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Superoxide Dismutase Gene Polymorphism is Associated With Ischemic Stroke Risk in the China Dali Region Han Population

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Background: Stroke is a serious cardiovascular disease, a major cause of disability and death in both developed and developing countries. Superoxide dismutases (SODs) are enzymes that catalyze the breakdown of superoxide into oxygen and hydrogen peroxide and play a key role in the antioxidant response. This study explored the relationship between single-nucleotide polymorphisms (SNPs) in *SOD* genes and the risk of ischemic stroke (IS) in the Chinese Han population of Dali City.

Methods: For this case-control study, the authors enrolled 144 patients who had an IS and 128 healthy controls. The SNPs rs17880487 and rs80265967 of the *SOD1* gene, rs4880 and rs2842960 of the *SOD2* gene, and rs2695232 and rs7655372 of the *SOD3* gene were detected through TaqMan polymerase chain reaction. Genotypes and allele frequencies of the 2 groups were compared. Odds ratio and 95% confidence intervals were calculated by unconditional logistic regression, and environmental factors were corrected with multivariate logistic regression analysis.

Results: Rs7655372 of *SOD3* was associated with a significantly increased risk of IS. Moreover, the A and GA genotypes of SNP rs7655372 were associated with increased risk of IS, whereas the A and GA genotypes were risk factors for IS. Furthermore, multivariate logistic regression analysis showed that the rs7655372 GA genotype is the independent risk factor for IS.

Conclusion: The *SOD3* gene rs7655372 locus polymorphism is a risk factor for IS in the Dali region.

Key Words: ischemic stroke, superoxide dismutases, gene polymorphism

(*The Neurologist* 2021;26:27–31)

BACKGROUND

Ischemic stroke (IS) is one of the most complex cardiovascular diseases associated with high morbidity, disability, death, and recurrence rate.[1,2] According to the World Health Organization, 15 million people suffer strokes worldwide each year, >6 million people die, and another 5 million are permanently disabled.[3,4] In China, IS is the second leading cause of death and one of the main causes of adult disability.[5,6] IS-associated pain and comorbidities significantly impact the quality of life of patients, increasing the burden on their families and society. Therefore, effective prevention and treatment strategies are urgently needed.

IS is a nervous system disorder with multiple complex factors, including modifiable risk factors (environment) and nonmodifiable risk factors (heredity). The traditional risk factors for IS include smoking, lack of exercise, an unhealthy diet, and some diseases, such as obesity, diabetes, arteriosclerosis, hypertension, atrial fibrillation, and dyslipidemia.[7] Epidemiology studies support that there are genetic factors associated with stroke, and gene polymorphisms may regulate the pathophysiological process of IS.[8]

Superoxide dismutases (SODs) are a class of antioxidant enzymes that play a pivotal role in reducing oxidative stress and maintain intracellular and extracellular oxidant/antioxidant balance. SODs exert their effects by catalyzing the dismutation of superoxide into oxygen and hydrogen peroxide, scavenging the oxygen-free radicals.[9] Oxidative stress is the excessive accumulation of reactive oxygen species (ROS) and is a major cause of cardiovascular disease.[10,11] There are 3 isoforms of SODs including the copper-and-zinc-containing SODs (CuZn-SOD/SOD1), which is primarily located in the cytoplasm; manganese SOD (Mn-SOD/SOD2), which is located in the mitochondria; and extracellular SOD (EC-SOD/SOD3).[12,13]

Recent studies have found that *SODs* gene variations are associated with the risk of different diseases, including cardiovascular diseases. The Alachkar study reported that the CC genotype of rs4880 is associated with increasing hepatotoxicity following asparaginase-based treatment.[14] Ghattas and Abo-Elmatty[15] reported that in the Egyptian population, individuals with rs2234694 CC genotype showed an increased risk of T2DM. Otaki et al[16] found, in a study on 2799 healthy subjects, that rsl041740 and rsl7880487 in the *SODl* gene were related to cardiovascular mortality. However, the relationship between the SOD and the risk of IS remains unclear.

