

Notes: ^aAll cases; ^bcases; ^ccontrols; A₁, mutant; A₂, wild-type; ^dA₁A₁/A₁A₂/A₂A₂.

Abbreviations: O (Het), observed heterozygosity; E (Het), expected heterozygosity; SNP, single nucleotide polymorphism; MAF, minor-allele frequency.

Table 3 χ^2 Results

SNP	A ₁	FA	FU	A ₂	χ^2	P	SE	OR (95% CI)
rs4977574	G	0.4856	0.459	A	1.619	0.2033	0.08396	1.11 (0.94–1.31)
rs10811661	C	0.5128	0.4546	T	7.584	0.005889	0.08476	1.26 (1.07–1.49)

Notes: SNP, single-nucleotide polymorphism; FA, frequency of allele in cases; FU, frequency of allele in controls; A₁, mutant; A₂, wild-type.

Table 4 Genotype Analysis

Intracranial aneurysms, n (%)	Controls, n (%)	OR (95% CI)	P	
rs10811661				
CC	147 (26.9)	115 (20.1)	1 (reference)	—
TC	266 (48.7)	291 (50.8)	1.27 (0.98–1.67)	0.0711
TT	133 (24.4)	167 (29.1)	1.47 (1.11–1.94)	0.0069
T	532 (48.7)	625 (54.5)	1.26 (1.07–1.49)	0.0061
rs4977574				
GG	139 (25.0)	112 (19.1)	1 (reference)	—
AG	261 (47.0)	313 (53.5)	0.97 (0.75–1.26)	0.8275
AA	155 (28.0)	160 (27.4)	1.41 (1.07–1.87)	0.0165
A	571 (51.4)	633 (54.1)	1.11 (0.94–1.32)	0.2012

between IA patients and controls (OR 1.26, 95% CI 1.07–1.49).

Haplotype Analysis

SNPs rs3217992 and rs1063192 were in obvious LD ($D'=98$, $r^2=22$) within block 1 and rs2285489 and rs2301612 were in LD ($D'=97$, $r^2=73$) within block 2 (Figure 1). No significant differences were observed in haplotype frequency between IA patients and control. Frequencies, ORs, and *P*-values for haplotypes are in Table 5.

Discussion

In this study, the *CDKN2A/CDKN2B* genetic relationship with IAs of a Chinese Han population was investigated. We observed that the SNPs rs10811661 and rs4977574

were related to IAs and the most frequently mutated sites of the *CDKN2A/CDKN2B* gene locus. Genotype and allele frequencies were statistically significant. The T allele of rs10811661 is a risk factor of IA in the Han population.

Genome-wide association studies on Japanese IA patients, including 419 sporadic IA cases and 408 controls confirmed a positive site of rs1333040.¹⁴ Bilguvar et al¹⁵ illustrated that rs1333040 (9p21), rs10958409 (8q11), and rs700651 (2q33) were associated with IA. However, we observed the variants rs10811661 and rs4977574 were associated only with sporadic IAs. It has been hypothesized that genetic heterogeneity among diverse ethnic populations can lead to such paradoxical results and may be relevant to variations among different populations with a positive family history.¹⁴ Genetic transmission suggests that a haplotype is shared by the four SNPs, namely rs3217992, rs1063192, rs2285489, and rs2301612. However, rs10811661 and rs4977574 did not demonstrate either an association or LD with them. An independent publication revealed the possibility of a small LD block between introns 7 and 15 of *CDKN2BAS*.¹⁶ The 9p21 locus of *CDKN2A/CDKN2B* has not only been associated with T2DM but also with atherosclerosis, and its SNPs play a crucial role in the formation of IAs.

In this study, two genetic variants, rs10811661 and rs4977574 in 9p21, were identified as independent risk elements for the onset of IAs in Chinese population. The results emphasize the need to investigate genetic associations in diverse ethnic populations and evaluate

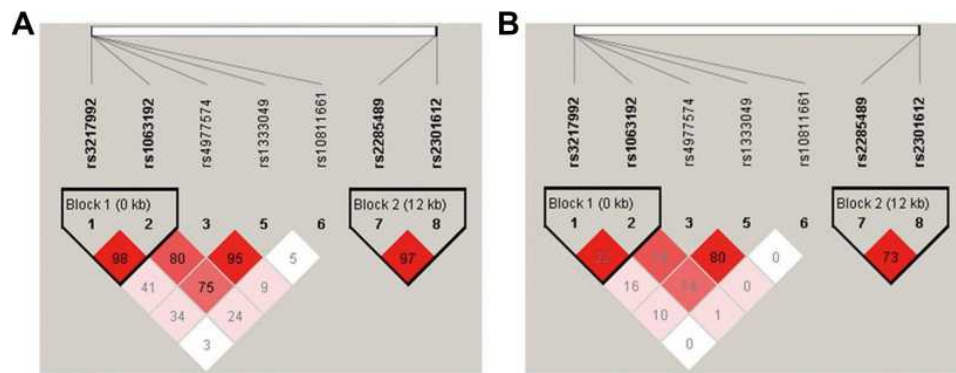


Figure 1 LD heat map (Haploview).

