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Original Article

Association of endothelial lipase genetic polymorphism with lacunar infarction in a Chinese population

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Abstract: Introduction: This study sought to investigate the correlation between the single nucleotide polymorphism (SNP) rs9958947C>T in the endothelial lipase (LIPG) gene promoter and lacunar infarction in the Han population in China. Materials and methods: A case-control method was applied in this study, which included 378 patients with lacunar infarction in the patient group and 404 healthy individuals who received a routine physical examination in the control group. The polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) methods were used to detect the SNP (rs9958947) in the LIPG promoter for the two groups. Results: The T allele frequency (51.32%) and CT+TT genotype frequency (77.78%) in the patient group were significantly higher than those in the control group (43.32% and 66.34%, respectively). Comparison of the T allele frequency and CT+TT genotype frequency between the two groups showed statistically significant differences. Logistic regression analysis showed that the T allele, male, smoking, hypertension, hyperlipidemia and diabetes were independent risk factors for lacunar infarction in the Han population in China. Conclusion: Therefore, we concluded that SNP rs9958947 in the LIPG gene promoter is associated with the incidence of lacunar infarction.

Keyword: Endothelial lipase, single nucleotide polymorphism, lacunar infarction

Introduction

The human endothelial lipase (LIPG, EL) gene is located on chromosome 18q21, and LIPG is a recently discovered member of the triglyceride lipase family. The family of triglyceride lipases includes hepatic lipase (HL), lipoprotein lipase (LPL) and pancreatic lipase (PL) [1]. Although the amino acid sequence of LIPG shares 45%, 40% and 27% homology with LPL, HL and PL, respectively, its phosphatase activity is greater than those of other triglyceride lipases [2]. LIPG is related to the metabolism of lipoproteins, particularly high-density lipoprotein cholesterol (HDL-C) [3], and has also been associated with monocyte aggregation in the early inflammatory stage of atherosclerosis [4]. Studies have shown that the synthesis of LIPG occurs in endothelial cells *in vitro*, and in liver, lung, kidney and placental tissues *in vivo* [5]. HDL particles are the primary substrate of LIPG, which can hydrate HDL-C through its phospholipase activity, and this effect is content-dependent [6]. Experiments using genetically modified mice showed that the expression of EL mRNA was significantly negatively correlated with the HDL-C level, while LIPG activity was also negatively correlated with the HDL-C level [5-8]. Recently, human genome-wide association studies (GWAS) found that the HDL-C level is related to the genetic variation of LIPG [9-14]. Studies have also confirmed that a decrease in the HDL-C level is a precise and controllable risk factor for atherosclerotic diseases including ischemic stroke [15]. Many studies have been carried out to assess the correlation between the genetic variation of LIPG and the HDL-C level as well as its related diseases [2, 4, 6, 16-17], but the conclusions have not been consistent.

In this study, the correlation between the single nucleotide polymorphism (SNP) rs9958947C>T in the LIPG gene promoter and lacunar infarc-

Table 1. The characteristics of the two groups

	lacunar infarction (n = 378)	Control (n = 404)	*P* Value
Age (year)	61.5 ± 4.3	61.6 ± 4.2	0.754
Gender (M/F, N)	220/158	229/175	0.365
Hypertension (n, %)	244 (64.5)	116 (28.7)	< 0.001
Smoking (n, %)	227 (60.1)	99 (24.5)	< 0.001
Alcohol drinking (n, %)	174 (46.0)	119 (29.5)	< 0.001
Diabetes (n, %)	83 (22.0)	20 (5.0)	0.001

Table 2. Biochemical indicators in the two groups

Biochemical indicators	Lacunar infarction (n = 378)	Control (n = 404)	*P* Value
FPG (mmol/L)	5.55 ± 1.87	5.12 ± 1.44	0.244
TG (mmol/L)	1.87 ± 1.05	1.34 ± 0.86	0.004
TC (mmol/L)	4.61 ± 1.33	4.54 ± 0.97	0.118
HDL-C (mmol/L)	1.24 ± 0.39	1.57 ± 0.34	0.021
LDL-C (mmol/L)	2.53 ± 0.88	2.60 ± 0.74	0.015
Apo-AL (g/L)	1.08 ± 0.21	1.30 ± 0.23	0.001
Apo-B (g/L)	0.97 ± 0.36	0.89 ± 0.27	0.188

Table 3. Hardy-Weinberg test between the two groups

Groups	Frequency	Genotype (n)			*P* value
		CC	CT	TT	
Case	Actual value	84	200	94	0.271
	Theoretical value	84.30	198.50	101.40	
Control	Actual value	136	186	82	0.364
	Theoretical value	138.39	188.44	79.43	

tion in the Chinese Han population was investigated. This locus was selected because single nucleotide variations in gene expression regulatory regions such as the promoter can directly affect the enzymatic activity of LIPG in the plasma, leading to changes in the blood lipid level and vascular disease.

