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Research article

Tryptophan hydroxylase 2 gene is associated with cognition in late-onset depression in a Chinese Han population

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HIGHLIGHTS

- There may be a major effect in TPH2 gene on cognition in LOD patients alone.
- An interaction of TPH2 gene and depression may be affect the cognition in LOD.
- Some domain of cognition may be affected by the severity of depression.

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ABSTRACT

Accumulating evidences suggest that Tryptophan hydroxylase 2 (TPH2) gene is associated with major depressive disorder (MDD) and cognitive function. In present study, we aimed to explore the association of cognitive disturbances in patients with late-onset depression (LOD) in the Chinese Han population. One hundred and ninety unrelated LOD patients who met DSM-IV criteria for major depressive disorder were recruited for the study and 155 normal controls were recruited from local community. All subjects completed the demographic assessments. Furthermore, 97 patients and 44 controls completed a series of neuropsychological tests. Patients and normal controls were genotyped for TPH2 (rs4290270 and rs7305115) variants using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). The results of our analysis indicated no significant differences in the frequencies of the single alleles and genotypes of two polymorphisms in TPH2 gene between LOD patients and normal controls. Haplotype association indicated that no differences were found in the frequencies of haplotype between two groups. A significant main effect of rs4290270 genotype on Verbal Fluency Test (VFT) test performance was found ($P < 0.05$). There was a significant interactive effect of rs7305115 polymorphisms and depression diagnosis on Symbol Digit Modalities Test (SDMT) ($P < 0.05$). After controlling for covariates, the subjects with carriers of GG genotype in rs7305115 had more better SDMT performance compared to AG and AA carriers in LOD groups. The result suggests that there is a major effect of rs4290270 in TPH2 on cognitive function alone. Moreover, an interaction of rs7305115 polymorphisms and depression diagnosis may be associated with the cognitive function. Further studies in a large sample are needed to replicate the genetic role in the LOD patients.

1. Introduction

Major depressive disorder (MDD) is one of the most prevalent mental disorders and is predicted to be the second leading cause of disability and death in the coming decade [1]. Recent research demonstrated that MDD is associated with cognitive impairment, and especially in late-onset depression patients, there is more severe cognitive impairment and increased risk of conversion to dementia [2–4]. For this reason, making clear the molecular mechanisms of cognitive dysfunction in LOD would help better prevention and treatment of this disease.

Serotonin (5-hydroxytryptamine, 5-HT) is one of the most important neurotransmittors, and increasing evidences indicate that 5-HT system has been implicated in pathophysiology of various neuropsychiatric syndromes, such as depression, suicide, cognition, bipolar disorder, aggression and so on [5,6]. Indeed, some

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clinical studies discovered that there were decreased concentrations of the 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid and brain tissues in depressed individuals and suicide victims/attempters [7]. Furthermore, selective serotonin reuptake inhibitors, like fluoxetine, which exert their effects by preventing the reuptake of serotonin, improve multiple cognitive domains, such as attention, episodic memory and executive function in depressive patients [8].

Tryptophan hydroxylase (TPH) is the rate-limiting enzyme in the biosynthesis of serotonin in the brain, transforming tryptophan into 5-hydroxy-tryptophan, which is the direct precursor of 5-HT [6]. In an animal study, it was found that the raphe neurons are completely devoid of 5-HT in Tph2 knockout mice [9]. The human TPH2 gene is located on chromosome12q15, covers a region of 93.5 kb and includes 11 exons [10]. TPH2 genetic variants has recently attracted much attention regarding their role in the genetics of MDD and cognition, since TPH2 is predominantly expressed in neurons in the brain producing serotonin [11]. For example, Zill et al. [10] pointed out that genetic variants of the TPH2 gene were associated with MDD in Caucasian populations. Another two polymorphisms of TPH2 (rs7305115 and rs4290270, respectively) were also discovered to be linked to MDD [12]. Furthermore, recent several studies showed the polymorphism of rs4570625 in the TPH2 gene was associated with cognitive function in healthy individuals, and TT genotype in rs4570625 was related to worse performance in cognitive tasks measuring prefrontal executive control [13].

To our knowledge, there have been no reports concerning the effect of the two polymorphisms of TPH2 gene (rs7305115 and rs4290270) in LOD as well as cognitive function in Asian populations. Therefore, in the present study, we aim to investigate the association between TPH2 polymorphisms and cognitive impairment in LOD patients in a Chinese Han population.

