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Original Article

Association of LRRFIP1 gene polymorphisms with susceptibility to ischemic stroke in a Chinese population

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Abstract: Previous studies showed that leucine-rich repeat (in FLII) interacting protein 1 (LRRFIP1) was proposed as one regulator of the toll-like receptor (TLR) pathway signaling. The activation of LRRFIP1 protein may regulate TLR pathway signaling culminating in the production of a range of inflammatory markers, and its gene expression was influenced by a functional polymorphism in the exon region. The genetic basis of the ischemic stroke has now been largely determined, so the aim of the study was to examine the role of LRRFIP1 genetic variants in the ischemic stroke (IS) risks in a Chinese population. We conducted a case-control study with 239 IS patients and 240 controls. SNP rs3769053 of LRRFIP1 gene was analyzed for association with risk of IS in Han population. The distributions of genotypes in LRRFIP1 gene were slightly different between IS groups and health controls. And then we evaluated the association between LRRFIP1 gene (rs3769053) polymorphisms and IS with multivariate logistic regression. We found that neither TC (OR=1.353, 95% CI: 0.457-4.008, P=0. 585) nor TT (OR=1.309, 95% CI: 0.850-2.016, P=0.221) genotype was significantly associated with the risk of IS. In summary, our study reveals that the LRRFIP1 gene polymorphism (C→T) may not be a risk factor for the development of IS in Chinese Han population.

Keywords: Case-control study, ischemic stroke, leucine-rich repeat (in FLII) interacting protein 1, polymorphism

Introduction

Stroke is the third cause of mortality and the first cause of serious disability in developed countries [1]. There are 2.5 million new stroke cases each year and 7.5 million stroke survivors in China [2]. Ischemic stroke (IS) accounted for 85-90% of strokes [3]. The occurrence and development of IS results mostly from genetic and environmental influences plus interaction effects between genes and behavior. The role and importance of gene polymorphisms have been confirmed by a large number of studies [4-9]. In recent years, the association of multitudinous gene polymorphisms with IS population were found in Chinese population [10-14]. LRRFIP1 (leucine-rich repeat (in FLII) interacting protein 1) is a poorly characterized protein that has been described as both a transcriptional repressor and as a MyD88 (myeloid differentiation primary response gene (88))-interacting protein [15-21]. Recently, several studies have identified its role in the toll-like receptor (TLR) signaling pathway via interactions with flightless I homolog (FliiH), which interacts with MyD88 [22, 23]. The Toll-like receptor (TLR) gene is recently proposed as one potential molecular link between obesity, inflammation, and insulin resistance [24]. TLRs also play a role in ischemic brain injury [25]. Hence, since IS is a complex disease that is commonly associated with an inflammatory state [26]. LRRFIP1 gene is identified one regulator of the TLR pathway signaling [27]. Moreover, it is recently reported that activation of the LRRFIP1 protein may lead to a cascade of signaling events culminating in the production of tumor necrosis factor-a and other marker of inflammation related to extracellular treats [28]. However IS results from a reduction in cerebral blood flow triggering a cascade of cellular and molecular events [29]. In addition, variations in the LRRFIP1 gene are associated with adiposity and inflammation [30], breast and colorectal cancers [31].

With the achievement of the Human Genome Project (HGP) and International HapMap Project (HapMap), genetic susceptibility has been a very hot subject in current research in functional genomics. Identification of disease susceptibility gene is of great significance for the early warning, prevention and individualized treatment. The overexpression of LRRFIP1 in cerebral ischemia has been described earlier [1] and LRRFIP1 gene is involved in stroke damage and recovery [32, 33]. Whether there is an association of polymorphism of LRRFIP1 gene with susceptibility to IS remains unknown. Therefore, we first investigate the relationship between LRRFIP1 gene polymorphism and the IS in a Chinese population.

Subjects and methods

Subjects

This study protocol was reviewed and approved by the Department of Science and Technology of Mudanjiang City and the local Ethics Committees of all the participating hospitals. Cases and controls were Han Chinese recruited consecutively from the same geographic region from September 2009 to June 2013 in Mudanjiang city and consented to provide biological samples for genetic analysis. A case-control study design was adopted. Cases were patients with new-onset IS registered in No.1, No.2 People's Hospital and Hongqi Hospital Affiliated to Mudanjiang Medical University in Mudanjiang city. We consecutively recruited 239 patients (147 males, 92 females; mean age, 55.45 years) with IS diagnosed by neurological examination and CT, or MRI, or both according to International Classification of Diseases (9th edition). Patients with hemorrhagic stroke, cancer, autoimmune disease, or chronic inflammation were excluded in this study. The control group consisted of 240 subjects (147 males and 93 females), who were unrelated healthy individuals without a history of stroke. 240 subjects were recruited from the same geographic region as controls. The controls had no clinical evidence of related neurological diseases according to the same exclusion criteria adopted for the case group and no a history of stroke. The cases and controls were interviewed by investigators using the same structured questionnaire. Besides history of hyper-tension, history of Diabetes, and history of coronary artery disease, the following vascular risk factors and environmental factors were recorded: history of cigarette smoking, tea-drinking, alcohol-drinking. All participants were measured for their current height and weight.

