



## Plasma resistin, associated with single nucleotide polymorphism -420, is correlated with C-reactive protein in Chinese Han patients with spontaneous basal ganglia hemorrhage

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**ABSTRACT.** We examined a possible relationship -420C>G SNP of the resistin gene with plasma resistin and C-reactive protein concentrations in intracerebral hemorrhage. Three hundred and forty-four Chinese Han patients with intracerebral hemorrhage and 344 age- and gender-matched healthy controls were included in our study. Plasma resistin and C-reactive concentrations were measured and SNP -420C>G was genotyped. The genotype frequencies in controls and patients were not significantly different ( $P = 0.672$ ). Plasma resistin and C-reactive protein levels were significantly different between the SNP -420C>G genotypes, even after adjustment for age, gender and body mass index. The common homozygote (C-C) had the lowest resistin and C-reactive protein plasma concentrations; the plasma resistin and C-reactive protein concentrations in the

heterozygote (C-G) and the rare allele homozygote (G-G) did not differ significantly. Plasma resistin levels were significantly associated with plasma C-reactive protein level. We conclude that SNP -420C>G of the resistin gene could be involved in the inflammatory component of intracerebral hemorrhage through enhanced production of resistin.

**Key words:** Resistin; Polymorphism; C-reactive protein; Intracerebral hemorrhage; Inflammatory reaction

## INTRODUCTION

Resistin belongs to a novel family of cysteine-rich proteins called resistin-like molecules or FIZZ (found in inflammatory zones) proteins (Steppan et al., 2001b). This 12.5-kDa protein was originally suggested to be a link between obesity and diabetes (Steppan et al., 2001a). It has recently been recognized as one of the inflammatory cytokines (Bokarewa et al., 2005) and associated with C-reactive protein (Piestrzeniewicz et al., 2009). Furthermore, it is evidenced that resistin could be produced by the brain and pituitary gland (Wilkinson et al., 2007). Moreover, resistin mRNA has been shown to be increased in the cortex of hypoxic/ischemic (Wiesner et al., 2006) and traumatic animal brain (Brown et al., 2008). In ischemic stroke, high plasma resistin level has been associated with mortality and disability (Efstathiou et al., 2007). We have recently found that this protein is also increased in the peripheral blood of patients with spontaneous intracerebral hemorrhage (Dong et al., 2010a) and traumatic brain injury (Dong et al., 2010b). In these patients, high plasma resistin level has been associated with mortality.

RETN, a gene coding for resistin, is located at chromosome location 19p13.3 (Steppan et al., 2001b). Several single-nucleotide polymorphisms (SNPs) have been found in the RETN promoter, intron and 3'-UTR (untranslated region) regions (Hivert et al., 2009). The variation in RETN most often reported in the literature is the promoter SNP -420C>G (rs1862513). It has also become evident that this SNP is associated with resistin (Cho et al., 2004; Osawa et al., 2007; Ukkola et al., 2008; Hivert et al., 2009). The SNP -420C>G effect on resistin expression may be due to its effect on transcription factor binding to the RETN promoter (Osawa et al., 2004). However, the effect of SNP -420C>G on plasma resistin concentration is still unclear in intracerebral hemorrhage. Therefore, the purpose of this study was designed to investigate whether resistin polymorphism -420C>G could be associated with the plasma resistin level and whether plasma resistin level could be correlated with plasma C-reactive protein level in Chinese Han patients with intracerebral hemorrhage.

## MATERIAL AND METHODS

### Study population

Our target group consisted of consecutive patients with spontaneous basal ganglia hemorrhage evaluated in the emergency rooms of the First Hangzhou Municipal People's

Hospital, Shengzhou People's Hospital and the Second People's Hospital of Cixi City within the first 6 h from stroke onset. Between January 2007 and December 2009, a total of 378 Chinese Han patients with spontaneous basal ganglia hemorrhage were initially evaluated. Exclusion criteria were existing previous neurological disease, head trauma, use of antiplatelet or anticoagulant medication, presence of other prior systemic diseases including uremia, liver cirrhosis, malignancy, and chronic heart or lung disease, with the exception of diabetes mellitus, hypercholesterolemia, obesity, and hypertension. Diabetes mellitus was defined as treatment with oral hypoglycemic drugs or insulin or previous diagnosis. Hypercholesterolemia was defined as treatment with cholesterol-lowering drugs or previous fasting total cholesterol >200 mg/dL. Obesity was defined as body mass index >25.0 kg/m<sup>2</sup>. Hypertension was defined as antihypertensive drug therapy or previous documented blood pressure >140/90 mmHg (systolic/diastolic). The patients who did not have blood samples available were also excluded. Finally, 344 patients were included.