Materials and methods

Ethnics

This study was approved by the ethics committee of the Third Military Medical University, and all subjects were explained the purpose of the study and signed an informed consent form.

Subjects

The patient group consisted of a total of 378 lacunar infarction patients admitted to the Department of Neurology, Xin Qiao Hospital, Third Military Medical University during the period from May 2012 to February 2014. Of these, 220 cases were male, and 158 cases were female, with an age range from 50-69 (61.5 ± 4.3) years old. These 378 cases in the patient group met the diagnostic criteria described previously [19], and the diagnoses were confirmed by brain computed tomography (CT) and magnetic resonance imaging (MRI), with an infarct diameter less than 15 mm. The 404 cases in the control group were matched according to gender and age and consisted of outpatients who received a routine physical examination in our hospital, showing no cardiovascular or cerebrovascular disease. Of these, 229 cases were male, and 175 cases were female, with an age range from 52-69 (61.6 ± 4.2) years old. Cases showing the following conditions were excluded: blood disease, arteritis, tuberculosis, cancer, atrial fibrillation, severe liver and kidney dysfunctions, combination of peripheral vascular disease or peripheral vascular thrombotic disease and treatment with any lipid-lowering drug within 1 week before admission.

Methods

Specimen collection: All subjects were fasted for 12-14 h, and then 5 ml of fasting venous blood was collected from each subject using ethylenediaminetetraacetic acid (EDTA) as an anticoagulant. The samples were stored at -20°C or immediately used for blood DNA extraction.

Extraction of genomic DNA from the blood: Genomic DNA was extracted from 0.5 ml of whole blood using a blood genomic DNA extraction kit (Beijing TIANGEN Company) according to the instructions provided by the manufacturer. The samples were then stored at -20°C for later use.

The primer sequences and restriction sites: The primers used amplify DNA fragments of the LIPG gene promoter flanking the rs9958974C > T polymorphism were designed using the software PremierPrimer 5.0 and Oligo 6.0. The appropriate restriction sites and the site-specific restriction endonuclease were selected

according to the specific sequence of the locus. The upstream primer was 5'-TTCTTCAAATCTGCAGCCTGT-3', and the downstream primer was 5'-CGACCTCGCCTCATTACTTT-3', both of which were synthesized by the Invitrogen Biotechnology Co. (Shanghai, China).

Polymerase chain reaction (PCR): The volume of the PCR amplification reaction was 25 μl, including 8.5 μl of double distilled water, 12.5 μl of Taq DNA polymerase (Beijing BioTeke Corporation), 10 pmol each of upstream and downstream primers and 40 ng of DNA template. The reaction conditions were as follows: denaturation at 95°C for 5 min, followed by 35 cycles of denaturation at 95°C for 30 s, annealing at 58°C for 40 s and extension at 72°C for 1 min and a final extension at 72°C for 10 min. After the amplification was completed, the PCR products were identified using 2% agarose gel electrophoresis, and the size of the target fragment as the amplified product was 274 bp.

Restriction digestion for the amplification product: The volume of the reaction system was 20 μl, including 9 μl of PCR product, 2 μl of 10× buffer, 0.5 μl of restriction endonuclease Msp I (New England Biolabs, Beijing) and 8.6 μl of nuclease free water, and this reaction was incubated at 37°C for 6 h. Restriction digestion of the amplification product with rs9958947 by Msp I generated three combinations of fragments at different sizes. The fragment sizes of the CC allele were 122 bp and 152 bp, the fragment size of the TT allele was 274 bp, and the fragment sizes of the CT allele were 274, 152, and 122 bp. The digestion products were subject to 2% agarose gel electrophoresis, and the gel images were photographed for subsequent analysis. The genotypes were determined according to the bands observed following electrophoresis.

Determination of relevant clinical data: A variety of indicators such as blood pressure, smoking and alcohol consumption were obtained from the questionnaires and on-site examination. Biochemical indexes such as total cholesterol (TC), triglyceride (TG) and blood glucose were measured using an automated microplate reader.

