Original Article

Polymorphism of TNIP1 was associated with atherosclerotic ischemic stroke in southern Han Chinese but unrelated with telomere

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Abstract: Objective: To evaluate the association between atherosclerotic ischemic stroke (AIS) and single-nucleotide polymorphisms (SNP) in gene TERT, TNIP1, OBFC1 in southern Chinese Han population. Methods: Sequenom MassARRAY system was used to genotype 12 SNPs (rs10069690, rs2242652, rs2853677, rs2853676 in TERT; rs7708392, rs10036748, rs960709 in TNIP1; rs9325507, rs3814220, rs12765878, rs11191865, rs9420907 in OBFC1) in both atherosclerotic ischemic stroke patients (n=400) and healthy controls (n=399). Association analyses were performed in SNPstats platform in five genetic models (dominant, recessive, additive, codominant, overdominant). Analysis of allele frequencies and linkage disequilibrium were also conducted. Odd ratio (OR) and 95% confidence interval (95% CI) were adjusted for confounding factors (age, gender, past medical history, smoke, alcohol, blood lipid). Results: SNP rs7708392 was significantly associated with an increased risk of AIS after adjustment for above confounding factors in our population (heterozygous model P=0.04, OR=1.62, 95% CI 1.01-2.61 and overdominant model P=0.037, OR=1.64, 95% CI 1.03-2.62). None of the rest SNPs was observed to associate with AIS susceptibility in allele or any genetic model. No significant difference was found between the common haplotype in OBFC1 and TNIP1 and the risk of AIS. And there were no statistical significance between telomere length, serum lipid levels, hypertension, diabetes mellitus and rs7708392 genotype in the control group. Conclusion: TNIP1 rs7708392 polymorphism was first found to be associated with the occurrence of AIS, but the association may be independent of telomere, hypertension and diabetes mellitus. Further study should be conducted to confirm the association and to explore the role of this variant in the pathogenesis of AIS.

Keywords: SNP, stroke, cerebral infarction, TNIP1, TERT, OBFC1

Introduction

Stroke is the second most common cause of death and leading cause of adult disability worldwide [1]. In China, the annual stroke mortality rate has become the first leading cause of death and adult disability over heart disease [2]. Ischemic stroke (IS) accounts for about 62.4%-69.6% of all stroke cases [3]. Modifiable risk factors including hypertension, metabolic disturbances, smoking, and obesity are the most common of stroke. However, the genetic risk factors involved in stroke remains elusive.

Telomeres consist of DNA-protein complexes located at the end of the chromosomes, protecting and maintaining genetic integrity and stability. Evidences suggested that shorter telomere length was associated with an increased risk of age-related disease [4, 5], such as cardiovascular disease and ischemic stroke [6-10]. Telomere length shortening was considered to be an indicator of the cumulative burden of inflammation and oxidative stress [11]. Loss of protein A20, which binds with the protein (ABIN-1) encoded by the gene TNF α-induced protein 3-interacting protein 1 (TNIP1), resulted in inflammation and autoimmune responses with elevation of IL-6 [12, 13]. However, present studies mostly focused on the associations between TNIP1 gene polymorphisms and systemic lupus erythematosus [13, 14]. An in vivo
study indicated that ABIN-1 involved in the regulation of chronic inflammation and cardiovascular disease [15]. Telomerase reverse transcriptase protein (TERT) was considered as rate limiting catalytic subunit of telomerase [16]. Cumulative studies confirmed that polymorphisms of gene TERT were associated with telomere-related diseases including cancers, myocardial infarction, and IS [4, 17-19]. Oligonucleotide/oligosaccharide binding fold containing 1 (OBFC1) codes for oligosaccharide-binding fold-containing protein 1 and is part of CST complex, which is bind to the telomeric 3’ overhang and plays an important role in telomere maintenance [30].

Up to now, there were only few studies conducted on the correlation between SNPs (rs10069690, rs2242652, rs2853677, rs2853676, rs10036748, rs960709, rs9325507, rs3814220, rs12765878, rs11191865, rs7708392 and rs9420907) and atherosclerotic ischemic stroke (AIS). Thus, this case-control study was designed to assess if these variants conferred risk to AIS in southern Han Chinese, and the possible relation with telomere.