Biochemical variables and genotyping

A 5 ml venous blood sample was drawn into tubes containing 5% EDTA after at least 12 to 14 h of fasting. Plasma total trigly-ceride, cholesterol, low-density lipoprotein cholesterol (LDL), and high-density lipopro-tein cholesterol (HDL) were measured using enzymatic methods. Plasma glucose was measured by a glucose oxidase procedure. In case of acute or other emergencies, blood samples were collected 6 days later. Genomic DNA was purified from whole blood samples using a DNA blood kit (QIAGEN, Hilden, Germany) according to the manufacturer's instructions. DNA samples were stored at -80°C before use. According to the information in the NCBI SNP database, SNPs which had a minor allele frequency of more than 5% or those established in the literature were chosen. TaqMan SNP genotyping assay was used to determine the polymorphism (rs3769053) of LRRFIP1 gene. The primers were forward, 5'-GACCTTGAGGCTGCATTTCT-AAA-3' and reverse, 5'-CCACTCTCACTTCTCA-ATGAACAAC-3'. The Taqman minor groove binding (MGB) probes for detection of C/T polymorphism were FAM-AAATTACTtGAAAGCTGC-MGB and HEX-AAATTACTcGAAAGCTG-MGB. The primers and probes were commercially supplied by Shanghai GeneCore Biotechnologies. Thermal cycling was performed on ABI 7500 systems from Applied Biosystems (Applied Biosystems, Foster City, CA, USA). Allele frequencies were also determined by ABI 7500 systems.

Statistical analysis

Epidata 3.0 was used to establish the database. Allele and genotype frequencies in patients and controls were compared by χ^2 test or Fisher exact test. A goodness-of-fit χ^2 test was used to observe the deviation of genotype distribution from Hardy-Weinberg equilibrium. Continuous variables were expressed as mean ± SE and categorical variables were assessed by χ^2 test or Fisher's exact test. First, risk factors were screened by Student's t test or χ^2 test, and then logistic regression models were used to evaluate the effects of risk factors. Odds

Table 1. Demographic characteristics and distribution of traditional risk factors

Variable	Case (n=239)	Control (n=240)	*Wald or F*	*P*
Age (year)	55.45±10.17	52.18±8.99	3.709	<0.001
Gender(M/F)	147/92	147/93	0.003	0.954
BMI				
≥25 (kg/ m^2)	146	143	0.113	0.736
<25 (kg/ m^2)	93	97		
History of hypertension	110	78	5.471	0.019
History of diabetes	33	14	8.605	0.003
History of heart diseases	33	26	0.981	0.322
Smoking	95	72	5.012	0.025
Alcohol drinking	87	87	0.001	0.972
Tea drinking	50	105	28.514	<0.001
Triglyceride (mmol/l)	2.11±2.03	1.94±0.97	1.182	0.238
Cholesterol (mmol/l)	5.06±1.87	5.15±0.81	0.710	0.478
HDL-C (mmol/l)	1.42±0.80	1.43±0.37	0.274	0.785
LDL-C (mmol/l)	2.91±0.92	2.47±0.98	6.147	<0.001
GLU	6.50±4.02	5.86±0.98	2.393	0.017

Table 2. Distribution of genotypes and alleles between case group and control group

Variables	Case n (%)	Control n (%)	χ^2	P*
Genotypes				
CC	10 (4.18)	10 (4.17)		
TC	94 (39.33)	78 (32.50)	0.156	0.693
TT	135 (56.49)	152 (63.33)	0.066	0.798
Alleles				
C	114 (23.85)	98 (20.42)		
T	364 (76.15)	382 (79.58)	1.638	0.201

**P* values: CC genotype and C allele as reference respectively when IS patients vs controls.

ratios with 95% confidence intervals (95% CI) were calculated to test the association between risk factors and IS. For all the tests, statistical significance was accepted at a *P* value less than 0.05 (two-tailed). All the research data were analyzed using the SPSS12.0 statistical package (SPSS Inc., Chicago, Illinois, USA).

Results

Characteristics of the subjects

The clinical and demographic data of the patients and controls are presented in **Table 1**. There were no significant differences in gender, BMI, history of heart disease, alcohol drinking, triglyceride, cholesterol and HDL-C between the two groups. There were significant differences in age (P<0.001), tea drinking (P<0.001) between the patients and controls. But the prevalence of conventional risk factors for vascular disease was higher in patients, and these risk factors included history of hypertension, history of diabetes, smoking, LDL-C and GLU (all P<0.05).