Statistical analysis: The SPSS 16.0 software package was used for the statistical analysis. The χ^2 goodness of fit test was applied to analyze whether the distribution of the genotype frequencies in the patient group and the control group fit the Hardy-Weinberg (HW) equilibrium. The measured data between the two groups were compared using a t test. For more than two groups, one-way analysis of variance (ANOVA) was applied, and the least-significant-difference (LSD) method was used for pairwise comparison. The enumeration data between the two groups were compared using a χ^2 test. The impacts of various risk factors on lacunar infarction were statistically analyzed using multivariate logistic regression analysis, and the respective odds ratios (OR) and 95% confidence intervals (CI) were calculated. $P < 0.05$ was considered statistically significant.

Results

Comparison of the clinical data between the patient group and the control group

The comparison of clinical data between the patient group and the control group showed that the differences in age and gender were not statistically significant. The number of cases with a history of primary hypertension, diabetes mellitus, smoking or drinking in the patient group was significantly higher than that in the control group, as shown in **Table 1**. The comparison of biochemical data between the patient group and the control group showed that the differences in fasting plasma glucose (FPG), TC and apolipoprotein B (Apo-B) were not statistically significant. However, the levels of HDL-C, low-density lipoprotein cholesterol (LDL-C) and apolipoprotein A1 (Apo-A1) in the patient group were significantly lower than those in the control group ($P < 0.05$). The TG level in the patient group was also significantly higher than that in the control group ($P < 0.05$), as shown in **Table 2**.

H-W equilibrium test

The results for the observed and expected values of the genotypes at the polymorphism locus rs9958947C>T in the patient group and the control group were in H-W equilibrium, with a good fit. For the patient group $P = 0.271$; for the control group, $P = 0.364$. These results indicated that the samples in both groups were representative of the population, as shown in **Table 3**.

Table 4. Comparison of genotypes and alleles in LIPG gene promoter rs9958947C>T between 2 groups

Models	Genotypes	Case [(n, %)]	Control [(n, %)]	*P* values	OR (95% CI)
Dominant	CC	84 (22.22)	136 (33.66)		
	CT+TT	294 (77.78)	268 (66.34)	0.004	1.7761 [1.292~2.441]
Recessive	CC+CT	284 (76.13)	322 (79.70)		
	TT	94 (24.87)	82 (20.30)	0.127	1.299 [0.928~1.820]
Co-Dominant	CC	84 (22.22)	136 (33.66)		
	CT	200 (52.91)	186 (46.04)	0.001	1.741 [1.242~2.440]
	TT	94 (24.87)	82 (20.30)	0.004	1.8560 [1.242~2.775]

Table 5. Genotypes in LIPG and lipids levels

Parameters	Genotype (n)			*P* value	
	CC (n = 220)	CT (n = 386)	TT (n = 176)	Dominant	Recessive
TG (mmol/L)	5.07 ± 1.18	4.79 ± 0.94	4.93 ± 0.89	0.443	0.307
TC (mmol/L)	1.30 ± 0.91	1.43 ± 0.94*	1.44 ± 0.81*	0.004	0.132
HDL-C (mmol/L)	1.45 ± 0.44	1.35 ± 0.36*	1.31 ± 0.34*	0.021	0.119
LDL-C (mmol/L)	2.58 ± 0.79	2.57 ± 0.61	2.62 ± 0.77	0.342	0.301
Apo-AL (g/L)	1.20 ± 0.21	1.26 ± 0.27	1.20 ± 0.25	0.321	0.563
Apo-B (g/L)	0.96 ± 0.33	0.97 ± 0.34	0.82 ± 0.27*	0.003	0.108

*: $p < 0.05$ when compared with CC group.

Table 6. Logistic regression analysis of risk factors for lacunar infarction

Parameters	OR	95% CI	*P* value
T allele	3.54	1.932~5.332	< 0.001
Gender	2.342	1.654~3.434	< 0.001
Smoking	15.23	10.218~30.212	< 0.001
Diabetes	3.121	1.765~5.673	< 0.001
Hyperlipidemia	2.131	1.342~2.986	0.004
Hypertension	12.212	8.021~20.132	< 0.001

Distribution of the genotype and allele of rs9958947C>T

The CT+TT genotype frequency in the patient group under the dominant model was greater than that in the control group, and this difference was statistically significant. The CT and TT genotype frequencies in the patient group under the dominant model were higher than those in the control group, and these differences were also statistically significant, as shown in **Table 4**.