A control group consisted of 344 age- and gender-matched healthy subjects with normal results on brain magnetic resonance imaging and without vascular risk factors.

Informed consent to participate in the study was obtained from them or their relatives. This protocol was approved by the Ethics Committee before implementation.

### **Clinical protocol**

Intracerebral hemorrhage was documented by computed tomographic scan. Initial disease severity was assessed by the Glasgow Coma Scale score. Hematoma volume was calculated according to the formula  $A \times B \times C \times 0.5$ , where A and B represent the largest perpendicular diameters through the hyperdense area on computed tomographic scan, and C represents the thickness of hematoma (the number of 10-mm slices containing hemorrhage) (Kothari et al., 1996).

### **Determination of plasma resistin and C-reactive protein**

Informed consent was obtained from the study population or family members in all cases before blood was collected. Venous blood was drawn on admission. The blood samples were immediately placed in sterile EDTA test tubes and centrifuged at 1500 g for 20 min at 4°C to collect plasma. Plasma was stored at -70°C until assayed. The concentration of resistin and C-reactive protein in plasma was analyzed by enzyme-linked immunosorbent assay using commercial kits (R&D Systems, Minneapolis, MN, USA) in accordance with manufacturer instructions.

### **Genotyping of polymorphism**

Genomic DNA was isolated from peripheral leukocytes using a DNA extraction kit (Stratagene). PCR-restriction fragment length polymorphism was performed to determine the RETN -420C>G polymorphism. The DNA fragment containing the polymorphic site in the 5'-flanking region of the RETN gene was amplified by PCR in a T1 Thermocycler (Biometra, Goettingen, Germany) using the following primers: forward primer, 5'-TGT CAT TCT CAC CCA GAG ACA-3' and reverse primer, 5'-TGG GCT CAG CTA ACC AAA TC-3'. PCR was

performed in a total volume of 20  $\mu\text{L}$  containing 2  $\mu\text{L}$  10X PCR buffer, 2 mM  $\text{MgCl}_2$ , 0.1 mM dNTPs, 0.25  $\mu\text{M}$  of each primer, 200 ng genomic DNA and 1 U Taq DNA polymerase (MBI Fermentas, Vilnius, Lithuania). The amplification cycle was carried out as follows: denaturation at 95°C for 7 min, pre-annealing at 64°C for 1 min, and then elongation at 72°C for 2 min, followed by 35 cycles of 30 s at 95°C, 30 s at 64°C and 1 min 15 s at 72°C, and finally an elongation at 72°C for 10 min. An aliquot of 3  $\mu\text{L}$  PCR products was digested with 5 U *Bbs*I (GAAGAC) restriction endonuclease (New England BioLabs, Waltham, MA, USA) in 1.5  $\mu\text{L}$  10X NEB buffer 2 (50 mM NaCl, 10 mM Tris-HCL, 10 mM  $\text{MgCl}_2$  and 1 mM dithiothreitol) and 9.5  $\mu\text{L}$   $\text{dH}_2\text{O}$  at 37°C for 12 h. The 534-bp PCR products were cleaved into two fragments of 317- and 207-bp in the presence of the C homozygous and three fragments of 543, 327 and 207 bp for heterozygote (CG), while the G homozygous remained uncleaved showing the 543-bp PCR product. The digestion products were separated on 1.5% agarose gel electrophoresis stained with 0.5  $\mu\text{g}/\text{mL}$  ethidium bromide and visualized under ultraviolet light. In addition, 10% of the samples were randomly selected to perform repeated assays, and the results were 100% concordant.