2. Methods

2.1. Subjects

The sample studied consisted of 190 unrelated MDD inpatients (46 males and 144 females, average age 64.60 ± 6.19 years) who were consecutively recruited from the Affiliated Brain Hospital of Nanjing Medical University and Wuhu 4th Hospital, between December 2009 and August 2013. According to the DSM-IV criteria for MDD, all patients were diagnosed by two senior psychiatrist using a Structured Clinical Interview for DSM-IV [14]. At the inclusion, the age of first episode for all patients was 55 years or older, and they had a minimum baseline score of 17 on the 17-item Hamilton Rating Scale (HDRS) and Mini-Mental State Examination (MMSE) scores were higher than 24. Exclusion criteria included other major psychiatric illness (including bipolar disorder, schizophrenia, dementia, history of alcohol or drug abuse or dependence), neurodegenerative illness and severe physical illnesses.

The 155 normal controls (90 males and 65 females; mean age 64.80 ± 6.19) were recruited from regular physical examination in the local community. Eligible participants had no a history of any psychiatric illness or major physical illness based on the Diagnostic Interview Schedule. In addition, all controls had HDRS scores <7 and MMSE scores >24.

The study protocol was approved by the local Ethics Committee. Written informed consent was obtained from all subjects after the program has been carefully explained. All subjects completed HDRS assessment and 97 LOD (33 males and 64 females; mean age 67.36 ± 5.94) and 44 normal controls (21 males and 23 females; mean age 65.09 ± 7.48) without a past history of disability unable to conduct neurocognitive testing completed a series of neuropsychological tests assessing various domains of cognition function by two senior psychiatrists who have been trained in standardized assessment and scoring procedures. Also, the patients were assessed on the first day of hospitalization and the controls completed the assessment on the day of physical examination. Neuropsychological battery includes Mini-Mental State Examination (MMSE), Rey Auditory Verbal Learning Test (RAVLT), Verbal Fluency Test (animal category), Verbal Fluency Test (verb category), Digit Span Test, Symbol Digit Modalities Test (SDMT), Trail Making Test A and B (TMT).

2.2. DNA extraction and genotyping

Genomic DNA was obtained from 250 μl EDTA-anticoagulated venous blood using AxyPrep Blood Genomic DNA Miniprep Kit (Axygen, Union City, CA, USA) according to the manufacturer's recommendations. TPH2 rs7305115 and rs4290270 genotyping were performed in accordance with the method used in our previous study [15].

2.3. Statistical data analysis

Statistical analysis was performed with SPSS for windows version 13.0. Demographic variables was tested with the two-tailed *t* tests for continuous data and a chi-square test for categorical data. Correlations between the HDRS and the scores of neuropsychological tests in LOD patients were calculated by Spearman's correlation. Hardy–Weinberg equilibrium test, linkage disequilibrium statistics, haplotype distribution, allele and genotype frequencies were calculated using SHEsis program [16]. General linear models were used to test for the effects of the subjects' status (patients or controls) and TPH2 genotype on the neurocognitive tests. Each neuropsychological test performance was the dependent variable. We also examined the main effects of depression diagnosis, TPH2 genotype and an interactive effect of depression diagnosis and TPH2 genotype on each neuropsychological test performance. For all these models, we adjusted for age, education, and gender. The Bonferroni test was applied to correct for multiple comparisons. All tests were two-tailed and the significance level for all statistical tests was 0.05.

3. Results

We found differences in years of education between LOD patients and healthy controls ($P < 0.01$). Significant differences were found in scores for HDRS, MMSE, RAVLT delayed recall, SDMT, Digit Span Test, and TMT A between cases and controls after controlling for age, education and gender (all $P < 0.01$)(Table 1). Furthermore, there was a significantly negative correlation between the score of HDRS and DST forward score in LOD patients ($r = -0.211$, $P = 0.038$).

There were no significant differences in genotype and allele frequencies of patients and controls for rs4290270 and rs7305115 (Table 2), and the haplotypes frequencies did not show significant differences between two groups (Table 3).

General linear models adjusted by age, education and gender examined the effects of genotype and depression diagnosis on neuropsychological tests among all participants. A significant main effect of rs4290270 genotype on VFT test performance was found ($F = 4.504$, $P < 0.05$) (Table 4), Pairwise comparisons revealed the AA carriers in rs4290270 of VFT scores were significantly higher than AT carriers, there was significant difference ($P < 0.01$); pairwise comparisons revealed that VFT scores were significantly ($P < 0.01$) higher in the AA carriers of the rs4290270 than in AT carriers. Moreover, we also found a significant interaction of rs7305115 genotype and depression diagnosis in the performance of SDMT score($F = 8.656$, $P < 0.05$) (Table 5). More prisely, SDMT scores were