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 by 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 SOD1 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)

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Million people suffer strokes worldwide each year, >6 million people die, and another 5 million are permanently disabled. In China, IS is the second leading cause of death and one of the main causes of adult disability. 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. Epidemiology studies support that there are genetic factors associated with stroke, and gene polymorphisms may regulate the pathophysiological process of IS.

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. Oxidative stress is the excessive accumulation of reactive oxygen species (ROS) and is a major cause of cardiovascular disease. There are 3 isoforms of SODs including the copper-and-zinc-containing SODs (Cu/Zn-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).

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 aspirin-based treatment. Ghattas and Abo-Ematty reported that in the Egyptian population, individuals with rs2234694 CC genotype showed an increased risk of T2DM. Otaki et al. found, in a study on 2799 healthy subjects, that rs014740 and rs7880487 in the SOD1 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...
(68 male and 60 female individuals), who were recruited from 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 diagnostic criteria for the 21st century1,2; (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 (SBP), 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 ddH2O, and 2 μL DNA sample. Reaction conditions were as follows: predenaturation 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 a χ2 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 models were used to assess these relationships. A P-value < 0.05 was considered significant.

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 SNPs and risk of IS.

| SNP | Primer | Sequence |
|-----|--------|----------|
| rs17880487 | CC | 5′-TATTATGAGGCTTAAAGAAGATCC-3′ |
| TT | 5′-TATTATGAGGCTTAAAGAAGATCTT-3′ |
| Reverse | 5′-ATGAAATGTCTTGATGATTAAATTT-3′ |
| rs80265967 | AA | 5′-GAGACTTTGGCAATTGTGACTGCTGA-3′ |
| CC | 5′-GAGACTTTGGCAATTGTGACTGCTGTA-3′ |
| Reverse | 5′-AGCACATCGCCCAACATCTTGGT-3′ |
| rs4880 | CC | 5′-TGGCTGAGGACGCTGAGACCCAC-3′ |
| TT | 5′-TGGCTGAGGACGCTGAGACCCACAAA-3′ |
| Reverse | 5′-AGCACACGAGCAGCTGTCGCCG-3′ |
| rs2842960 | CC | 5′-GAGACCCACATTTCCCACAGACGC-3′ |
| TT | 5′-GAGACCCACATTTCCCACAGACGTA-3′ |
| Reverse | 5′-ATTGAAAATGTCTTGATGATTAAATTT-3′ |
| rs2695232 | CC | 5′-TTTCCTCTCTGCTCCAAACAGACCC-3′ |
| TT | 5′-TTTCCTCTCTGCTCCAAACAGACACT-3′ |
| Reverse | 5′-GGCGGAAATGGTACCCAGAGTGGA-3′ |
| rs7655372 | AA | 5′-TCCCTTATGAGAGATGTGGACATGA-3′ |
| GG | 5′-TCCCTTATGAGAGATGTGGACATG-3′ |
| Reverse | 5′-CTCCAAGCCCGATTTAGGCGCACA-3′ |

SNP indicates single-nucleotide polymorphism.

| 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 (10^3/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 ± 0.73 | 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.
were found to increase the risk of stroke (FBG, RBC, WBC, TC, TG, LDL, and SBP, the allele 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 3. Hardy-Weinberg Results of Control and IS

| SNP      | Control | IS | OR (95% CI) | P       | Adjusted OR (95% CI) | Adjusted P |
|----------|---------|----|-------------|---------|----------------------|------------|
| rs7880487| 0.258   | 0.347| 0.611       | 0.556   | 0.879 (0.277-2.789)  | 0.827      |
| rs4880   | 0.21    | 0.55 | 0.65        | 0.46    | 0.86 (0.277-2.789)   | 0.827      |
| rs2642960| 0.68    | 0.23 | 0.41        | 0.63    | 0.879 (0.277-2.789)  | 0.827      |
| rs2659532| 4.078   | 0.155| 0.053       | 0.693   | 0.879 (0.277-2.789)  | 0.827      |
| rs7655372| 0.07    | 0.589| 0.786       | 0.442   | 0.879 (0.277-2.789)  | 0.827      |

