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Research paper

Genetic variations in the p11/tPA/BDNF pathway are associated with post stroke depression

Jinfeng Liang[a,b], Yingying Yue[a,b], Haitang Jiang[a,b], Deqin Geng[c], Jun Wang[d], Jianxin Lu[e], Shenghua Li[f], Kezhong Zhang[g], Aiqin Wu[h], Yonggui Yuan[a,b,*]

[a] Department of Psychosomatics and Psychiatry, ZhongDa Hospital, Medical School of Southeast University, Nanjing 210009, PR China
[b] Institute of Psychosomatics, Medical School of Southeast University, Nanjing 210009, PR China
[c] Department of Neurology, Affiliated Hospital of Xuzhou Medical College, Xuzhou 221000, PR China
[d] Department of Neurology, Nanjing First Hospital, Nanjing 210006, PR China
[e] Department of Neurology, The Peoples' Hospital of Gaochun County, Nanjing 211300, PR China
[f] Department of Neurology, Jiangning Nanjing hospital, Nanjing 211100, PR China
[g] Department of Neurology, the Affiliated First hospital of Nanjing Medical University, Nanjing 210029, PR China
[h] Department of Psychosomatics, the First Affiliated Hospital of Soochow University, Suzhou 215006, PR China

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ABSTRACT

Background: The effects of BDNF on post stroke depression (PSD) may be influenced by genetic variations in intracellular signal transduction pathways, such as the p11/tPA/BDNF pathway. In this study, we aimed to determine the association of polymorphisms in candidate genes of the gene transduction pathway with PSD, as well as the effects of the interactions between genes in our Chinese sample.

Methods: Two-hundred-fifty-four Chinese samples with acute ischaemic stroke included 122 PSD patients and 132 nonPSD patients. Sixty-five single nucleotide polymorphisms (SNPs) in six genes (p11, tPA, PAI-1, BDNF, TrkB and p75NTR) of the p11/tPA/BDNF pathway with minor allele frequencies > 5% were successfully genotyped from an initial series of 76 SNPs. The severity of depressive symptoms was assessed by the 17-item Hamilton Depression Rating scale score. Environmental factors were measured with the life events scale and social support rating scale for all patients. SNP and haplotype associations were analysed using gPLINK software. Gene-gene interactions were evaluated with generalized multifactor dimensionality reduction software.

Results: The results showed that TrkB polymorphisms (rs11140793AC genotype, rs7047042CG genotype, rs1221CT genotype, rs2277193TC genotype and rs2277192AG genotype) were significantly associated with PSD. Three haplotypes (AT, GG, and AAT) of TrkB were significantly associated with PSD. Seven haplotypes (GC, AG, ACG, CGC, GCT, ACGC and ACAT) of BDNF were significantly correlated with PSD. We identified significant gene-gene interactions between the p11 (rs11204922 SNP), tPA (rs8178895, rs2020918 SNPs) and BDNF (rs6265, rs2049046, rs16917271, rs727155 SNPs) genes in the PSD group. We also identified significant gene-gene interactions between the BDNF (rs2049046, rs7931247 SNPs) and TrkB (rs7816 SNP) genes with increased occurrence of PSD and sig gene-gene interactions between the BDNF gene (rs6265, rs56164415, rs2049046, rs4923468, rs2883187, rs16917271, rs1491850, rs727155, rs2049048 SNPs) and p75NTR gene (rs2072446, rs11466155) in the PSD group.

Conclusion: These findings provides evidence that the TrkB gene, BDNF and TrkB haplotypes, and gene-gene interactions between p11, tPA and BDNF are all associated with PSD, which suggests that genetic variations in the p11/tPA/BDNF pathway may play a central role in regulating the underlying mechanism of PSD.