Here, we conducted a case-control study to investigate the polymorphisms in the *SOD* genes of 144 patients who had an IS and 128 healthy controls to determine whether these SNPs are associated with increased risk of IS in the China Dali region Han population. Our results are expected to contribute valuable insights into the potential role of *SOD* gene polymorphisms in IS, which might help in the development of prevention and targeted treatment strategies for IS.

METHODS

Study Subjects

The study subjects consisted of 144 patients who had an IS (80 male and 64 female individuals) and 128 control patients

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X.Y.: designed the experiments, draft the manuscript. S.Y. and H.X.: analyzed the data. X.Y. and D.L.: collect specimen. Y.Z. and G.W.: revised the manuscript.

This study was supported by National Natural Science Foundation of China (No. 81360206); Scientific research fund project of Yunnan education department (2019J0775); Colleges joint-specific project in Yunnan Province [2019FH001-(020)].

The authors declare no conflict of interest.

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ISSN: 2331-2637/21/2602-0027
DOI: 10.1097/NRL.0000000000000301

(68 male and 60 female individuals), who were recruited from outpatient and inpatient services in the first affiliated hospital of Dali University from August 2018 to August 2019. The diagnosis of IS was on the basis of the World Health Organization standards of thrombotic patients with cerebral infarction and neurological abnormalities confirming thrombotic cerebral infarction with computed tomography or magnetic resonance imaging. The inclusion criteria for the group which included patients who had an IS were as follows: (1) IS diagnosis was according to the updated definition of stroke for the 21st century[17]; (2) the individual and their family were residents of Dali City for >3 generations. Patients with the following conditions were excluded: hemorrhagic stroke, transient ischemic attack, cerebrovascular malformation, and IS caused by trauma. The control group individuals were free of cardiovascular and cerebrovascular diseases, autoimmune disorders, malignant tumors, immunologic diseases, neurological deficits, severe hepatic, and renal dysfunction. Furthermore, there was no sibship between the selected control subjects and the patients who had an IS or study subjects from the Dali region who had lived there for over 3 generations. In this study, some clinical data were collected, such as age, sex, fasting blood glucose (FBG), red blood cells (RBCs), white blood cells (WBCs), total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), systolic blood pressure (SPB), diastolic blood pressure (DBP), and body mass index (BMI). The study protocol was approved by the Medical Ethics Committee of the first affiliated hospital of Dali University, and all participants provided informed consent.

SNP Selection and Genotyping

About 5 mL of peripheral blood samples were collected into tubes containing ethylenediaminetetraacetic acid. Genomic DNA was extracted according to the manufacturer's protocols (Bomaide Technology, Beijing, China) and stored at −80°C until analysis. Six SNPs of *SODs* were genotyped with TaqMan polymerase chain reaction.

According to the National Center for Biotechnology Information database, 6 SNPs rs17880487, rs80265967, rs4880, rs2842960, rs2695232, and rs7655372 of SODs were selected. The amplification was performed in a 25 μL volume, 12.5 μL 2×Taq enzyme mixture, 0.5 μL CF forward primer, 0.5 μL TF forward primer, 1 μL R reverse primer, 8.5 μL ddH_2O, and 2 μL DNA sample. Reaction conditions were as follows: predegeneration at 95°C for 5 minutes, denaturation at 95°C for 10 seconds, annealing at 60°C for 30 seconds, followed by 30 cycles of extension at 72°C for 2 minutes, and conservation at 16°C for 5 minutes. Primers were designed using the Primer 5 software. The sequences of the primers and probes from Anhui General Biosystems are listed in Table 1.

