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Systolic hypertension related single nucleotide polymorphism is associated with susceptibility of ischemic stroke

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Abstract. – OBJECTIVE: Isolated systolic hypertension (ISH) is the most important risk factor for ischemic stroke. Genetic variants influencing hypertension can also be risk factors for ischemic stroke. Here, we examined the how single nucleotide polymorphisms (SNPs) associated with blood pressure impact the risk for ischemic stroke.

PATIENTS AND METHODS: We selected 300 ischemic stroke patients and 300 controls. Then, we genotyped three single nucleotide polymorphisms associated with systolic hypertension in both groups.

RESULTS: Logistic regression analysis showed that the rs11099098 genotype was associated with a significantly decreased risk of IS (Dominant model: OR = 0.55, 95% CI = 0.37-0.82, p = 0.003). Two other SNPs, rs880315 and rs11072518, showed a trend towards association with stroke risk, but did not reach statistical significance.

CONCLUSIONS: Our study suggests that genetic variants in systolic pressure-related genotypes may contribute to the etiology of ischemic stroke.

Key Words:
Ischemic stroke, SNPs, Systolic pressure, Susceptibility.

Introduction

Stroke is a common cause of death and morbidity worldwide[1]. In China, it is the leading cause of death and adult disability[2]. About eighty percent of stroke cases are caused by ischemia. Ischemic stroke (IS) is a multifactorial disease, which can be influenced by genetic factors, environmental factors, and their interactions[1]. Using genome-wide association study (GWAS) and candidate case-control association methods, a number of genes have been found to associate with ischemic stroke. These genes include MTHFR, PAL-1, TNF, APOA, APOE, ACE, Factor V Leiden, ALOX5AP, Angiopoietin-1, CRP, CYP4AII, CYP4F2, CYPIIB2, DDAH1, NOS3, PCSK9, GP1BA, GPIIIa, IL-6, LTC4S2, NPY, PDE4D, SGK1, VKORC1, NINJ2, PRKCH, PITX2, ZFHX3, and the prothrombin gene[3]. However, the identified genes only explain a small portion of the heritability in ischemic stroke, suggesting that additional genetic variants still need to be identified.

Hypertension is the most important risk factor for ischemic stroke. Antihypertensive drug treatment in older persons with isolated systolic hypertension can reduce the incidence of ischemic stroke[4]. Based on this rationale, we hypothesized that genetic variants influencing hypertension could also be risk factors for ischemic stroke. In 2014, a genome-wide association study identified several single nucleotide polymorphisms (SNPs) associated with blood pressure[5]. Ischemic stroke is mainly associated with systolic hypertension[4]. Therefore, we selected the novel SNPs affecting systolic pressure as risk factors for the develop-

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ment of stroke, including rs880315, rs11099098, and rs11072518.

Patients and Methods

Patients

We identified 300 ischemic stroke patients and 300 healthy controls at the Department of Neurology, Jiangyin People's Hospital and Huai'an People's Hospital, China. All patients were diagnosed as ischemic stroke according to the World Health Organization criteria. After admission to the hospital, all patients received computed tomography (CT) or magnetic resonance imaging (MRI) within 48 hours. Neck vascular ultrasound, magnetic resonance angiography, or CT angiography were used to evaluate blood vessels. The Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria were used to determine the subtype of ischemic stroke[6]. Patients with brain tumors, brain trauma, intracranial hemorrhage, and post-seizure palsy were excluded. This study was approved by the Ethics Committee of Huai'an People's Hospital. Signed written informed consents were obtained from all participants before the study.

Data Collection

Risk factors for ischemic stroke among stroke and control groups were assessed using a questionnaire. The questionnaire collected information on demographics, medical history (hypertension, diabetes mellitus), history of alcoholism, daily cigarette smoking, obesity, and hypercholesterolemia. Hypertension was defined as blood pressure ≥ 140/90 mmHg (average of three independent measures) or the use of antihypertensive drugs. Diabetes mellitus was defined as fasting glucose level ≥7 mmol/L and/or level ≥ 11.1 mmol/L 2 h after oral glucose challenge, or receiving antidiabetic drugs. Subjects who smoked more than 10 cigarettes per day for 5 years were considered as smokers. Subjects who drank more than 50 ml alcohol per day for 5 years were considered as drinkers. Subjects with body mass index (BMI) oho5 kg/m^2 were considered as obese. The National Institutes of Health Stroke Scale (NIHSS) score was used to quantify stroke severity of patients at the time of presentation and discharge.

