Poststroke depression (PSD) is one of the common complications of stroke, which increases its fatality and morbidity rate. Approximately one third of all patients experience significant depressive symptoms after the onset of stroke, which may occur not only in the first few months of the disease.

The serotonin transporter gene (SLC6A4, GenBank L05568) is considered a candidate gene containing the serotonin transporter-linked promoter region (5-HTTLPR) and the single-nucleotide polymorphism rs25531, which have been the targets of recent investigation. The association of the S/S genotype with PSD has been found in studies from several ethnic groups, although the distribution differs by race and ethnicity. Although a positive association between 5-HTTLPR and depression was found in a study from Sichuan, China, the association of the gene with PSD has not been reported from mainland China. We sought to compare the distribution of the serotonin transporter gene SLC6A4 polymorphism between depressed and nondepressed poststroke patients.

Methods

Patients with acute ischemic or hemorrhagic stroke admitted to the Shanghai Ninth Hospital during the period July 2008 to June 2009 were recruited into the study; patients who were unable to complete the scale examination or who had been previously diagnosed with depression were excluded. Information was collected from patients including age, sex, stroke lesion location, and modified Rankin Scale score at 1 month after stroke.

A diagnosis of PSD was made according to the Diagnostic and Statistical Manual-IV for depression. The Hamilton Rating Scale for Depression (17 items) was conducted at 1 month after stroke for patients who had clinical depressive symptoms lasting ≥2 weeks and whose self-rating depression scale score was ≥7. PSD was rated according to the Hamilton Rating Scale for Depression: any score ≥8 was considered indicative of depression, whereas any score ≤7 was considered indicative of nondepression.

After the patients with PSD were determined, 1:1 control subjects were selected from the patients without PSD, which was confirmed by interview or telephone at 6 months after stroke. Variables matched for each pair of cases and controls were sex, age (±5 years), stroke type (ischemic or hemorrhage), and modified Rankin Scale score (±1 point).

For sample collection and genotyping, 5-mL blood samples were collected from all cases and controls, and oligonucleotide primers were designed as reported. Then polymerase chain reaction and restriction enzyme digestion were conducted.

Statistical analysis was performed with SPSS 13.0, with the t test for comparing group means and the McNemar test for comparing differences between paired proportions, and the significance level was set at P<0.05.

Informed consent was obtained from each study participant.

Results

During the study period, 421 patients with acute cerebral stroke were admitted. After excluding 54 patients, 367 patients were enrolled in a 1:1 case-control study. All cases and controls were genotyped for polymorphism of the serotonin transporter-linked promoter region and the single-nucleotide polymorphism rs25531.

Results

Among 367 patients with cerebral stroke, 57 (15.5%) were diagnosed with poststroke depression at 1 month after stroke. In the patients with poststroke depression, 7 genotypes of the serotonin transporter gene SLC6A4 were detected, and the frequency of S/S homozygotes was significantly higher (P=0.049) than that in controls.

Conclusions—S/S homozygosity may be positively associated with the occurrence of poststroke depression in Chinese patients. (Stroke. 2011;42:1461-1463.)

Key Words: case-control study ■ poststroke depression ■ SLC6A4 gene polymorphism
patients were enrolled in the study, and 57 patients (15.5%) were diagnosed with PSD. Variables matched for the PSD group and the control group are presented in Table 1.

With respect to genotype frequency, the distribution of the 5-HTTLPR and rs25531 polymorphisms in all 114 cases and controls was in Hardy-Weinberg equilibrium ($5$-$H_{11005}^2$, $P_{11005}^0.221$; rs25532 $5$-$H_{11005}^2$, $P_{11005}^0.267$). In all 114 cases and controls, 7 genotypes were detected in PSD patients and 8 in controls (the Figure and Table 2). After having compared different combinations of alleles between the 2 groups, we found that the frequency of the $S/S$ genotype was significantly higher ($P_{11005}^0.049$) in the PSD group than in the control group, whereas there were no significant differences in frequencies of $S/L$, $L/L$, $A/A$, $G/G$, $A/G$, $S_A$, $S_G$, $L_A$, $L_G$ between the 2 groups ($P_{11005}^0.05$).

**Discussion**

A study from Hong Kong reported that 16.4% of patients were diagnosed with PSD at 3 months after stroke, a figure similar to ours (15.5%). In the current study, 7 genotypes appeared in the PSD group and 1 more appeared in the control group. Our results for genotype distributions are not consistent with those from other reports: not only are they different from those in white and black samples, but also they are different from a sample of Chinese Parkinson disease patients with depression. The differences might be explained by different characteristics of the samples or various criteria for the inclusion of cases.

It has been known that patients with 1 or 2 $S$ allele copies exhibit more depressive symptoms and have more diagnosable depression than do individuals homozygous for the $L$
allele. In our study, the frequency of S/S homozygotes was more predominant in the PSD group, which suggests a positive association between the S allele and PSD. A study with a small sample of white subjects reported a similar result: that the S allele was related to major depression after stroke. The possible mechanism proposed was that the S allele could decrease serotonin transporterexpression, leading to lower reuptake and storage of the neurotransmitter. An American study with multiracial patients showed that the 5-HTTLPR genotype was higher in the PSD group and that individuals with the 5-HTTLPR S/S genotype had a 3-fold increased odds of PSD compared with those with the L/L or L/XL genotype.

Except for the S/S genotype, other combinations, including S/L, L/L, A/A, G/G, A/G, S_A, L_A, S_G, and L_G, were not associated with PSD in our results. Hu et al reported that the G allele had a predictive value for depression, which could decrease serotonin transporter. From other studies on PSD, some authors have claimed that the effect of L_G was the same as that of the S allele and that the low-expressing single-nucleotide polymorphism was also associated with PSD.

The aforementioned Canadian study also had the same result for L_G. Although the result for L_G in the current study was not statistically significant, some tendency was displayed. The frequency of L_G was 6.1% in the control group, similar to the 6.5% reported in the general population, whereas in the PSD group, the proportion was ~2 times higher (12.3%).

Until now, little has been known about the effects of S/L or A/G alleles in Asian PSD patients. Our results are based on the information from a small sample; more well-designed investigations with larger samples are needed in the field.

### Source of Funding

This study was supported by funds from the Shanghai Ninth Hospital, which is affiliated with the Medical School of Shanghai JiaoTong University.

### Disclosures

None.

### References


Serotonin Transporter Gene Polymorphism in Chinese Patients With Poststroke Depression: A Case-Control Study
Jing Fang, Weihong Yan, Guo-Xin Jiang, Wei Li and Qi Cheng

Stroke. 2011;42:1461-1463; originally published online March 24, 2011;
doi: 10.1161/STROKEAHA.110.598672
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/42/5/1461

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/