Statistical Analyses

The statistical analyses were performed using SPSS V.19.0 software. Hardy-Weinberg equilibrium (HWE) was assessed by HWE software for SOD SNP genotype distribution in the controls. A *P*-value >0.05 indicated a balanced genetic and Mendelian population. Count data and quantitative data were processed using the *t* test and χ^2 test, respectively. Multivariate logistic regression analysis was performed after adjusting for age, gender, FBG, WBC, RBC, TC, TG, LDL, SBP, DBP, and BMI to test the correlation between gene variation and risk of IS. Odds ratio (OR) and 95% confidence interval (CI) were calculated using unconditional logistic regression, and codominant, dominant, recessive, and additive were used to assess these relationships. A *P*-value <0.05 was considered significant.

TABLE 1. Primer Sequences Used in This Study

SNP	Primer	Sequence
rs17880487	CC	5′-TATTATGAGGCTATTAAAAGAATCC-3′
	TT	5′-TATTATGAGGCTATTAAAAGAATCTT-3′
	Reverse	5′-ATCAGAGCTAATTTAGTTTGAATTT-3′
rs80265967	AA	5′-GAGACTTGGGCAATGTGACTGCTGA-3′
	CC	5′-GAGACTTGGGCAATGTGACTGCTGC-3′
	Reverse	5′-AGACACATCGGCCACACCATCTTTG-3′
rs4880	CC	5′-TGCCTGGAGCCCAGATACCCCAAAG-3′
	TT	5′-TGCCTGGAGCCCAGATACCCCAAAA-3′
	Reverse	5′-AGCACCAGCAGGCAGCTGGCTCCGG-3′
rs2842960	CC	5′-GAGACCAAACATTTCCCCAAAGCAC-3′
	TT	5′-GAGACCAAACATTTCCCCAAAGCAT-3′
	Reverse	5′-ATTGAAATTGTTCTTGTTGTATAAT-3′
Rs2695232	CC	5′-TTCTCCTCTGCTCCAACAGACACCC-3′
	TT	5′-TTCTCCTCTGCTCCAACAGACACCT-3′
	Reverse	5′-GGCGAAGGTGAGACCTCAGAGTGGA-3′
Rs7655372	AA	5′-TGCCCTAGATGAGAGATGTGCAGTA-3′
	GG	5′-TGCCCTAGATGAGAGATGTGCAGTG-3′
	Reverse	5′-CTCCAAGCCCAAGGTTTAGGCACCA-3′

SNP indicates single-nucleotide polymorphism.

RESULTS

Clinical Characteristics

The main clinical characteristics of the control and IS groups are summarized in Table 2. Significant differences between the groups were found in the following tests: FBG, WBC, RBC, TC, TG, LDL, and SBP. However, no significant differences were noted in age, sex, DBP, or BMI (Table 2).

Hardy-Weinberg Balance Analysis

The genotype frequencies of 6 SNPs followed HWE in the control subjects ($P > 0.05$ for 6 SNPs), these results indicated a balanced genetic and Mendelian population, the results as demonstrated in Table 3.

SODs Polymorphism and Risk of IS

The genotype distributions of 6 SNPs of SOD genes between the IS and controls and their association with IS are summarized in Table 4.

Rs80265967 of the *SOD1* gene showed no polymorphism, whereas the other 5 sites showed polymorphism. Different genetic models were used to analyze the association between