SNP Selection and Genotyping

Based on information in the NCBI SNP database (http://www.ncbi.nlm.nih.gov/SNP), the International HapMap project data for the Han Chinese population (http://hapmap.ncbi.nlm.nih.gov/), and previous studies on hypertension-related genes[5,7], we selected the polymorphisms of rs880315, rs11099098, and rs11072518. Fasting venous blood (10 ml, EDTA anticoagulant) was harvested from patients and controls. Total DNA from leukocytes was extracted using the salt fractionation method in accordance with a standard protocol[8]. TaqMan allelic discrimination assay on ABI PRISM 7900HT Sequence Detection system (Applied Biosystems, San Diego, CA, USA) was used to genotype single nucleotide polymorphism. Each genotyping assay contained one pair of primers and one pair of probes (sequences provided in Supplementary Table S1). The allelic discrimination mode of the SDS 2.3 software package (Applied Biosystems, Foster City, CA, USA) was used to calculate the genotyping results, and a 100% concordant was achieved.

Statistical Analysis

All statistical analyses were performed using Stata/SE (V.12.0 for Windows; StataCorp LP, College Station, TX, USA). Demographic data were compared using two-sample *t*-tests, chi-square (χ^2) test. The association of genotypes with ischemic stroke susceptibility, severity, and short-term recovery were estimated by odds ratio (OR) and 95% CI using multivariate logistic regression analysis, with adjustment for age, sex, smoking, drinking, diabetes mellitus, hypertension, total cholesterol. All statistical tests were two-sided and a $p < 0.05$ was considered as statistically significant.

Results

Clinical Data of Participants

The detailed clinical data for IS patients and controls are presented in Table I. Although the age of subjects in the two groups was similar, the stroke group had more males compared with the control group. Also, the IS group had significantly more smokers and drinkers, and more patients suffered hypertension and diabetes (Table I). However, we found no significant differences in serum triglycerides, HDL-C, LDL-C concentration, and BMI between the stroke and control groups (Table I). These observations confirm the higher incidence of stroke in males and the role of smoking, drinking, diabetes mellitus, and hypertension as risk factors.

Table I. Demographic characteristics of patients and control subjects.

Characteristics	Stroke (n=300)	Control (n=300)	*p*-value
Age (years)	65.49 ±10.91	67.12 ± 9.31	0.061
Sex (male) (%)	176 (58.7)	139 (46.3)	0.002
Smoker (%)	113 (37.7)	74 (24.7)	0.001
Drinker (%)	138 (46.0)	62 (20.7)	<0.001
Diabetes mellitus (%)	63 (21.0)	38 (12.7)	0.006
Hypertension (%)	184 (61.3)	118 (39.3)	<0.001
BMI ≥ 25 kg/m^2 (%)	110 (36.7)	99 (33.0)	0.563
Total cholesterol (mmol/L)	4.40 ± 1.12	5.18 ± 0.95	<0.001
Triglycerides (mmol/l)	1.76 ± 1.49	1.57± 1.27	0.084
HDL-C (mmol/L)	1.24 ± 0.53	1.18 ± 0.27	0.070
LDL-C (mmol/L)	2.45 ± 0.96	2.66± 0.60	0.249

Abbreviation: SD, standard deviation.

Table II. Association of SNP genotypes with IS susceptibility.

Genotype	Control (n=303)	Stroke (n=320)	OR (95% CI)	*p*-value
rs11099098				
GG	93 (31.0 %)	116 (38.7%)	1.00	
GT	141 (47.0%)	139 (46.3%)	0.59 (0.39-0.90)	0.015
TT	66 (22.0%)	45 (15%)	0.46 (0.26-0.80)	0.006
Dominant			0.55 (0.37-0.82)	0.003
Additive			0.66 (0.51-0.87)	0.003
rs880315				
AA	119 (39.7%)	121 (40.3%)	1.00	
AG	130 (43.3%)	143 (47.7%)	1.09 (0.73-1.65)	0.653
GG	51 (17.0%)	36 (12.0%)	0.75 (0.42-1.36)	0.345
Dominant			1.01 (0.69-1.49)	0.960
Additive			0.92 (0.70-1.21)	0.555
rs11072518				
TT	63 (21.0%)	70 (23.3%)	1.00	
TC	159 (53.0%)	146 (48.7%)	0.78 (0.49-1.25)	0.308
CC	78 (26.0%)	84 (28.0%)	0.86 (0.50-1.46)	0.581
Dominant			0.81 (0.52-1.26)	0.350
Additive			0.93 (0.71-1.22)	0.619

Logistic regression analyses adjusted for age, sex, smoking, drinking, diabetes mellitus, hypertension, total cholesterol.