### Statistical analysis

Statistical analysis was performed with SPSS 10.0 (SPSS Inc., Chicago, IL, USA). The normality of data distribution was assessed by the Kolmogorov-Smirnov test or Shapiro-Wilk test. All values are reported as median (lower quartile, upper quartile), means  $\pm$  standard deviation or counts (percentage). Comparisons were made by using 1) the chi-square test for categorical data, 2) analysis of variance (ANOVA) for continuous normally distributed variables, and 3) the Kruskal-Wallis H-test for continuous non-normally distributed variables. Hardy-Weinberg equilibrium (HWE) for genotype frequencies was estimated by the chi-square test. The least significant difference method was used for the *post hoc* test. The difference in the plasma resistin levels between the genotypes was tested by analysis of covariance with adjustment for confounding variables that included age, gender and body mass index. Correlations of plasma C-reactive protein level with other variables were analyzed by the Spearman test, the Pearson test and multivariate linear regression. For multivariate analysis, we included the significantly different variables as assessed in univariate analysis. A P value of less than 0.05 was considered to be statistically significant.

## RESULTS

### Patient characteristics

A total of 344 patients were enrolled, including 238 men and 106 women. The median age was 62 years (range, 42-80 years). The distribution of disease was as follows: 322 patients (93.6%) suffered from hypertension; 88 patients (25.6%), diabetes mellitus, and 150 patients (43.6%), hypercholesterolemia. The mean body mass index was 24.8 (range, 20.4-30.8). The median Glasgow Coma Scale score was 9 (range, 5-15); the median hematoma volume, 40 mL (range, 5-80 mL). The other laboratory data are provided in Table 1.

**Table 1.** Clinical characteristics of SNP -420C>G genotypes.

	All patients (N = 344)	CC (N = 173)	CG (N = 143)	GG (N = 28)	P value
Gender (male/female)	238/106	113/60	105/38	20/8	0.288
Age (years)	62 (57, 67)	60 (56, 71)	64 (61, 66)	63 (52, 73)	0.246
Hypertension	322 (93.6%)	159 (91.9%)	138 (96.5%)	25 (89.3%)	0.156
Diabetes mellitus	88 (25.6%)	47 (27.2%)	32 (22.4%)	9 (32.1%)	0.442
Hypercholesterolemia	150 (43.6%)	85 (49.1%)	53 (37.1%)	12 (42.9%)	0.098
Body mass index	24.8 ± 2.2	24.7 ± 2.1	24.8 ± 2.2	25.2 ± 2.4	0.568
Glasgow Coma Scale score	9 (7, 12)	10 (8, 12)	9 (7, 12)	9 (6, 12)	0.395
Hematoma volume (mL)	40 (23, 58)	40 (26, 55)	40 (23, 60)	50 (30, 67)	0.275
Systolic arterial pressure (mmHg)	183 (158, 205)	184 (160, 206)	173 (156, 206)	185 (168, 201)	0.679
Diastolic arterial pressure (mmHg)	101 (94, 109)	101 (91, 108)	102 (94, 111)	100 (97, 106)	0.101
Mean arterial pressure (mmHg)	128 (115, 140)	130 (112, 139)	126 (114, 142)	128 (120, 136)	0.732
White blood cell count (x10 <sup>9</sup> /L)	8.4 (5.8, 11.3)	7.9 (5.8, 11.0)	8.7 (6.0, 11.3)	8.5 (5.5, 11.6)	0.380
Blood glucose level (mM)	9.2 (7.8, 10.6)	9.3 (8.0, 10.3)	8.7 (7.3, 12.5)	8.6 (7.8, 10.5)	0.764
Triglycerides (mg/dL)	129 (104, 143)	128 (104, 144)	129 (104, 141)	134 (89, 147)	0.811
Total cholesterol (mg/dL)	181 (159, 234)	192 (164, 234)	172 (153, 236)	171 (151, 228)	0.084
High-density lipoprotein cholesterol (mg/dL)	47 (35, 62)	45 (37, 59)	50 (35, 64)	44 (31, 59)	0.195
Low-density lipoprotein cholesterol (mg/dL)	108 (85, 154)	112 (90, 158)	102 (82, 150)	112 (85, 155)	0.102
Creatine kinase (U/L)	96 (78, 142)	97 (78, 127)	94 (79, 143)	166 (72, 158)	0.712
Plasma resistin level (ng/mL)	25.2 ± 7.6	23.8 ± 7.1	26.5 ± 7.3	27.2 ± 10.0	0.002
Plasma C-reactive protein level (mg/L)	8.0 ± 2.5	7.5 ± 2.3	8.4 ± 2.6	8.7 ± 3.1	0.001
Plasma fibrinogen level (g/L)	4.9 ± 1.3	4.8 ± 1.3	5.0 ± 1.3	4.9 ± 1.5	0.411
Plasma D-dimer level (mg/L)	1.95 (1.30, 2.47)	1.90 (1.31, 2.39)	2.04 (1.33, 2.44)	2.27 (1.25, 3.32)	0.135