TABLE 2. Characteristics of IS Patients Who Had an IS and Controls

Characteristics	Patients Who Had an IS	Controls	*P*
Age (y; mean ± SD)	58.63 ± 12.97	57.59 ± 14.01	0.516
Male gender (n)	80	68	0.824
FBG (mmol/L; mean ± SD)	6.25 ± 2.73	4.75 ± 0.87	0.000
WBC (10^{12}/L; mean ± SD)	7.79 ± 2.32	6.27 ± 1.57	0.000
RBC (10^{12}/L; mean ± SD)	4.81 ± 0.72	4.97 ± 0.55	0.004
TC (mmol/L; mean ± SD)	5.01 ± 1.29	4.33 ± 0.42	0.000
TG (mmol/L; mean ± SD)	1.72 ± 1.40	1.35 ± 0.75	0.008
LDL (mmol/L; mean ± SD)	3.05 ± 1.06	2.82 ± 0.72	0.033
SBP (mm Hg; mean ± SD)	144.92 ± 25.88	133.85 ± 15.34	0.000
DBP (mm Hg; mean ± SD)	86.46 ± 13.02	84.66 ± 10.40	0.205
BMI (kg/m^2; mean ± SD)	23.15 ± 3.28	22.84 ± 3.91	0.478

BMI indicates body mass index; FBG, fasting blood glucose; IS indicates ischemic stroke; SNP, single-nucleotide polymorphism.

TABLE 3. Hardy-Weinberg Results of Control and IS

	χ^2		*P*	
SNP	**Control**	**IS**	**Control**	**IS**
rsl7880487	0.258	0.347	0.611	0.556
rs4880	0.21	0.55	0.65	0.46
rs2842960	0.68	0.23	0.41	0.63
rs2695232	4.078	0.155	0.053	0.693
rs7655372	0.07	0.589	0.786	0.442

IS indicates ischemic stroke; SNP, single-nucleotide polymorphism.

the tested SNPs and the risk of IS in the 5 loci of the *SOD* genes. Allele A and genotype GA of rs7655372 were related to significantly increased risk of IS. In the log-additive, GA/GG was associated with a 2.722-fold increase in IS risk (OR = 2.722; 95% CI, 1.039-7.132; $P = 0.042$; adjusted OR = 5.128; 95% CI, 1.558-16.881; $P = 0.007$). The allele A/G was associated with a 2.722-fold increase in IS risk (OR = 2.722; 95% CI, 1.039-7.132; $P = 0.042$; adjusted OR = 5.128; 95% CI, 1.558-16.881; $P = 0.007$). Following adjustments for age, sex, FBG, RBC, WBC, TC, TG, LDL, and SBP, the allele GA/GG were found to increase the risk of stroke ($P = 0.007$).

TABLE 5. Rs7655372 Multivariate Logistic Regression Analysis of Independent Risk Factors for IS

Variables	***B***	**SE**	**Wals**	***P***	**OR**	**95% CI**
Sex	0.150	0.272	0.305	0.581	1.162	0.682-1.979
Age	0.011	0.010	1.178	0.278	1.011	0.991-1.032
Hypertension	2.189	0.638	11.785	0.001	8.928	2.558-31.156
Hyperlipidemia	1.057	0.275	14.798	0.000	2.879	1.680-4.935
Diabetes	1.105	0.320	11.948	0.001	3.020	1.614-5.652
GA	1.159	0.527	4.832	0.028	3.188	1.134-8.962

The genotype GG was defined as 1, logistics regression calibration traditional risk factors (sex, age, hypertension, hyperlipidemia, and diabetes).

B indicates partial regression coefficient; CI, confidence interval; IS, ischemic stroke; OR, odds ratio; SE, standard error of partial regression coefficient; Wals: ratio of square *B* to SE.

Independent risk factors (sex, age, hypertension, hyperlipidemia, and diabetes) were identified for IS in rs7655372 by multivariate logistic regression analysis. As depicted in Table 5, after calibration results are still statistically significant, additive model GA risk of stroke in GA was 3.188-fold that in GG ($P = 0.028$; 95% CI, 1.134-8.962), indicated that rs7655372 may be an independent risk factor for stroke.