Materials and methods

Study population and sample collection

From February 2015 to March 2016, atherosclerotic ischemic stroke patients were recruited from the Department of Neurology of Affiliated Haikou Hospital of Xiangya Medical College of Central South University in Haikou city, Hainan province, China. The diagnostic criteria were defined as a sudden focal or global disturbance of cerebral function caused by vascular occlusion over 24 hours or longer, and further confirmed with computed tomography (CT) or magnetic resonance imaging (MRI). Newly diagnosed and only LAA (large vessel atherosclerosis) cases classified on TOAST [21] (Trial of Org 10172 in Acute Stroke Treatment) were included. Patients who had the following conditions were excluded: cardioembolism, brain trauma, tumors, transient ischemic attack, or cerebrovascular malformation; and inflammatory disease, collagenosis, or severe heart, liver, renal diseases. At the same time, the controls were enrolled from the health checkup center in the same hospital. The exclusion criteria included subjects diagnosed with any history of cerebrovascular and cardiovascular disease.

The case-control study protocol was approved by the Clinical Research Ethics of Haikou Municipal Hospital. Written informed consent was obtained from all the subjects or families participating in the present study.

A 3-5 ml sample of peripheral venous blood was collected from each participant, and temporarily stored at -20°C in the hospital central lab. Then the further study was completed in Northwest University (Xi’an city, Shaanxi province, China).

DNA isolation and genotyping assay

Genomic DNA was taken with the GoldMag-Mini Purification Kit (GoldMag Co. Ltd. Xian city, China) according to manufacturer’s protocols. DNA concentrations were qualified with the NanoDrop 2000 (Thermo Scientific, Waltham, Massachusetts, USA). Genotype were performed on the Sequenom MassARRAY RS1000 [22]. The results were managed and analyzed by Sequenom Typer 4.0 Software (Sequenom, Inc.).

Telomere length measurement

Real-time quantitative PCR (RT-PCR)-based method was used to calculate the relative telomere length (RTL) in a LightCycler®480 QPCR System (Roche, Basel, Switzerland). RTL was the ratio between the copy number of telomere repeats (T) and a single-copy gene copy number (S).

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables were shown as counts. Hardy-Weinberg equilibrium (HWE) in control group was tested by $\chi^2$ test. Kruskal-Wallis H test was used to assess the difference of telomere length among genotype of rs7708392. Independent sample t test and Chi-square ($\chi^2$) tests were used to test for the differences of measurement data and enumeration data between groups. The odds ratio (OR) and 95% confidence interval (CI) were calculated on SNPS-tats platform in five genomic models including dominant, co-dominant, additive, recessive, and overdominant model. A two-sided $P<0.05$ was considered to be statistically significant. Data analyses were done by Microsoft Excel.
The results suggested that rs7708932 within TNIP1 was associated with an increased risk of ischemic stroke. None of the rest SNPs had a significant difference with AIS susceptibility. The haplotype analysis showed that none of the common haplotype in TNIP1 and OBFC1 was associated with AIS risk.

Atherosclerosis, which originated from endothelial dysfunction, is a major cause of ischemic stroke. The detailed information about all SNPs included in this study was shown in Table 2. There was no significant difference from HWE in genotype frequencies in the control group for all SNPs. All the SNPs were not associated with AIS in allele model. CC genotype was not observed for rs9420907 in both case and control group. None of the following SNPs: rs10069690, rs2242652, rs2853677, rs2853676, rs10036748, rs960709, rs9325507, rs3814220, rs12765878, rs11191865, and rs9420907 were significantly different in any model after adjustment for the confounding factors between the AIS patients and the controls. Table 3 presented the association of rs7708392 with the risk of AIS in genetic models after adjustment for gender, age, smoking, alcohol, diabetes history, hypertension history, BMI, TC, TG, HDL-C, and LDL-C. A statistically significant difference was found in heterozygous (P=0.04, OR=1.62, 95% CI 1.01-2.61) and over-dominant model (P=0.037, OR=1.64, 95% CI 1.03-2.62).

Haplotypes and the risk of AIS

For further investigation of the correlation between SNPs and risk of AIS, linkage disequilibrium and haplotype analysis were conducted for the SNPs within the same gene. There was strong linkage disequilibrium among rs10036748, rs7708392, rs960709 within TNIP and rs9325507, rs3814220, rs12765878, rs11191865 within OBFC1. The common haplotype was shown in Table 4. However, none of the haplotypes were associated with AIS susceptibility.

