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Association Between *NFKB1* −94 Insertion/Deletion ATTG Polymorphism and Risk of Intracranial Aneurysm

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Objective: Growing evidence indicates that vascular inflammation is a common phenomenon in the pathogenesis of intracranial aneurysms (IAs). Nuclear factor kappa B is a key molecule that is involved in the vascular inflammation of IA. We hypothesized that an insertion/deletion (ins/del) ATTG polymorphism located between two putative key promoter regulatory elements in the *NFKB1* gene may be related to the risk of IA. *Methods:* We performed a case–control study, including 164 patients with IA and 525 healthy controls in a Chinese population using a polymerase chain reaction–polyacrylamide gel electrophoresis assay. *Results:* A significantly decreased risk of IA was observed in the ATTG1/ATTG2 and ATTG2/ATTG2 genotypes compared with the ATTG1/ATTG1 genotype (ATTG1/ATTG2 vs. ATTG1/ATTG1: odds ratio [OR] = 0.58, 95% confidence interval [95% CI] = 0.39–0.87, $p = 0.007$; ATTG2/ATTG2 vs. ATTG1/ATTG1: OR = 0.12, 95% CI = 0.06–0.23, $p < 0.001$), and also the ATTG2 allele (ATTG2 vs. ATTG1: OR = 0.41, 95% CI = 0.32–0.54, $p < 0.001$). *Conclusion:* These findings suggest that the *NFKB1* −94ins/del ATTG polymorphism may contribute to the risk of IA.

Introduction

Intracranial aneurysms (IAs) are common brain vascular abnormalities with a prevalence rate of 3.2% in the general population (Juvela, 2011) and a 1% annual risk of rupture (Investigators ISoUIA, 1998; Wermer *et al.*, 2007). Despite recent diagnostic and therapeutic advances, occurrence of the lethal subarachnoid hemorrhage occurs in up to 65% of cases (Wiebers *et al.*, 2003) and the disability rate is up to 50% (Nieuwkamp *et al.*, 2009). Approximately 25% of IAs die of the ruptured aneurysms (Fogelholm *et al.*, 1993).

It is widely accepted that genetic factors play a key role in the pathogenesis of IA, in addition to environmental ones (Krex *et al.*, 2001; Clarke, 2008). Vascular inflammation is common in the pathogenesis of IA. A significant hallmark of IA is the infiltration of inflammatory cells, especially macrophages (Chyatte *et al.*, 1999; Kataoka *et al.*, 1999; Frosen *et al.*, 2004). Histopathologic evidence from both human aneurysm tissue (Chyatte *et al.*, 1999; Frosen *et al.*, 2004; Frosen *et al.*, 2006) and animal models of IA (Aoki *et al.*, 2007a; Kanematsu *et al.*, 2011) has confirmed that inflammation is involved in the formation and progression of IA.

In human, the *NFKB1* gene encodes two proteins (i.e., p105 and p50). p105 is a non-DNA binding, cytoplasmic molecule and p50 is a DNA-binding protein that corresponds to the N-terminus of p105 and locates at the long arm of chromosome 4 (4q24) (Le Beau *et al.*, 1992). Many genes regulated by the nuclear factor kappa B (NF-κB) signaling pathway play important roles in the immune system (Tak and Firestein, 2001; Kumar *et al.*, 2004). Aoki *et al.* (2007b) reported that NF-κB was overexpressed in the walls of IA in rats and inhibition of NF-κB can block the formation of aneurysms. Furthermore, NF-κB was reported to be involved in the progression of inflammation in IA in different ways. For example, Mohan *et al.* (1997) reported that the shear stress exerted on vessel walls activated NF-κB, and the activation of NF-κB amplifies chronic inflammation. Meanwhile, NF-κB modulates several proinflammatory genes, including matrix metalloproteinases (MMPs), monocyte chemoattractant protein-1 (MCP1), and cytokines, which are directly involved in aneurysm formation (Aoki and Nishimura, 2011). So, the inappropriate expression or activity of NF-κB itself or the effect on the downstream genes may affect the susceptibility to IA. Previously, a polymorphism of −94 insertion/deletion (ins/del) ATTG in the *NFKB1* promoter region has been reported to influence the transcription of the *NFKB1* gene (Karban *et al.*, 2004). Subsequently, the association between the polymorphism and autoimmune and inflammatory diseases has been investigated extensively (Karban *et al.*, 2004; Butt *et al.*, 2005; Kim *et al.*, 2005; Mirza *et al.*, 2005; Orozco *et al.*, 2005; Glas *et al.*, 2006; Kurylowicz *et al.*, 2007; Yalcin *et al.*, 2008). However, its association with IA is still unclear. The aim of this study was to determine the possible susceptibility of the *NFKB1* −94ins/del ATTG polymorphism on the occurrence of IA.