TABLE 4. Genotype Frequencies of SODs Gene Polymorphisms in Cases and Controls and Their Associations With IS

		n (%)					
SNP	**Genotype**	**Case**	**Control**	**OR (95% CI)**	***P***	**Adjusted OR (95% CI)**	**Adjusted *P***
rsl7880487	CC	131 (90.97)	117 (91.41)	Reference	Reference		
	CT	13 (9.03)	11 (8.59)	1.056 (0.455-2.447)	0.900	0.879 (0.277-2.789)	0.827
	TT	0	0				
	C	275 (95.49)	245 (95.70)	Reference	Reference		
	T	13 (4.51)	11 (4.30)	1.056 (0.455-2.447)	0.900	0.879 (0.277-2.789)	0.827
rs80265967	AA	155 (100)	122 (100)	—	—	—	—
rs4880	TT	105 (72.92)	96 (75)	Reference	Reference		
	TC	37 (25.69)	29 (22.66)	1.167 (0.667-2.041)	0.589	1.045 (0.486-2.250)	0.91
	CC	2 (1.39)	3 (2.34)	0.610 (0.10-3.726)	0.592	0.86 (0.104-7.108)	0.889
Dominant	CC+CT vs TT			1.114 (0.647-1.918)	0.696	1.026 (0.490-2.149)	0.945
Recessive	CC vs CT+TT			0.587 (0.096-3.569)	0.563	0.851 (0.104-6.974)	0.88
	T	247 (85.76)	221 (86.33)	Reference	Reference		
	C	41 (14.24)	35 (13.67)	1.049 (0.643-1.709)	0.849	1.005 (0.527-1.914)	0.989
rs2842960	CC	106 (73.61)	94 (73.43)	Reference	Reference		
	CT	34 (23.61)	30 (23.44)	1.005 (0.572-1.767)	0.986	0.947 (0.438-2.047)	0.889
	TT	4 (2.78)	4 (3.13)	0.887 (0.261-3.645)	0.868	0.868 (0.128-5.886)	0.885
Dominant	TT+TC vs CC			0.991 (0.578-1.700)	0.974	0.963 (0.462-2.007)	0.921
Recessive	TT vs TC+CC			0.886 (0.217-3.616)	0.866	0.105 (0.179-6.832)	0.915
	C	246 (85.42)	226 (85.61)	Reference	Reference		
	T	42 (14.58)	38 (14.39)	0.981 (0.618-1.555)	0.934	0.985 (0.531-1.829)	0.962
rs2695232	CC	53 (36.81)	44 (34.37)	Reference	Reference		
	CT	67 (46.53)	71 (55.47)	0.783 (0.465-1.319)	0.358	1.024 (0.513-1.829)	0.962
	TT	24 (16.66)	13 (10.16)	1.533 (0.699-3.358)	0.286	1.334 (0.475-3.742)	0.585
Dominant	TT+TC vs CC			0.899 (0.547-1.479)	0.676	1.083 (0.560-2.094)	0.813
Recessive	TT vs TC+CC			1.769 (0.860-3.641)	0.121	1.316 (0.506-3.423)	0.574
	C	173 (60.07)	159 (62.11)	Reference	Reference		0.65
	T	115 (39.93)	97 (37.89)	1.096 (0.767-1.567)	0.614	1.117 (0.692-1.803)	0.65
rs7655372	GG	127 (88.19)	122 (95.31)	Reference	Reference		
	GA	17 (11.81)	6 (4.69)	2.722 (1.039-7.132)	0.042※	5.128 (1.558-16.881)	0.007※
	AA	0	0				
	G	271 (94.10)	250 (97.66)	Reference	Reference		
	A	17 (5.90)	6 (2.34)	2.722 (1.039-7.132)	0.042※	5.128 (1.558-16.881)	0.007※

Adjusted by age, sex, fasting blood glucose, red blood cells (RBCs), white blood cells (WBCs), total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), systolic pressure (SPB) and diastolic pressure (DBP).

※*P*-value < 0.05 was considered significant.

CI indicates confidence interval; IS, ischemic stroke; SOD, superoxide dismutase.