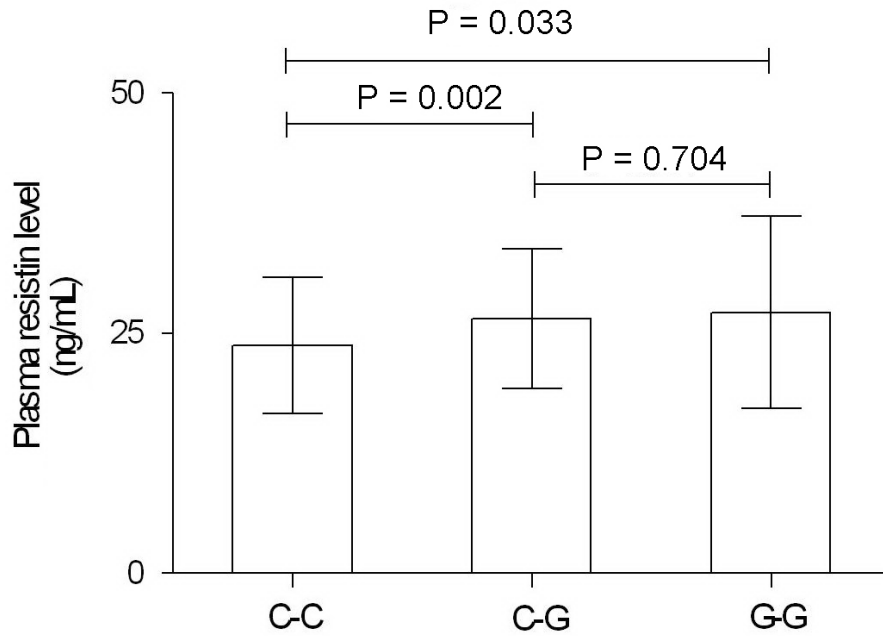
All values are reported as median (lower quartile, upper quartile), means ± standard deviation or counts (percentage). Numerical variables were analyzed by analysis of variance or the Kruskal-Wallis H-test. Categorical variables were analyzed by the chi-square test.