1. Introduction

Depression is a common mood disorder that is recognized as an important complication of stroke. It is particularly prevalent among stroke survivor, which is referred to as post stroke depression (PSD), with an incidence rate of 30% (Hackett et al., 2005; Whyte and Mulsant, 2002). PSD not only negatively affects functional and cognitive recovery after stroke but is also associated with social withdrawal and increases mortality (Bhogal et al., 2004). To date, the underlying mechanisms of PSD may be explained by two hypotheses: the biological

* Correspondence to: Department of Psychosomatics and Psychiatry, ZhongDa Hospital, School of Medical, Southeast University, No.87 Dingjiaqiao Road, Nanjing City 210009, China.
E-mail address: yygylh2000@sina.com (Y. Yuan).

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and psychological factors. Among the biological factors, biological genetic changes may play a pivotal role in the aetiology of PSD.

During previous decades, rapid development and advancement of gene-detecting technologies provided potential analyses for gene loci and resulted in remarkable discoveries. However, the results based on single gene loci are often inconsistent, with a very low replication rate in psychiatric disorders (Bosker et al., 2011; Kendler, 2004). It is commonly accepted that psychiatric disorders may be caused by functionally related genes through their dynamic interaction and regulation between each other rather than the action of a single gene alone (Jia et al., 2011, 2010; Purcell et al., 2009). There is also accumulating evidence that gene- and pathway-based association analyses are effective relative to single nucleotide polymorphism (SNP) based association studies, as they increase the power to identify true associations (Huang et al., 2011). However, it should be noted that gene-gene interaction based analyses have rarely been applied to PSD. Thus, the current study seeks to shed light on the potential contribution of the p11/tPA/BDNF pathway to PSD based on comprehensive gene- and pathway association analyses.

p11, also called S100A10, is a member of the S100 family of proteins and is widely distributed in cerebral cortex, hippocampus and hypothalamus (Kassam et al., 1998a, 1998b; Svenningsson and Greengard, 2007). Well-documented evidence suggested that p11 is implicated in depression (Alexander et al., 2010; Egeland et al., 2010; Svenningsson et al., 2013; Warner-Schmidt et al., 2010). A decrease in the levels of p11 expression was identified in the brains of humans with depressive symptoms and mouse models of depression, and this expression was up-regulated following antidepressant drug treatment (Svenningsson et al., 2006; Warner-Schmidt et al., 2009). Verma et al. (Verma et al., 2007) also reported that the p11 gene rs4845720 SNP is significantly associated with MDD patients compared with controls. It has been established that two subunits of p11 bind to tPA on the extracellular surface and stimulate a 300-fold increase of tPA-mediated plasminogen activation (Kassam et al., 1998a, 1998b; Svenningsson and Greengard, 2007). A previous study showed the plasma level of tPA is low in elderly patients with depression (Shi et al., 2010); however, no tPA gene in association with depression has been reported to date. Nevertheless, there is evidence that tPA gene polymorphism increase the risk of the occurrence of stroke (Jannes et al., 2004). In consideration of this valuable biochemical information of p11and tPA regarding depression and stroke, we speculated that the p11 and tPA genes play a role in the occurrence of PSD.

tPA also plays a critical part in promoting the conversion of proBDNF to mBDNF by activating the extracellular protease plasmin and thus affects the balance of proBDNF/mBDNF and the functional activity of BDNF (Daniel et al., 2007; Ding et al., 2011). BDNF is involved in synaptic plasticity and nerve regeneration in the central nervous system (CNS) (Chao, 2003; Gomez-Pinilla et al., 2002; Huang and Reichardt, 2001). Kim et al. (Kim et al., 2007) reported that BDNF met/met genotypes are associated with PSD (both major and minor types). Zhou et al. (2011) reported that the decreased serum level of BDNF is correlated with PSD; however, no significant differences were identified between the genotype and allele of the Val66Met BDNF gene with serum protein and PSD. As indicated by these previous studies, the results of the BDNF gene in correlation with the genetic susceptibility to PSD are not consistent. Therefore, we aimed to determine whether the genetics pathway of the BDNF involved acts on the increased risk occurrence of PSD.