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

| SNP      | Genotype | Case | Control | OR (95% CI) | P       | Adjusted OR (95% CI) | Adjusted P |
|----------|----------|------|---------|-------------|---------|----------------------|------------|
| rs7880487| CC       | 131  | 117     | Reference   | Reference| 1.056 (0.455-2.447)  | 0.900      |
|          | CT       | 13   | 11      | 1.056       | 0.900   | 0.879 (0.277-2.789)  | 0.827      |
|          | TT       | 0    | 0       | 1.056       | 0.900   | 0.879 (0.277-2.789)  | 0.827      |
| rs4880   | C        | 275  | 245     | Reference   | Reference| 1.056 (0.455-2.447)  | 0.900      |
|          | T        | 13   | 11      | 1.056       | 0.900   | 0.879 (0.277-2.789)  | 0.827      |
| rs80265967| AA      | 155  | 122     | Reference   | Reference| 1.056 (0.455-2.447)  | 0.900      |
| rs4880   | CC       | 105  | 96      | Reference   | Reference| 1.056 (0.455-2.447)  | 0.900      |
|          | TC       | 37   | 29      | 1.167       | 0.538   | 1.045 (0.486-2.250)  | 0.91       |
|          | TT       | 2    | 3       | 1.167       | 0.538   | 1.045 (0.486-2.250)  | 0.91       |
| rs8765372| AA       | 155  | 122     | Reference   | Reference| 1.056 (0.455-2.447)  | 0.900      |
|          | CT       | 37   | 29      | 1.167       | 0.538   | 1.045 (0.486-2.250)  | 0.91       |
|          | TT       | 2    | 3       | 1.167       | 0.538   | 1.045 (0.486-2.250)  | 0.91       |

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 than in GG (P = 0.028; 95% CI, 1.134-8.962), indicated that rs7655372 may be an independent risk factor for stroke.

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

| Variables | B      | SE     | Wals  | P       | OR (95% CI) | Adjusted OR (95% CI) | Adjusted P |
|-----------|--------|--------|-------|---------|-------------|----------------------|------------|
| Sex       | 0.150  | 0.272  | 0.305 | 0.581   | 1.162       | 0.682-1.979          | 0.007      |
| Age       | 0.011  | 0.010  | 1.178 | 0.278   | 1.011       | 0.991-1.032          | 0.007      |
| Hypertension | 2.189  | 0.638  | 11.785| 0.000   | 8.928       | 2.558-31.156         | 0.007      |
| Hyperlipidemia | 1.057  | 0.275  | 14.798| 0.000   | 2.879       | 1.680-4.935          | 0.007      |
| Diabetes   | 1.105  | 0.320  | 11.948| 0.000   | 3.020       | 1.614-5.652          | 0.007      |
| GA        | 1.159  | 0.527  | 4.832 | 0.028   | 3.188       | 1.558-8.962          | 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 (SBP) 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. 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. Ischemic stroke results in increased levels of ROS such as superoxide anions (O2−), hydroxyl radical (OH·), and hydrogen peroxide (H2O2) in the blood. Increased ROS levels are associated with reperfusion injury. ROS damaged cellular proteins, lipids, DNA, disrupted normal cellular signaling, and gene regulation.

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. 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. 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. 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.

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. R80265967 is located on chromosome 21:31667290, presenting a missense variant and a coding sequence variant. Otaki et al. reported that rs17880487 was associated with cardiovascular mortality, but the present study showed no correlation between the rs17880487 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. 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. Studies have shown that rs4880 SNP (T > C changes at the nucleotide level) at codon 16 causes alanine (GCT) to replace valine (GTT). 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; 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 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. Takahiro studied the correlation between the polymorphism of SOD3 and cerebral infarction. The frequency of 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 haplotype C-C might be a marker of female cerebral infarction.
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 rs76555372 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.

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