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Table 1. Demographics of the Patients with Intracranial Aneurysm and Controls

Variables	*Controls* n = *525 (%)*	*Patients with IA* n = *164 (%)*
Age (years)	50.0 ± 8.9	53.1 ± 13.1
Sex		
Male	220 (41.9)	60 (36.6)
Female	305 (58.1)	104 (63.4)
Number of aneurysms		
1		142 (86.6)
>1		22 (13.4)
Site of aneurysms		
ICAS		152 (92.7)
Vertebrobasilar artery		12 (7.3)
Rupture or not		
Rupture		140 (85.4)
Unrupture		24 (14.6)

IA, intracranial aneurysm; ICAS, internal carotid arterial system.

Materials and Methods

Study subjects

The case–control study was approved by the institutional review board of the West China Hospital. Clinical and biological characteristics of cases and controls are shown in Table 1. Between January 2008 and September 2009, 164 newly diagnosed patients with IA without restriction regarding age and sex and 525 healthy controls were included in the study. All patients were newly diagnosed incident cases when they came to the hospital because of the rupture of IA or digital subtraction angiography confirmed general clinical symptoms such as headache or dizziness. General characters and clinicopathological parameters were obtained when possible from hospital clinical records. The mean age of the cases (60 males and 104 females) was 53.1 ± 13.1 years. The control subjects were genetically unrelated to the cases without an individual history of diseases in the central nervous system, and frequency matched to patients based on gender, age, and ethnic background. Screening for the controls was done to ensure that there was no history or symptoms of IA. The controls were also checked for IA history based on their past medical records and/or asked directly for their previous history. The mean age of the controls (220 males and 305 females) was 50.0 ± 8.9 years. Written informed consent had been obtained from each subject.

Genotyping

About 2 mL blood samples were collected in EDTA containing tubes from each subject and stored at −20°C until use. Genomic DNA was extracted from the stored blood using a DNA Extraction Kit. The polymorphism was genotyped by polymerase chain reaction–polyacrylamide gel electrophoresis. The primer sequences and reaction conditions were reported previously for the amplification of the target region of the *NFKB1* polymorphism (Zhou *et al.*, 2009). Genotype analysis was performed by two persons independently. About 10% of the samples were randomly selected for repeated genotyping for confirmation, and the results were 100% concordant. Great care was taken to minimize sources of bias and avoid the overestimation of results.

Statistical analyses

The characteristics of the study were compared using the chi-square test or the Student's *t*-test. The associations between *NFKB1* genotypes or alleles and risk of IA were estimated by using the chi-square test. Tests for the Hardy–Weinberg equilibrium were performed for the SNP in the control subjects. The odds ratios (ORs) and the 95% confidence interval (95% CI) were used to describe the strength of the association. A *p*-value of less than 0.05 was considered as statistically significant. The Fisher's exact *p*-value was used when appropriate. All the statistical analyses were performed with the software SPSS version 19.0 (SPSS, Inc., Chicago, IL).