The rs7708392 genotype and telomere, serum lipid levels

The association between rs7708392 genotype and telomere, serum lipid levels in control group was presented in Table 5. There was no statistical difference for relative telomere length among these three genotypes. No difference was found for each lipid level, hypertension, and diabetes mellitus among them.

Discussion

We performed this case-control study to assess the correlation between some polymorphisms in TERT, TNIP1 and OBFC1 and the risk of AIS in southern Chinese Han population. The results suggested that rs7708392 within TNIP1 was associated with an increased risk of ischemic stroke. None of the rest SNPs had a significant difference with AIS susceptibility. The haplotype analysis showed that none of the common haplotype in TNIP1 and OBFC1 was associated with AIS risk.

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TNIP1 polymorphism and atherosclerotic ischemic stroke

Table 2. Candidate SNPs in this study

<table>
<thead>
<tr>
<th>SNP</th>
<th>Position</th>
<th>Band</th>
<th>Alleles</th>
<th>Gene</th>
<th>MAF (%)</th>
<th>ORs</th>
<th>95% CIs</th>
<th>P</th>
<th>HWE</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs10069690</td>
<td>1279790</td>
<td>5p15.33</td>
<td>T/C</td>
<td>TERT</td>
<td>0.14</td>
<td>0.88</td>
<td>0.67-1.17</td>
<td>0.39</td>
<td>1</td>
</tr>
<tr>
<td>rs2242652</td>
<td>1280028</td>
<td>5p15.33</td>
<td>A/G</td>
<td>TERT</td>
<td>0.15</td>
<td>0.88</td>
<td>0.67-1.15</td>
<td>0.36</td>
<td>0.1</td>
</tr>
<tr>
<td>rs2853677</td>
<td>1287194</td>
<td>5p15.33</td>
<td>G/A</td>
<td>TERT</td>
<td>0.38</td>
<td>0.89</td>
<td>0.73-1.09</td>
<td>0.24</td>
<td>0.54</td>
</tr>
<tr>
<td>rs2853676</td>
<td>1288547</td>
<td>5p15.33</td>
<td>T/C</td>
<td>TERT</td>
<td>0.15</td>
<td>0.89</td>
<td>0.68-1.17</td>
<td>0.41</td>
<td>0.47</td>
</tr>
<tr>
<td>rs7708392</td>
<td>150457485</td>
<td>5q33.1</td>
<td>G/A</td>
<td>TNIP1</td>
<td>0.38</td>
<td>0.89</td>
<td>0.73-1.09</td>
<td>0.44</td>
<td>0.33</td>
</tr>
<tr>
<td>rs10036748</td>
<td>150458146</td>
<td>5q33.1</td>
<td>C/T</td>
<td>TNIP1</td>
<td>0.25</td>
<td>1.09</td>
<td>0.87-1.38</td>
<td>0.44</td>
<td>0.54</td>
</tr>
<tr>
<td>rs960709</td>
<td>150461049</td>
<td>5q33.1</td>
<td>A/G</td>
<td>TNIP1</td>
<td>0.25</td>
<td>1.09</td>
<td>0.87-1.37</td>
<td>0.46</td>
<td>0.78</td>
</tr>
<tr>
<td>rs9325507</td>
<td>105645622</td>
<td>10q24.33</td>
<td>T/C</td>
<td>OBFC1</td>
<td>0.35</td>
<td>0.93</td>
<td>0.75-1.13</td>
<td>0.41</td>
<td>0.59</td>
</tr>
<tr>
<td>rs3814220</td>
<td>105647300</td>
<td>10q24.33</td>
<td>G/A</td>
<td>OBFC1</td>
<td>0.35</td>
<td>0.91</td>
<td>0.74-1.12</td>
<td>0.42</td>
<td>0.52</td>
</tr>
<tr>
<td>rs12765878</td>
<td>105672842</td>
<td>10q24.33</td>
<td>A/G</td>
<td>OBFC1</td>
<td>0.35</td>
<td>0.91</td>
<td>0.74-1.12</td>
<td>0.42</td>
<td>0.52</td>
</tr>
<tr>
<td>rs11191865</td>
<td>105676465</td>
<td>10q24.33</td>
<td>C/A</td>
<td>OBFC1</td>
<td>0.02</td>
<td>2.42</td>
<td>0.85-6.89</td>
<td>0.09</td>
<td>1</td>
</tr>
</tbody>
</table>

A/B minor/major allele, SNP single nucleotide polymorphism, HWE Hardy-Weinberg equilibrium, MAF minor allele frequency, OR odd ratio, CI confidence interval.

