Association of Variants in *KCNK17* Gene with Ischemic Stroke and Cerebral Hemorrhage in a Chinese Population

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Background: KCNK17 (potassium channel, subfamily K, member17) has a role in the pathogenesis of stroke. We reported previously that rs10947803 single-nucleotide polymorphism (SNP) in *KCNK17* is associated with cerebral hemorrhage in a Chinese population. The aim of the present study was to examine other SNPs in the *KCNK17* gene that are associated with cerebral hemorrhage and other subtypes of stroke in the Chinese population. *Methods:* A total of 1356 subjects with stroke and 1225 control patients were examined by a case-control methodology. The SNPs (rs12214600, rs12195376, rs2758912, and rs10807204) in *KCNK17* gene were genotyped with the TaqMan real-time polymerase chain reaction assay. *Results:* rs12214600 SNP in *KCNK17* was significantly associated with cerebral hemorrhage (unadjusted odds ratio = .55, 95% confidence interval = .35-.86, $P = .008$, q = .0328) under the allele model. After adjusting for age, sex, and hypertension, we found that the association remained significant (odds ratio = .56, 95% confidence interval = .35-.90, $P = .0158$). There was no association detected for other SNPs in *KCNK17* with cerebral hemorrhage, and none of the SNPs in *KCNK17* had an association with ischemic stroke. *Conclusions:* The T carrier of an SNP (rs12214600) is associated with reduced risk of cerebral hemorrhage in the Chinese population, together with previous findings that SNPs rs10947803 and rs12214600 in the *KCNK17* gene are associated with hemorrhagic stroke, but none of the SNPs tested had an association with ischemic stroke. *KCNK17* may be important in the pathogenesis of cerebral hemorrhage. **Key Words:** Ischemic stroke—cerebral hemorrhage—*KCNK17*—SNP.

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Introduction

Stroke is one of the most common causes of death worldwide and contributes to a major burden in health care.[1,2] But the prevalence, prophylaxis, and treatment in stroke may be different in various regions or race. Some researchers have found that there are some differences between Japanese and European Guidelines for the management of ischemic stroke published between 2008 and 2011.[3] In China, stroke is the leading type of cardiovascular disease.[4] Ischemic stroke has the dominant proportion, which is approximately 43.7%-78.9% of overall strokes in Chinese population.[5] Cerebral hemorrhage is a significant subtype of stroke and plays an important role in the Chinese population.[6] Recent epidemiologic studies in the Chinese population reveal that approximate 30% of stroke cases, even much more, can be accounted for by hemorrhagic stroke, which indicates that hemorrhagic stroke is more frequent in Chinese than in the white patients.[7,8] As a complex disease, stroke is assumed to result from both genetic and environmental factors as well as their interactions[9]; however, its responsible genetic and molecular mechanisms have remained largely unknown.

KCNK17 (potassium channel, subfamily K, member 17) is located in chromosome 6p21.1 in humans and belongs to 1 of the 2-pore-domain potassium channels superfamily of background K^+ channels, which generate the negative membrane potential in excitable and nonexcitable cells and contribute to the resting membrane potential in various tissues.[10,11] The mutations of *KCNK17* gene could bring about abnormal opening of potassium channels and then increase the concentration of extracellular potassium ion, which might produce marked dilation of cerebral blood vessels. It could play an important role in cardiovascular diseases.

Since 2007, Matarin et al[12] have identified 3 significant single-nucleotide polymorphisms (SNPs) in *KCNK17* that are associated with ischemic stroke in white patients. After that, Domingues-Montanari et al[13] replicated the finding in a Spanish cohort; however, different results, which indicate that the SNP in *KCNK17* is not associated with ischemic stroke, have been reported in Chinese population.[14] Ma et al[15] reported that the rs10947803 SNP in *KCNK17* is associated with cerebral hemorrhage in a Chinese population; however other SNPs in *KCNK17* were been tested in that report. It is necessary to investigate whether the other SNPs in *KCNK17* gene are associated with cerebral hemorrhage in a Chinese population. Therefore, we selected 4 representative SNPs (rs12214600, rs12195376, rs2758912, and rs10807204) by their minor allele frequency greater than 10% in Chinese with Haploview software (version 4.0)[16] in the block located from 39376714 bp to 39383260 bp in chromosome 6 and tested the susceptible variants in *KCNK17* associated with cerebral hemorrhage and other subtypes of stroke in the Chinese population.

Materials and Methods

Subjects

The Stroke Hypertension Investigation in Genetics (SHINING) study was conducted by the Beijing Hypertension League Institute. Patients and control subjects from 6 geographical regions in China were recruited for the case–control study between 1997 and 2000, and 70% subjects came from or nearby Beijing.[17] The SHINING study consisted of the subjects of Chinese Han ethnicity only.[18] Any stroke patients who suffered a stroke within the past 5 years were eligible to participate in the study.[17,18] All patients had medical records that indicated with a diagnosis of stroke confirmed by brain computed tomography/magnetic resonance imaging.

In the initial study, patients with ischemic stroke, cerebral hemorrhage, ischemic/hemorrhage stroke, subarachnoid hemorrhage, transient ischemic attacks (TIA), and cryptogenic stroke were included.[15] In considering the sample size of each subtype of stroke, we chose only 3 subtypes for the present study, namely, ischemic stroke, cerebral hemorrhage, and TIA. Control subjects were selected according to the case–control study criteria (control subjects matched to cases by sex, age within 3 years, geographic location, and blood pressure category [$<$140/90 mmHg, $\geq$140/90 mmHg, and $\leq$180/105, $>$180/105 mmHg]).[18] Data collected included age, sex, body mass index, systolic blood pressure, diastolic blood pressure, and hypertension. Hypertension was defined as having current or past antihypertensive medication, systolic blood pressure $\geq$140 mmHg, or diastolic blood pressure $\geq$90 mmHg.[17,18] Written informed consent was obtained from all study participants, and the study was approved by ethics committees of the Beijing Hypertension League Institute.

Selection of SNPs

After excluding the SNPs that are not representative and with less than 10% MAF in Chinese, we selected 4 SNPs (rs12214600, rs2758912, rs12195376, and rs10807204) within the position of chromosome six from 39376714 bp to 39383260 bp, which were representative SNPs in Chinese.

DNA Extraction and Genotyping

Genomic DNA had been extracted from the whole blood with salting out procedure. DNA concentration was measured by NanoDrop 2000. DNA was diluted to a concentration of 5 ng/μL before we genotyped the samples. A total of 3119 participants (1559 stroke cases and 1560 controls) were recruited for the SHINING study, and of these, 2581 participants (1356 stroke cases and 1225 controls) had DNA samples available in the present study. All the selected SNPs in