Results

The distributions of genotype and allele frequencies are presented in Table 2. No deviation from the Hardy–Weinberg equilibrium was detected in controls on the basis of allele prevalence. A significantly decreased risk of IA was found in both ATTG1/ATTG2 and ATTG2/ATTG2 genotypes compared with the ATTG1/ATTG1 genotype (ATTG1/ATTG2 vs. ATTG1/ATTG1: OR = 0.58, 95% CI = 0.39–0.87, $p = 0.007$; ATTG2/ATTG2 vs. ATTG1/ATTG1: OR = 0.12, 95% CI = 0.06–0.23, $p < 0.001$; ATTG2 vs. ATTG1: OR = 0.41, 95% CI = 0.32–0.54, $p < 0.001$), suggesting that the ATTG2 allele may be a protective factor for the development of IA. The effect of the *NFKB1* −94ins/del ATTG polymorphism was further evaluated based on the clinical characteristics of patients with IA. However, we did not find any association between clinical characteristics of IA patients and prevalence of alleles or genotypes for the *NFKB1* −94ins/del ATTG polymorphism (Table 3).

Table 2. Genotype and Allele Frequencies of the *NFKB1* −94 Insertion/Deletion ATTG Polymorphism Between Patients with Intracranial Aneurysm and Controls

NFKB1 −*94 Polymorphism*	*Controls* (n = *525)*	*Patients* (n = *164)*	*OR (95% CI)*	p-*Value*
Genotypes				
ATTG1/ATTG1	107 (20.4)	64 (39.0)		1 (Ref.)
ATTG1/ATTG2	252 (48.0)	88 (53.7)	0.58 (0.39–0.87)	0.007
ATTG2/ATTG2	166 (31.6)	12 (7.3)	0.12 (0.06–0.23)	<0.001
Alleles				
ATTG1	466 (44.4)	216 (65.9)		1 (Ref.)
ATTG2	584 (55.6)	112 (34.1)	0.41 (0.32–0.54)	<0.001

OR, odds ratio; CI, confidence interval.

Table 3. Association Between the *NFKB1* −94 Insertion/Deletion ATTG Polymorphism and Patients' Characteristics

Characteristics	Genotypes					Alleles			
	ATTG1/ ATTG1	*ATTG1/ ATTG2*	*ATTG2/ ATTG2*	*OR (95% CI)*	p	*ATTG1*	*ATTG2*	*OR (95% CI)*	p
Median age									
≤54	36 (42.9)	43 (51.2)	5 (5.9)	1.35 (0.71–2.57)	0.37	115 (68.5)	53 (31.5)		
>54	28 (35.0)	45 (56.3)	7 (8.7)	1.80 (0.52–6.28)	0.35	101 (63.1)	59 (36.9)	1.27 (0.80–2.00)	0.31
Number of aneurysms									
1	53 (37.3)	79 (55.6)	10 (7.1)	0.55 (0.21–1.42)	0.21	185 (65.1)	99 (34.9)		
>1	11 (50.0)	9 (40.9)	2 (9.1)	0.97 (0.19–5.02)	1.00	31 (70.5)	13 (29.5)	0.78 (0.39–1.57)	0.49
Site of aneurysms									
ICAS	58 (38.2)	83 (54.6)	11 (7.2)	0.58 (0.17–2.00)	0.53	199 (65.5)	105 (34.5)		
Vertebrobasilar artery	6 (50.0)	5 (41.7)	1 (8.3)	0.88 (0.10–8.03)	1.00	17 (70.8)	7 (29.2)	0.78 (0.31–1.94)	0.59
Rupture or not									
Unrupture	6 (25.0)	16 (66.7)	2 (8.3)	0.47 (0.17–1.27)	0.13	28 (58.3)	20 (41.7)		
Rupture	58 (41.4)	72 (51.4)	10 (7.1)	0.52 (0.09–2.93)	0.61	188 (67.1)	92 (32.9)	0.69 (0.37–1.28)	0.23

Fisher's exact *p*-value was used when appropriate.