### RETN SNP -420C>G frequencies in the study population

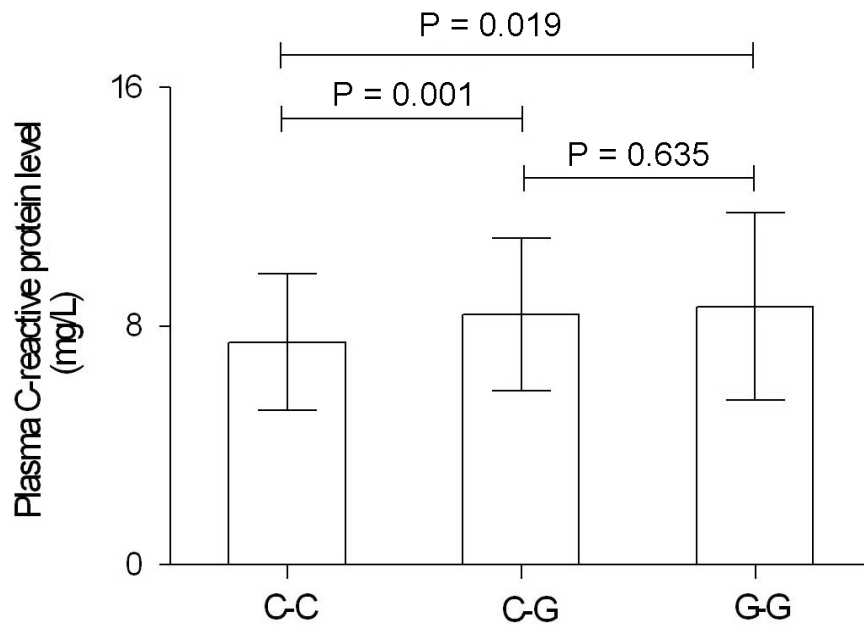
In SNP -420C>G, the C and G allele frequencies of the patients were 71.1 and 28.9%, respectively. The genotype CC, CG and GG frequencies of the patients were 50.3, 41.6 and 8.1%, respectively. In SNP -420C>G, the C and G allele frequencies of the controls were 68.9 and 31.1%, respectively. The genotype CC, CG and GG frequencies of the controls were 47.1, 43.6 and 9.3%, respectively. The genotype frequencies of the -420C>G polymorphism of resistin gene were in HWE. The genotype frequencies between controls and patients showed no significant differences ( $P = 0.672$ ).

### Association of RETN SNP -420C>G with levels of resistin and C-reactive protein in plasma

Plasma resistin and C-reactive protein levels were significantly different between the genotypes in the SNP -420C>G. The results are shown in Table 1. Even after adjustment for age, gender and body mass index, these associations still remained significant ( $P = 0.003$  and  $0.001$ , respectively). The common homozygote (CC) had the lowest plasma resistin and C-reactive protein concentrations; the resistin and C-reactive protein concentrations between heterozygote (CG) and rare allele homozygote (GG) did not differ significantly (Figures 1 and 2).



**Figure 1.** Graph showing plasma resistin levels of each genotype in patients with intracerebral hemorrhage. Data are reported as means ± standard deviation.



**Figure 2.** Graph showing plasma C-reactive protein levels of each genotype in patients with intracerebral hemorrhage. Data are reported as means ± standard deviation.

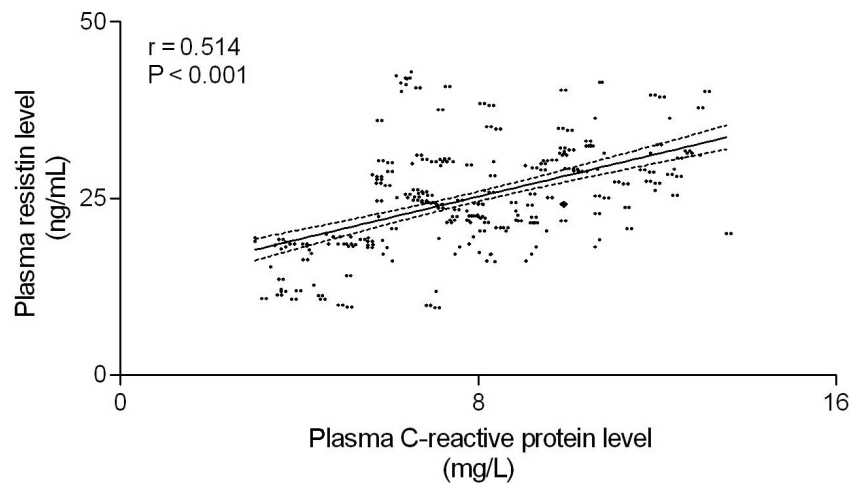
### Correlation of plasma C-reactive protein level with plasma resistin level

A significant correlation emerged between plasma C-reactive protein and resistin level, as well as other variables, as shown in Table 2. Plasma resistin level ( $t = 7.032$ ,  $P < 0.001$ ) and Glasgow Coma Scale score ( $t = -4.845$ ,  $P < 0.001$ ) were associated with plasma C-reactive protein level, using multivariate linear regression (Figure 3).