Distribution of LRRFIP1 gene polymorphism in two groups

Genotypes were obtained for all subjects for rs3769053 polymorphism as shown in **Table 2**. The genotypes of rs3769053 in LRRFIP1 gene were in accordance with Hardy-Weinberg equilibrium in controls (HWP=0.338). The distribution of three genotypes frequencies in LRRFIP1 gene (CC, TC, TT) were 4.18%, 39.33% and 56.49% in patients and 4.17%, 32.50% and 63.33% in controls. The distribution of two alleles frequencies (G and A) were 23.85%, 76.15% in patients and 20.42%, 79.58% in controls. There were no statistically significant differences in the distribution of LRRFIP1 gene genotypes (TC, TT) between the patients and controls with CC genotype as a reference genotype (P=0.693, P=0.798, respectively). There was no statistically significant differences in the distribution of T allele between two groups compared with G allele (P=0.201).

Association of the genotypes with the risk of IS

Finally, we had assessed the association between LRRFIP1 gene (rs3769053) polymorphisms and IS with multivariate logistic regression which was shown in **Table 3**. Crude and adjusted ORs for IS were used with and without adjustment for confounding factors. Without adjusting for smoking (0, negative; 1, positive), tea drinking (0, negative; 1, positive), history of hypertension (0, negative; 1, positive), history of diabetes (0, negative; 1, positive), age, BMI (0, BMI<25; 1, BMI≥25), GLU, and LDL, multivariate logistic regression revealed that TC, TT genotypes were not associated with IS (OR=1.205, P=0.693; OR=0.888, P=0.798, respectively). After adjustment for the above-mentioned confounding factors, the relationship between LRRFIP1 gene (rs3769053) poly-

Table 3. Association of the genotypes of LRRFIP1 gene (rs3769053) with the risk of IS

Genotypes	OR (95% CI)	P	Adjusted OR (95% CI)*	P
CC	1.000		1.000	
TC	1.205 (0.477-3.044)	0.693	1.353 (0.457-4.008)	0.585
TT	0.888 (0.359-2.199)	0.798	1.309 (0.850-2.016)	0.221

*adjusted for smoking (0, negative; 1, positive), tea drinking (0, negative; 1, positive), history of hypertension (0, negative; 1, positive), history of diabetes (0, negative; 1, positive), age, BMI 0, BMI<25; 1, BMI≥25), GLU, and LDL.

morphisms and IS were not still found (OR=1.353, P=0.585; OR=1.309, P=0.221, respectively).

Discussion

Gene variations may induce pathological changes of intracranial vessels, resulting in cerebral hemorrhage and IS [34]. IS accounts for 85-90% of cerebrovascular disease cases, with intracerebral or subarachnoid hemorrhages constituting the remaining 10%-15% [3]. It is clear that stroke remains one of the top causes of mortality and disability-adjusted life-years (DALYs) lost globally. The association between genetics and cerebrovascular disease has become a focus of investigation in recent years. The etiology and pathogenesis of IS are not yet known, but all evidence available points to a multifactor mode of causation because of the interaction of genetic predisposition and environment factors.

The aim of this study was to evaluate the relationship between LRRFIP1 gene polymorphisms and IS in a Chinese Han population. Our results showed that the SNP rs3769053 was not significantly associated with the risk of IS. LRRFIP1 was a poorly characterized protein that had been described as both a transcriptional repressor and as a MyD88-interacting protein [15-21]. It could relieve the FliiH-mediated inhibition of TLR signaling [21]. However, TLRs play a key role in initiating events that contribute to ischemic brain injury [35]. We speculate that the variation in rs3769053 can potentially affect RNA splicing and regulation of TLR pathway signaling. TLR is considered a molecular link between obesity, inflammation, and insulin resistance [24]. Moreover, the activation of LRRFIP1 protein might lead to a cascade of signaling events culminating in the production of tumor necrosis factor-α and other marker of inflammation related to extracellular treats [28]. The overexpression of LRRFIP1 in cerebral ischemia has been described earlier [1] and LRRFIP1 gene is involved in stroke damage and recovery [32, 33]. It is conceivable that genetic variation in these genes may be associated with IS. However, our study results did not support a relationship between rs3769053 C/T polymorphism with the risk of IS in Chinese Han population.

To our knowledge, this is the first study to investigate an association of polymorphisms of the LRRFIP1 gene with the risk of ischemic stroke in the Chinese Han population. Our study indicated that the relationship between rs3769053 C/T polymorphism and IS in Chinese Han population was missing. However, our study has the limitations of the relatively small sample size, selection bias tend to occur, few polymorphisms of SNPs studied and may be most likely to attenuate observed association. Thus, we hope to genotype larger samples and more LRRFIP1 gene polymorphisms in the future prospective studies. Furthermore, studies in the other populations, both regional Chinese populations and different ethnicities, will be useful to confirm our results.

Conclusion

In summary, our study reveals that the LRRFIP1 gene polymorphism (C→T) may not be a risk factor for the development of IS in Chinese Han population.

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Disclosure of conflict of interest

None.

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