Notes: White to red represents the degree of linkage from low to high, and deep red indicates full chain ($r^2=100$). (A) D values; (B) R^2 values.

the disease-related genes due to genetic heterogeneity. It is difficult to discover the exact loci associated with IA because of the long sequences of the *CDKN2A* and *CDKN2B* genes. The interaction of genes and racial differences both equally affect the formation process of IA, which is a complex genetic disease.¹⁷ Although lncRNAs, *CDKN2A* or *CDKN2B* plays a critical role in regulating the expression of gene loci in their vicinity in disease conditions.¹⁴ Bai et al reported that there are major differences in several lncRNA genes between aneurysm and normal cerebrovascular tissue, and showed that *CDKN2A* and *CDKN2B* affect atherosclerosis progress by regulating the expression of *CARD8*.^{18–20} Although the SNPs associated with IA in overseas groups (rs10811661 and rs4977574) had the highest mutation rates and associations of rs10811661-T with IA in two independent populations are firmly suggestive of a substantial association with IAs in our study population, there is a hypothesis that different populations are more susceptible to IA due to *CDKN2A/CDKN2B*.

The underlying mechanism of *CDKN2A/CDKN2B* variants affecting IA risk remains to be elucidated.

Table 5 Haplotype Analysis

Frequency	Case: Control Ratios	Case, Control Frequency	χ^2	
Block 1				
TA	0.48	536.5:569.5, 560.4:619.6	0.485, 0.475	0.237
CA	0.32	363.0:743.0, 369.5:810.5	0.328, 0.313	0.591
CG	0.198	205.0:901.0, 248.5:931.5	0.185, 0.211	2.278
Block 2				
CC	0.841	940.1:171.9, 985.8:192.2	0.845, 0.837	0.313
TG	0.122	132.4:979.6, 147.9:1,030.1	0.119, 0.126	0.223
CG	0.034	38.3:1,073.7, 40.2:1,137.8	0.034, 0.034	0.002

Functional studies have demonstrated 9p21 leads to CAD via atherosclerosis induced by variants located near *CDKN2A* and *CDKN2B*, which are involved in regulating vascular smooth-muscle cell (VSMC) proliferation, aging, senescence, and apoptosis, or by modulating the inflammatory pathway involved in the atherosclerosis process. Some studies have identified the *ANRIL* gene, which encodes a ncRNA, as a genetic susceptibility locus associated with IA. Also, a mouse model confirmed a key role of *ANRIL* in regulation of *CDKN2A/CDKN2B* expression via a *cis*-acting mechanism and its effect on proliferation and senescence.¹³ ET₁ and its receptors, ET_A and ET_B, have been known to play an important role in the physiopathology of IA. ET_A is located predominantly on VSMCs of the cerebrovascular system and mediates vasoconstriction and proliferation. A study performed functional analysis with *CDKN2BAS* genetic variants on ET_A. The variant affected the expression of ET_A and subsequently contributed to IA susceptibility.¹³ A series of studies on Chinese populations have suggested the association of haplotypes at 9p21 with metabolic syndrome, CAD, peripheral artery disease, and T2DM.^{12,21} In this study, four SNPs — rs3217992 and rs1063192, rs2285489, and rs2301612 — also demonstrated strong LD in the Chinese Han population. These results indicate that the risk loci belonging to 9p21 region may confer susceptibility to IA.

Several limitations should be noted. This was not a cohort study and may not be adequate for assessing the effect of these SNPs on the formation of IAs. Molecular biology experiments and a reliable animal model are required to give a more accurate assessment of the relationship between these SNPs and the progression of IAs and enable a better understanding of the biological mechanism of IA formation.

Conclusion

This study implicates rs10811661 and rs4977574 as independent genetic risk factors of the formation of IA in the Chinese Han population and emphasizes the critical role of 9p21 in the disease.

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Disclosure

The authors report no conflicts of interest in this work.

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