Genotype of rs9958947C>T and the level of blood lipids

The genotypes of polymorphism rs9958947C>T in the LIPG gene promoter includes three genotypes of CC/CT/TT. The study subjects were grouped based on their genotype and the genetic models, and the corresponding serum lipid levels were calculated for each genotype. Comparison of the genetic models showed that the differences in age and gender among the different groups were not statistically significant. The dominant model was CT+TT compared to CC, the recessive model was TT compared to CT and TT, and the co-dominant models were CT compared to CC and TT compared to CC. In the CT+TT group of the dominant model, the levels of Apo-B and HDL-C were lower than those in the CC group, while the TG level was higher than that in the CC group, and the differences were statistically significant. The differences of various indicators among different groups of the recessive model were not statistically significant. In the co-dominant model, the TG, TC and Apo-A1 levels in the CT group and TG level in the TT group were statistically significantly different compared with the CC group ($P < 0.05$). The detailed data are shown in **Table 5**.

Multivariate logistic regression analysis of risk factors for lacunar infarction

All subjects in the patient group and the control group were analyzed as a single group. With the

factors of gender, age, smoking, high cholesterol, diabetes and T allele as the dependent variables, the stepwise logistic regression analysis was performed with multiple variables. The results showed that the T allele, male sex, smoking, hypertension, hyperlipidemia and diabetes were risk factors of lacunar infarction. The detailed data are shown in **Table 6**.

Discussion

The mortality of stroke has dropped significantly in recent years [19]. However, stroke remains a main cause of death in undeveloped or developing countries. Because a therapeutic drug with significant effects has not been found, prevention is currently the best way to reduce the burden on health care for individuals, families and the community. For complex diseases such as stroke, the key is to identify the risk factor of the pathogenesis. External risk factors such as lifestyle and the environment are easy to control with intervention, while the genetic factors are not easy to change or control; therefore, identifying these genetic risk factors is crucial for prevention in individuals with a high risk. Because environmental factors can affect the susceptibility of genetic factors to stroke, correlation studies for genetic factors and stroke incidence have been carried out after a variety of environmental factors were controlled.

Lacunar infarction is one subtype of cerebral infarction, and its occurrence is related to sustained hypertension and cerebrovascular atherosclerotic lesions. With the improvement of living conditions, the incidence of lacunar infarction continues to rise. The LIPG gene is related to lipid metabolism and the occurrence of atherosclerosis. Recent studies have further shown that LIPG can regulate the metabolism of HDL-C [3], and variations in the LIPG gene sequence can affect the HDL-C level in the plasma [10]. Animal experiments have also demonstrated that, in a hypertension model, angiotensin-2 and phorbol-12-myristate-13-acetate (PMA) stimulated the over-expression of LIPG, and the EL level in a model of hypertension in rats was up-regulated in a variety of tissues including the heart. The 584 C>T polymorphism in the UPG gene is associated with the main form of atherosclerotic cerebral infarction in Japanese women. No *et al.* [18] found that the rs9958947C>T polymorphism in the LIPG gene promoter was associated with the incidence of ischemic stroke in elderly and female patients in South Korea.

The current study investigated the correlation between the rs9958947C>T SNP in the LIPG gene promoter and lacunar cerebral infarction in China. The results revealed that the rs9958947C>T polymorphism is associated with the incidence of lacunar infarction in the Han population. In particular, individuals carrying the T allele are at a significantly increased risk of lacunar infarction, and the T allele of this locus may therefore serve as an independent risk factor of lacunar infarction. The polymorphism at this locus was also associated with abnormal lipid metabolism, as T allele carriers showed elevated TG levels and lowered levels of Apo-B and HDL-C. Combined with the logistic regression analysis, our findings suggest that the possible mechanism for the correlation between the polymorphism at this locus and cerebral infarction may be that the C/T allele at this locus directly results in the occurrence of lacunar infarction, further causing cerebral infarction by affecting the levels of HDL-C and other components in the plasma. Due to the geographical and population differences for correlation studies between genes and diseases, further study is needed to confirm our results in different populations and different areas in order to clarify the pathogenesis of ischemic cerebrovascular disease.

Conclusion

SNP rs9958947 in the LIPG gene promoter is associated with the incidence of lacunar infarction in Han Chinese population.

Disclosure of conflict of interest

None.

Abbreviations

SNP, Single nucleotide polymorphism; LIPG, endothelial lipase gene; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; HL, hepatic lipase; LPL, lipoprotein lipase; PL, pancreatic lipase; HDL-C, High-density lipoprotein cholesterol; GWAS, genome-wide association studies; CT, computed tomography; MRI, magnetic resonance imaging; EDTA, ethylenediaminetetraacetic acid; TC, total cholesterol; TG, Triglyceride; HW, Hardy-Weinberg; ANOVA, one-way analysis of vari-

ance; LSD, least-significant-difference; OR, odds ratios; CI, confidence intervals; FPG, fasting plasma glucose; LDL-C, low-density lipoprotein cholesterol; Apo-A1, apolipoprotein A1.

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