Table 3. Association between rs7708392 and the risk of atherosclerotic ischemic stroke in genetic models

<table>
<thead>
<tr>
<th>Model</th>
<th>Genotype</th>
<th>Control</th>
<th>Case</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codominant</td>
<td>C/C</td>
<td>236</td>
<td>224</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>G/C</td>
<td>135</td>
<td>152</td>
<td>1.62 (1.01-2.61)</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>G/G</td>
<td>25</td>
<td>24</td>
<td>0.87 (0.34-2.25)</td>
<td>0.83</td>
</tr>
<tr>
<td>Dominant</td>
<td>C/C</td>
<td>236</td>
<td>224</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>G/C-G/G</td>
<td>160</td>
<td>176</td>
<td>1.48 (0.94-2.32)</td>
<td>0.09</td>
</tr>
<tr>
<td>Recessive</td>
<td>C/C-G/G</td>
<td>371</td>
<td>376</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>G/G</td>
<td>25</td>
<td>24</td>
<td>0.73 (0.29-1.84)</td>
<td>0.5</td>
</tr>
<tr>
<td>Overdominant</td>
<td>C/C-G/G</td>
<td>261</td>
<td>248</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>G/C</td>
<td>135</td>
<td>152</td>
<td>1.64 (1.03-2.62)</td>
<td>0.037</td>
</tr>
<tr>
<td>Log-additive</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>1.22 (0.85-1.76)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

*adjusted for gender, age, smoking, alcohol, diabetes history, hypertension history, body mass index, total cholesterol, total triglyceride, high density lipoprotein-cholesterol, low density lipoprotein-cholesterol.

Table 4. Haplotype frequencies and the risk of AIS

<table>
<thead>
<tr>
<th>Gene</th>
<th>Haplotype</th>
<th>Case Freq</th>
<th>Control Freq</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNIP1</td>
<td>T-C-G</td>
<td>0.75</td>
<td>0.76</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C-G-A</td>
<td>0.25</td>
<td>0.22</td>
<td>1.25 (0.86-1.81)</td>
<td>0.25</td>
</tr>
<tr>
<td>OBFC1</td>
<td>G-T-A-C-A</td>
<td>0.63</td>
<td>0.62</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A-C-G-T-A</td>
<td>0.35</td>
<td>0.37</td>
<td>0.90 (0.65-1.24)</td>
<td>0.52</td>
</tr>
<tr>
<td></td>
<td>G-T-A-C-C</td>
<td>0.02</td>
<td>0.006</td>
<td>1.64 (0.24-11.05)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

AIS atherosclerotic ischemic stroke, Freq frequency, OR odd ratio, CI confidence interval, P adjusted for gender, age, smoking, alcohol, diabetes history, hypertension history, body mass index, total cholesterol, total triglyceride, high density lipoprotein-cholesterol, low density lipoprotein-cholesterol.

Atherosclerotic ischemic stroke, especially in the carotid and intracranial arteries. Evidence manifested the association among vascular function, inflammation factors and atherosclerosis in rheumatoid arthritis and systemic lupus erythematosus [23, 24]. TNIP1, a gene which codes for TNFAIP3-interacting protein-1 (ABIN-1), is a regulatory molecule that stops signal way by several receptors, including TNF-alpha, TLR and PPAR [25]. Previous studies had confirmed the variants in TNIP1 gene were associated with an increased risk of systemic lupus erythematosus in European, Chinese and Japanese population [26]. Naveed Akbar, et al reported that ABIN-1 was associated with cardiovascular disease in mice [15]. However, up to now, there was no report on the association between TNIP1 polymorphisms and risk of AIS. Therefore, we conducted the disease association between three variants rs10036748, rs7708392, rs960709 and the risk of IS. The results showed that rs-7708392 was associated with an increased risk of IS in heterozygous and overdominant model. For exploration of the possible reason, we also performed the association analysis between rs7708392 genotype and hypertension, blood lipid levels and diabetes mellitus in the control group. However, none of them showed a significant difference among them. Although the difference disappeared after Bonferroni correction, this polymorphism...
TNIP1 polymorphism and atherosclerotic ischemic stroke