**Table 2.** Factors that correlated with plasma C-reactive protein level.

	r value	P value
Glasgow Coma Scale score	-0.425	<0.001
Hematoma volume (mL)	0.397	<0.001
Blood glucose level (mM)	0.282	<0.001
Creatine kinase (U/L)	0.118	0.028
Plasma resistin level (ng/mL)	0.514	<0.001
Plasma fibrinogen level (g/L)	0.275	<0.001
Plasma D-dimer level (mg/L)	0.294	<0.001

Correlations of plasma C-reactive protein level with other variables were analyzed by the Spearman test or the Pearson test.



**Figure 3.** Graph showing correlation between resistin and C-reactive plasma levels in patients with intracerebral hemorrhage.

### DISCUSSION

The aim of the present study was to clarify the association of the -420C>G polymorphism of the resistin gene with plasma resistin concentration in hemorrhagic stroke patients. In our study, the plasma resistin levels were significantly increased according to the presence of mutations in the resistin gene at -420C>G. The results imply that this SNP seems to have a role in the determination of plasma resistin level. Interestingly, it was also found that this SNP and plasma resistin level were associated with the concentration of C-reactive protein in plasma. In addition, the genotype frequencies between controls and patients showed no significant differences.



In accordance with earlier studies (Cho et al., 2004; Osawa et al., 2007; Ukkola et al., 2008; Hivert et al., 2009), in the present study, G allele carriers had higher resistin levels than non-carriers even after further adjustment for age, gender and body mass index. This SNP exists in the promoter region, and it has been determined that transcription factors Sp1 and Sp3 are upregulated in the G allele (Osawa et al., 2004). Therefore, the data suggested that the influence of SNP -420C>G on resistin promoter activity seemed to be among the factors influencing resistin concentration in hemorrhagic stroke patients.

Resistin has been shown to be involved in inflammatory processes. Some pro-inflammatory agents, such as tumor necrosis factor- $\alpha$  (Fasshauer et al., 2001), interleukin-6 (Kaser et al., 2003) and lipopolysaccharide (Lu et al., 2002), can regulate resistin gene expression. Other studies have also shown the regulation of pro-inflammatory cytokine expression by resistin (Bokarewa et al., 2005; Silswal et al., 2005; Pang and Le, 2006). Moreover, resistin is proposed as an inflammatory marker in human atherosclerosis (Reilly et al., 2005) and rheumatoid arthritis (Bokarewa et al., 2005). Recent studies have also reported that resistin is positively correlated with C-reactive protein in patients with coronary artery disease (Al-Daghri et al., 2005), diabetes mellitus (Shetty et al., 2004) and rheumatoid arthritis (Yoshino et al., 2011). Our study, in agreement with recent data, showed that resistin was correlated with C-reactive protein. Furthermore, resistin can strongly upregulate the expression of pentraxin 3, a close homolog of C-reactive protein, probably via nuclear factor- $\kappa$ B (Kawanami et al., 2004). Thus, it was suggested that resistin was involved in the inflammatory process of hemorrhagic stroke. Simultaneously, it was reasonable to suppose that our observation of an association between RETN -420C>G polymorphism and the increased levels of C-reactive protein may be due to the higher resistin concentration, which was RETN -420C>G polymorphism.

Recently, it was reported that resistin SNP -420C>G did not have any influence on the plasma resistin levels in a group of patients with atherothrombotic cerebral infarction, lacunar infarction and intracerebral hemorrhage (Lin et al., 2007). Interestingly, the prevalence of ischemic stroke was found to be significantly correlated with serum resistin levels, which were increased according to the presence of resistin SNP -420C>G (Tsukahara et al., 2009). Our series showed that the plasma resistin levels in hemorrhagic stroke were significantly associated with resistin SNP -420C>G. This discrepancy may be due to differences in study populations and study designs. However, interactions with other genes and environmental factors may partly explain the discrepancy between genetic association studies. Due to linkage disequilibrium, the effects of one polymorphism can be seen in association studies of other polymorphisms located in the same region. Accordingly, further study is also needed.

## CONCLUSIONS

Our results imply that RETN -420C>G polymorphism seems to be potentially involved in the inflammatory component of intracerebral hemorrhage through an enhanced production of resistin.

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