Discussion

To the best of our knowledge, this is the first study to investigate whether the *NFKB1* −94del/ins ATTG polymorphism was associated with the risk of IA. In the study, we found that the *NFKB1* −94del/ins ATTG polymorphism was associated with a decreased risk of IA. This finding indicates that the ATTG2 allele may be a protective factor against the development of IA.

Virchow first reported inflammation occurring in IAs in 1847 (Virchow, 1847). Further evidence confirmed that inflammatory cells infiltrated in IA, especially in the neck of IA (Hassler, 1961). Proinflammatory factors, including MMPs (Jin *et al.*, 2007), tumor necrosis factor-alpha (Jayaraman *et al.*, 2005), and MCP-1 (Cao *et al.*, 2002), were reported highly expressed in human IA walls, suggesting that the inflammation may be involved in IA formation.

Recently, chronic inflammation that was mediated by NF-κB activation has been reported to increase the risk of IA formation (Aoki *et al.*, 2007b; Aoki and Nishimura, 2010). The mechanical force of shear stress exerted on the vessel, a cause for IA formation (Hashimoto *et al.*, 1980; Takeuchi and Karino, 2010), activated prostaglandin E_2-prostaglandin E receptor$_2$ signaling and evoked chronic inflammation through the activation of NF-κB both in rodent models of IA (Aoki *et al.*, 2011) and human patients (Chyatte *et al.*, 1999; Takagi *et al.*, 2002; Jayaraman *et al.*, 2005). Activated NF-κB also functions through regulating various proinflammatory genes in IA walls, including MMPs, inducible nitric oxide synthase, interleukin-1β, and MCP-1, which have been reported to be involved in the pathogenesis of IA (Fukuda *et al.*, 2000; Sadamasa *et al.*, 2003; Moriwaki *et al.*, 2006; Aoki *et al.*, 2007b, Aoki *et al.*, 2009; Nuki *et al.*, 2009).

Karban *et al.* (2004) reported the association between the *NFKB1* −94ins/del ATTG polymorphism and susceptibility to ulcerative colitis for the first time. It was reported that the ATTG1 allele may result in decreased NF-κB promoter activity and p50/p105 NF-κB protein production *in vitro* study (Karban *et al.*, 2004). The ATTG1 allele of the polymorphism leads to less activation of NF-κB transcription, which seems inconsistent to the overexpression of NF-κB in IA (Aoki *et al.*, 2007b). Even though the exact mechanism is still unknown, the possibilities should be considered to explain the roles of the *NFKB1* −94ins/del ATTG polymorphism in the development of IA. The ATTG1 allele means less activity of NF-κB transcription, then fewer available p50 and inhibitory p50/p50 homodimers, and eventually more transcription of inflammatory genes and stronger NF-κB-induced immune responses. Less p50 means less of its precursor p105, and the p105 has a homology domain to the inhibitor of κB (IκB) family members in the C-terminal and can play the same role as an IκB *in vivo* (Verma *et al.*, 1995). Moreover, the expression of a cytokine that inhibits inflammation could be promoted by p50, while the expression of inflammatory genes can be directly inhibited by the p50 homodimer (Erdman *et al.*, 2001). Obviously, changes that have effect on the level of NF-κB or downstream genes in NF-κB signaling may make a difference in the immune response. The positive result in this study, therefore, seems to be biologically plausible.

Although the association between the *NFKB1* −94ins/del ATTG polymorphism and risk of IA was detected in our study, there were limitations. One is that the detailed lifestyle and follow-up information is blank, which limited our further analysis. Another is that the study subjects were of a single ethnicity and small in number. Further studies in different ethnicities and of a larger scale are needed to verify our results.

In conclusion, we found that the −94 ATTG2 allele frequency was significantly lower in IA patients compared to healthy controls, suggesting that the *NFKB1* −94ATTG2 allele has a protective effect on the risk of IA. However, additional studies with more detailed data on environmental exposure and survival data are required to verify these findings.

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Author Disclosure Statement

No competing financial interests exist.

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