Table 5. Genotype of rs7708392 and telomere, hypertension, diabetes mellitus and serum lipid in controls

<table>
<thead>
<tr>
<th>Genotype</th>
<th>n</th>
<th>Telomere (M)</th>
<th>HBP (%)</th>
<th>DM (%)</th>
<th>HDL</th>
<th>LDL</th>
<th>TG</th>
<th>TC</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>236</td>
<td>1.08</td>
<td>17.8</td>
<td>6.4</td>
<td>5.22 ± 0.89</td>
<td>3.13 ± 0.74</td>
<td>1.49 ± 0.52</td>
<td>5.22 ± 0.89</td>
</tr>
<tr>
<td>GC</td>
<td>135</td>
<td>1.12</td>
<td>13.3</td>
<td>6.9</td>
<td>1.38 ± 0.53</td>
<td>3.11 ± 0.71</td>
<td>1.52 ± 0.60</td>
<td>5.18 ± 0.81</td>
</tr>
<tr>
<td>GG</td>
<td>24</td>
<td>1.15</td>
<td>20</td>
<td>12</td>
<td>1.31 ± 0.54</td>
<td>3.10 ± 0.64</td>
<td>1.42 ± 0.46</td>
<td>4.94 ± 0.77</td>
</tr>
<tr>
<td>p</td>
<td></td>
<td>0.56</td>
<td>0.47</td>
<td>0.56</td>
<td>0.76</td>
<td>0.94</td>
<td>0.68</td>
<td>0.3</td>
</tr>
</tbody>
</table>

M median, HBP hypertension, DM diabetes mellitus, TC total cholesterol, TG triglyceride, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol.

was still a potential target in developing atherosclerosis and further ischemic stroke, which deserved further investigation in multiracial and larger sample studies.

Telomerase prolongs telomere sequence during DNA replication by adding the short telomere repeats (TTAGGG) to maintain chromosomal integrity and stability. TERT is a rate-limiting catalytic component of this enzyme. Therefore, mutations in the TERT gene may change the telomerase enzyme activity, shorten telomere length and further induce the development of some disease [27, 28]. The variants rs10069690 and rs2242652 were found to increase the risk of lung cancer, but not in rs2853676 [27]. And rs2736100 was associated with coronary artery disease in European population [4]. We performed the study on the association between rs2853676, rs2853677, rs10069690 and rs2242652 and risk of AIS. However, our results demonstrated that no statistical difference was found between them after adjustment for confounders in any model.

Oligonucleotide/oligosaccharide binding fold containing 1 (OBFC1) codes for oligosaccharide-binding fold-containing protein 1. Some study suggested that OBFC1 could bind to telomeric single-stranded DNA in vitro, and overexpression of OBFC1 mutant resulted in elongated telomeres [29]. GWAS meta-analysis showed that many SNPs including rs9325507, rs3814220, rs12765878 and rs9420907 were associated with leukocyte telomere length and further confirmed in replication [30]. Some previous study manifested that mutations in OBFC1 were associated with an increased risk in ischemic heart disease [20]. For ischemic stroke, five polymorphisms including rs9325507, rs3814220, rs12765878, rs11191865 and rs9420907 were selected to test the association with the risk of AIS. Our results indicated that no CC genotype was observed in rs9420907, and no significant difference was found in allele or genotype or any genetic model.

The results from our study should be interpreted with caution in light of several limitations. Firstly, the statistic difference existed in age between cases and controls. The present study had a disproportionate number of subjects under the age of 40 (20.1% in controls and only 2% in cases). Secondly, there were significantly higher blood lipid levels in controls compared to the case group. This might be due to the use of lipid-lowering drugs or more attention was given on physical activity and healthy life style in the case group.

We concluded that variants within the TERT and OBFC1 genes probably played no major role in the determination of AIS. SNP (rs7708392) within the TNIP1 gene was associated with an increased risk of AIS, which maybe unlikely to be caused by telomere shortening, hypertension, diabetes and serum lipid. Haplotype analysis showed no significant difference between the case and the control within TNIP1 and OBFC1.

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Disclosure of conflict of interest

None.

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