DISCUSSION

IS is a complex neurological disease caused by many factors, which is related to environmental factors and genetic factors, and gene variation has become one of the important factors of ischemic stroke. This cerebrovascular disease is related to age, sex, and genetic factors, and is directly related to hypertension, smoking, diabetes, hyperlipidemia, coronary heart disease, hyperhomocysteine, and other factors.[18] Recent epidemiology studies suggested that IS was closely related to genetic factors. Single-nucleotide polymorphisms (SNPs) are the most common types of deoxyribonucleic acid (DNA) variants in humans caused by the stable substitution of a single nucleotide from a point mutation in the genome. Today, the latest advances in molecular genetics have allowed people to realize that an SNP was closely related to the pathogenesis of a stroke.[19] Ischemic stroke results in increased levels of ROS such as superoxide anions (O^{2-}), hydroxyl radical (OH^-), and hydrogen peroxide (H_2O_2) in the blood. Increased ROS levels are associated with reperfusion injury.[20] ROS damaged cellular proteins, lipids, DNA, disrupted normal cellular signaling, and gene regulation.[21]

In a normal physiological state, a major source of ROS would be the mitochondria. ROS is the product of oxidative phosphorylation in the mitochondrial respiratory chain, where it scavenges catalase, glutathione peroxidase, glutathione reductase, and superoxide dismutase through antioxidants.[22] SODs are endogenous enzymes that convert superoxide anions into hydrogen peroxide and oxygen; SOD1 is considered an important cellular enzyme as it plays a key role in the protection of cells from damage caused by superoxide free radicals under stress conditions such as high temperature and humidity. Moreover, SOD1 acts as an antioxidant enzyme that maintains the oxidation/antioxidant balance either intracellularly and extracellularly, catalyzed the mutation of superoxide radicals into oxygen and hydrogen peroxide.[23] SOD2 scavenged about 80% of the free radicals in the oxidation and phosphorylation processes associated with the mitochondria. Incomplete scavenging of ROS leads to increased free radical levels, which could cause lipid peroxidation and severe cell and tissue damage.[24] SOD3, which is encoded by a gene distinct from that of CuZn-SOD, is composed of 240 amino acids and harbors an 18-amino-acid-long signal peptide that targeted proteins for the extracellular compartment.[25]

In the case-control study, 6 SNPs of *SOD* genes were investigated to determine their association with the risk of IS in the China Dali region Han population. SNP rs7655372 was found to be associated with an increased risk of IS in the Dali population; however, no significant correlation was found between IS and the other investigated SNPs. Six sites were included: rs17880487 and rs80265967 in the *SOD1* gene, rs4880 and rs2842960 in the *SOD2* gene, and rs2695232 and rs7655372 in the *SOD3* gene.