Association of SNP Genotypes with IS Susceptibility

The frequencies of the three selected SNPs in the stroke and control groups are shown in Table II. Our statistical analysis confirmed that the three SNPs were in Hardy–Weinberg equilibrium distribution in the controls. We found no significant differences in the distribution of the rs880315 and rs11072518 SNPs between the stroke and control groups (Table II). However, we observed a significantly different distribution of the rs11099098 SNP between the stroke and healthy control groups. Logistic regression analysis showed that the variant genotypes were associated with a significantly decreased risk of IS (Dominant model: OR = 0.55, 95% CI = 0.37-0.82, p = 0.003).

Association of rs11099098 SNP with IS Severity and Short-Term Recovery

After finding an association of the rs11099098 polymorphism with stroke, we next investigated its relationship to IS severity and short-term recovery. Since the NIHSS score was skewed and could not be transformed to a normal distribution, we decided to dichotomize it for logistic regression analysis. We set the cut-off for mild and severe IS between 6 and 7 according to previous studies[9,10]. Short-term recovery was measured as a change in NIHSS from presentation to discharge (ΔNIHSS). The cut-off for short-term recovery was set at 0, where < 0 means clinical improvement and on to discharge (ΔNIHSS). The cut-off 212 stroke patients were classified as

Table III. Association of rs11099098 polymorphism with IS severity and short-term recovery.

a) SNPs associated with IS severity				
Genotype	**Mild (n=212)**	**Severe (n=88)**	**OR (95% CI)**	***p*-value**
rs11099098				
GG	78 (36.8%)	38 (43.2%)	1.00	
GT	99 (46.7%)	40 (45.5%)	0.76 (0.42-1.34)	0.340
TT	35 (16.5%)	10 (11.3%)	0.49 (0.21-1.16)	0.104
Dominant			0.68 (0.39-1.18)	0.172
Additive			0.72 (0.48-1.06)	0.096
b) SNPs associated with IS short-term recovery				
Genotype	**Improvement (n=168)**	**No change/ deterioration (n=132)**	**OR (95% CI)**	***p*-value**
rs11099098				
GG	62 (60.3%)	54 (73.3%)	1.00	
GT	82 (37.4%)	57 (25.3%)	0.79 (0.47-1.34)	0.387
TT	24 (2.3%)	21 (1.4%)	0.88 (0.43-1.81)	0.724
Dominant			0.81 (0.50-1.33)	0.414
Additive			0.90 (0.64-1.28)	0.567

Logistic regression analyses adjusted for age, sex

mild IS and 88 as severe IS. Table III shows the distribution of the rs11099098 genotypes according to IS severity. After adjusted for age and sex, logistic regression analysis showed that the minor alleles of rs11099098 had a trend towards milder IS. However, we found no significant association between rs11099098 variants and IS severity. The relationship of was next analyzed. We also found no significant association between rs11099098 SNP and IS short-term recovery, only a trend towards improvement in minor alleles (Table III).

Discussion

Hypertension is one of the most important risk factors for ischemic stroke. Studies have described a strong genetic component for hypertension, with a heritability for blood pressure had of 30-50%[11]. Thus, the heritability of hypertension is likely to affect the risk of ischemic stroke. A GWAS study found that the risk score of 29 SNPs was related to both stroke and hypertension[12]. Furthermore, isolated systolic hypertension (ISH) is particularly associated with stroke. The Systolic Hypertension in the Elderly Program (SHEP), the Systolic Hypertension in Europe study (Syst-Eur), and the Systolic Hypertension in China study (Syst-China) demonstrated that antihypertensive drug therapy for elderly patients with ISH reduces the risk of stroke[13]. A previous study also showed that ISH was associated with increased mortality, in addition to the increased risk of stroke[14,15]. Therefore, it is important to explore the contribution of the genetic factors of systolic pressure to IS susceptibility. To the best of our knowledge, limited evidence is available for the association of systolic pressure-related SNPs and IS.

In the present research, we investigated the association between three hypertension-related SNPs (rs880315, rs11099098, and rs11072518) and ischemic stroke. We observed that the minor allele of rs11099098 correlated with a decreased risk of IS in Chinese Han population and found not association with rs880315 and rs11072518. Overall, the rs11099098 GT or TT genotypes were protective factors for IS.

The limitations of this work include the relatively small sample size, which may lower our statistical power. Thus, although we found a trend for the polymorphisms of rs880315 and rs11072518 and IS risk, we could not conclude whether or not they influence IS. Since only survivors of ischemic stroke are examined, there may be a bias in the selection of subjects for mild or minor strokes. Finally, our findings also need to be further verified in different ethnic populations.

Conclusions

This is the first evaluation of the association between systolic pressure-related genotypes and susceptibility for IS. Our study suggests that individuals harboring GT or TT genotypes of rs11099098 may have a reduced risk of ischemic stroke.

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Conflict of interest

The authors declare no conflicts of interest.

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