It has been proposed that p11 may act through the tPA/plasminogen/BDNF pathway to achieve its effect on depression (Tsai, 2007); consequently, the current study was designed with the goal to help address this important gap regarding the role of the p11/tPA/BDNF gene pathway in PSD. We analysed the association between these single genes in the polymorphic variability of p11, tPA, PAI-1, BDNF, TrkB, and p75NTR from this pathway and PSD. We also investigated whether there is an effect of interactions between gene and gene in the pathway on the risk of PSD.

2. Methods

2.1. Study population

Patients with acute ischaemic stroke were included in the study and were diagnosed by neurologists with definite lesions on computed tomography (CT) or magnetic resonance imaging (MRI) scans. We recruited 122 individuals with a diagnosis of PSD from July 2013 to December 2014, who were admitted to the Institute of Psychosomatics, Medical School of Southeast University of China. One hundred thirty-two stroke without depression (nonPSD) patients, matched for sex and age with PSD patients, were used as controls, which included 73 male and 58 female participants, with a median age of 65.5 years (range, 36–80). The inclusion criteria for nonPSD patients included the presence of determined stroke lesions, no psychiatric disorders or other neurological illnesses, such as dementia, and free of psychiatric drugs. PSD patients were satisfied with the following diagnostic criteria (Yue et al., 2015): (1) Stroke occurs prior to depressive symptoms; (2) Presence of at least two depressive symptoms except core criterion symptoms of depressed mood and loss of interest or pleasure in nine symptoms of major depressive disorder in DSM-IV; (3) Functional impairment affects personal life and work; (4) Depressive symptoms last more than one week; (5) Free of other major psychiatric disorders, including schizophrenia, bipolar disorder, or substance abuse (caffeine, nicotine and alcohol). The PSD and nonPSD groups were members of a homogeneous Chinese population. Each participant provided informed consent for the study, which was approved by the Ethics Committee of the Human Participants Ethics Committee of ZhongDa Hospital of Southeast University (NO.2013ZDSYLL011.0).

2.2. Demographic characteristics and neuropsychological assessment

The following data were collected from each patient: age, gender, educational level, Body Mass Index (BMI, kg/m^2), and risk factors for neurovascular disease, such as hypertension , diabetes, coronary heart disease, hypercholesterolemia, smoking habits and alcohol consumption (both past and current). All data were recorded according to the information obtained from the participants or their caregivers. The Barthel Index (BI) (Mahoney and Barthel, 1965), modified Rankin scale (mRS) (Banks and Marotta, 2007), and National Institute of Health Stroke Scale (NIHSS) (Goldstein et al., 1989) were used in the evaluation of the functional status of stroke patients by the same neurologists on the first day after stroke. The severity of depression was evaluated by the 17-item Hamilton Depression Rating scale (HDRs) (Hamilton, 1960) and the Mini Mental State Examination (MMSE) (Cockrell and Folstein, 1988) was used to assess the cognitive function of all participants by the same psychiatrists on the first day admitted to hospital, as well as at day 7, day 15, one month, three month, nine month, and 12 month, respectively. Environmental factors were evaluated by the Life Events Scale (LES) and Social Support Rating Scale (SSRS). The LES is a 48-item self-report questionnaire (28 family-related items, 13 working and studying related items, 7 social intercourse and other items; individuals have the option to add two other event items), which has generally been applied in clinical studies and research in China and has established good psychometric validity and reliability (Yang and Zhang, 1999). The SSRS is classified into three aspects, including 3 objective supports, 4 subjective supports and 3 availabilities of social support; it was also developed for Chinese individuals and has established good psychometric properties (Xiao and Yang, 1987).

2.3. DNA extraction, next generation sequencing and SNP selection

After enrolling individuals in the study, 2 ml samples of EDTA blood were obtained. Genomic DNA extracted from fresh blood was used with