Rs17880487 is located on chromosome 21:31668917, presenting a 3′ UTR variant and a downstream transcript variant. Rs80265967 is located on chromosome 21:31667290, presenting a missense variant and a coding sequence variant. Otaki et al[16] reported that rsl7880487 was associated with cardiovascular mortality, but the present study showed no correlation between the rsl7880487 and IS in the Dali population. Furthermore, rs80265967 did not exhibit polymorphisms in this study. Rs4880 is located on chromosome 6:159692840, presenting a coding sequence variant, missense variant, and 5′ UTR variant. Rs2842960 is located on chromosome 6:159692289, presenting an intron variant and a 3′ UTR variant. Rs4880 and rs2842960 loci are located in the promoter region of the *SOD2* gene. Promoter region SNPs could alter gene expression, leading to the development of various diseases. The spatial conformation of a signal peptide could be changed by the rs4880 mutation of the *SOD2* gene, thus reducing the rate of transport to the mitochondria and the entry of SOD2 into the mitochondria, where it plays an antioxidant role. This disruption of SOD2 transport increases oxidative stress, leading to cardiovascular disease. The mutation is allele C transform into T could change alanine (Ala) to valine (Val) in the position of the signal peptide, at this point, the signal peptide space transformed from α helix to β fold, α helix is amphiphilic, which induced SOD2 from the cytoplasm to the mitochondria; β folding affected the proper identification of the signal peptides and related receptors on the mitochondrial membrane, exhibited reduced the transcriptional activity of SOD2 to the mitochondria by 30% to 40% affect the entry of SOD2 into mitochondria to play an antioxidant role, the convert increased the risk of coronary artery disease.[26] Mutations in the *SOD2* gene increase the risk of developing cancer; *SOD2* SNP rs4880 (T > C) resulted in conformational changes of the protein helix structure, an increased risk of oral cancer, and has been linked to a variety of others cancers.[27] Studies have shown that rs4880 SNP (T > C changes at the nucleotide level) at codon 16 causes alanine (GCT) to replace valine (GTT).[28] The C allele of *SOD2* rs4880 has been reported to retain the protein helix structure in many diseases and maintained the normal activity of the enzymes related to Alzheimer's disease[29]; however, the polymorphism of rs2842960 (C > T) has been rarely studied, and therefore, the association with disease is unclear. In the present study, our results showed that there was not a significant association between rs4880, rs2842960 polymorphism, and IS in the Dali population. Rs2695232 is located on chromosome 4: 24800327, presenting a noncoding transcript variant and a 3′ UTR variant. Rs7655372 is located on chromosome 4: 24797264, presenting an intron variant. Currently, there are no reports of these 2 SNPs being associated with diseases. However, studies have shown that the polymorphism of the other *SOD3* locus was correlated with disease. The *SOD3* Ala40Thr missense mutation (GCG-ACG) was associated with susceptibility to type 2 diabetes by increasing the risk of type 2 diabetes.[30] Takahiro studied the correlation between the polymorphism of *SOD3* and cerebral infarction. The frequency of C-C-C haplotype in the female *SOD3* polymorphisms (rs13306703, rs699473, and rs1799895) was significantly higher in patients with cerebral infarction than in the control group. Therefore, SOD3 haploid C-C-C might be a marker of female cerebral infarction.[31]

In this study, the rs7655372 A allele and GA genotype increased the risk of IS; allele A/G and log-additive GA/GG were associated with a 2.722-fold increase in IS risk. By multivariate logistic regression analysis, the A and GA genotypes were risk factors for IS, indicated that *SOD3* gene polymorphism is associated with the risk of stroke, and rs7655372 A and GA were risk factors for IS in the Chinese Han population of Dali City. Polymorphisms of the other loci had no correlation with the risk of IS. We analyzed the genotype of rs7655372 (G > A) locus and found that there was no homozygous of AA; therefore, allele (A/G) and additive (GA/GG) were selected for analysis. The allele testing and the additive model indicated that rs7655372 increased the risk of IS 2.722-fold. After adjusting the risk factors, A and GA of rs7655372 were still found to be risk factors for IS in the Chinese Han population of the Dali City. In addition to traditional stroke risk factors such as hypertension, hyperlipidemia, and diabetes, this SNP might be an independent risk factor for stroke. However, no data about

the relationship between rs7655372 and the risk of IS have been reported.

Our results indicate that polymorphisms of rs7655372 increase the risk of IS in the Chinese Han population of the Dali City. However, this study has some limitations: first, our samples were generated from the Han Chinese population of Dali City, and hence, the findings are not applicable to other ethnicities. In addition, the regional disparity could lead to possible inconsistencies in the role of the SNPs of the same locus in similar diseases of different ethnic groups and different diseases of the same ethnic group.

CONCLUSION

We found that the association of rs7655372 of *SOD3* with the risk of IS in the Dali population and that the rs7655372 allele A and GA genotype significantly increased the risk of IS. The findings provide valuable insights for future explorations of IS pathogenesis, which could enable the development of prevention, early detection, and treatment strategies.

ACKNOWLEDGMENTS

The authors thank all patients in this study and all the research staff for their contributions to this project.

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