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Research report

Interaction of tryptophan hydroxylase 2 gene and life events in susceptibility to major depression in a Chinese Han population

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ABSTRACT

Background: Major depression (MD) results from a complex synergy between genetic and environmental factors. The aim of this study is to analyze the interaction of tryptophan hydroxylase 2 gene (*TPH2*) variation and negative life events in the pathogenesis of MD. Three *TPH2* polymorphisms, −703G/T (rs4570625), −473T/A (rs11178997), and 1463G/A (rs120074175), were selected based on previous findings of associations with MD.

Methods: In this study, 289 patients with MD and 289 age- and sex-matched control subjects were genotyped. The frequency and severity of negative life events were assessed by the Life Events Scale (LES). Gene-environment interactions (G × E) were assessed using the generalized multifactor dimensionality reduction (GMDR) method.

Results: Differences in rs11178997 and rs120074175 allele frequencies and genotype distributions were observed between MD patients and controls. Significant G × E interactions between negative life events and allelic variation of rs4570625, rs11178997, and rs120074175 were also observed. Individuals carrying the T^- genotype of rs4570625 (GG), T^- genotype of rs11178997 (AA), or A^- genotype of rs120074175 (GG) were susceptible to MD only when exposed to high-negative life events. However, individuals with the T^+ genotypes of rs11178997 (TA, TT) and A^+ genotypes of rs120074175 (AG, AA) were susceptible to MD when exposed to low-negative life events.

Limitation: Assessment of negative life events was influenced by subjective interpretation.

Conclusions: Interactions between multiple TPH2 gene alleles and negative life events were revealed by GMDR analysis. Chinese Han individuals with at least one rs11178997 T allele or rs120074175 A allele are susceptible to MD even in the relative absence of high-negative life events.

1. Introduction

Major depression (MD) is an important public health problem, afflicting an estimated 7–11% of the general population (Kessler et al., 2007; Klengel and Binder, 2013). Moreover, MD is one of the strongest risk factors for attempted and completed suicide (Witte et al., 2009). Both genetic and environmental factors are implicated in the etiology of MD. Genetic predisposition contributes 30–40% of MD risk (Kessler et al., 2007), and a number of candidate genes and associated biological traits have been tested for influences on MD susceptibility (Elder and Mosack, 2011; Mandelli et al., 2009). Genetic variation in genes associated with the brain serotoninergic (5-HT) system is a major determinant of individual behavioral traits and responses to environmental stressors (Balestri et al., 2014) as well as the susceptibility to psychiatric disorders such as MD (Gao et al., 2012).

The tryptophan hydroxylase 2 gene (*TPH2*, 12q15) is the rate-limiting enzyme in the synthesis of brain serotonin and so is a critical regulator of serotonergic transmission (Mandelli et al., 2012; Walther et al., 2003). The association of TPH2 genetic variance with MD incidence has been widely investigated. Zill et al. found two single nucleotide polymorphisms (SNPs) in TPH2 associated with MD in Caucasians (Zill et al., 2004). Subsequently, Zhang et al. identified 1463G/A (rs120074175), a rare variant (allele

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frequency of 1%) that causes 80% loss of 5-HT production in vitro and correlates with MD (Zhang et al., 2005). A more common promoter polymorphism, −703G/T (rs4570625), was associated with MD (Gao et al., 2012), neurocognitive endophenotypes of depression (Brown et al., 2005), and emotional processing (Herrmann et al., 2007). Furthermore, another common polymorphism in the 5′-regulatory region, −473T/A (rs11178997), was associated with MD and stress responses (Shishkina et al., 2007) as well as with both unipolar and bipolar disorder (Van Den Bogaert et al., 2006).

However, many of these findings have not been replicated. Genome-wide studies have confirmed that the contributions of single genetic polymorphisms to MD incidence are small and thus difficult to replicate across studies (Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium, 2013). Moreover, genetic factors do not act in isolation but rather interact with environmental factors such as stressful life events. Indeed, numerous studies suggest that MD is a complex disorder resulting from the interaction of genetic and environmental factors (Uher, 2009; Walther et al., 2003), with neither genes nor environment likely to act in isolation to increase MD susceptibility (Liu et al., 2013). Gene-environment interaction (G × E) research provides a potential pathway for understanding how genetic differences influence the likelihood that exposure to environmental stress will result in psychopathology (Nugent et al., 2011).

Negative life events, such as loss, separation, interpersonal or family problems, occupational stress/unemployment, and poor social contacts/support, have long been recognized to play a pivotal role in both MD and suicide (Paykel, 1976, 2003). A meta-analysis of 25 studies confirmed the association between negative life events and MD (Kraaij et al., 2002), and Rice et al. found a positive correlation between negative life events and MD severity (Rice et al., 2003). The gene encoding for TPH2 is an excellent candidate susceptibility gene that may interact with negative life events (Mandelli and Serretti, 2013). Animal studies suggest that TPH2 allelic variation modulates the behavioral response to adverse environments and episodes, with certain genotypes increasing the risk of unfavorable behavioral outcomes that resemble emotional disorders (Waider et al., 2011).

The present study was designed to examine the interaction between TPH2 allelic variation and negative life events in a northern Han Chinese population.

2. Methods

2.1. Subjects and clinical assessments

A total of 289 patients with MD (79 males and 210 females; mean age 42.74 ± 12.18 years, range 18–60 years) and 289 age- and sex-matched control subjects with no history of neuropsychiatric disorders were assessed between March 2012 and February 2014. Both patients and control subjects came from the same geographical areas of Northern China and all were of Chinese Han origin. General demographic and clinical information on patients and controls is summarized in Table 1. Major depression was diagnosed according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria (American Psychiatric Association, 2000). Patients were interviewed by at least two trained psychiatrists using the Structured Clinical Interview for DSM-IV disorders (SCID-I). The inter-rater reliability kappa value of SCID was 0.82. Only subjects with a minimum score of 21 on the 24-item Hamilton Rating Scale for Depression (HAMD) entered the study. Patients did not receive any psychotropic medication within four weeks of assessment. Patients with organic brain disorders, a history of alcohol or drug abuse, or major neurological diseases were excluded.

Table 1
Characteristics of study participants.

	MD	Controls
Number of samples	289	289
Age (mean ± SD)	42.74 ± 12.18	41.97 ± 11.91
Sex (male/female)	79/210	83/206
HAMD score	30.41 ± 6.54	

This study was approved by the Ethics Committee for Medicine of Harbin Medical University, China. All participants provided written informed consent.

2.2. Assessment of negative life events

Negative life events were assessed using the Life Events Scale (LES) developed by Desen Yang and Yalin Zhang. The LES is composed of 48 items classified into three domains: family life (28 items), work (13 items), and social and other aspects (7 items) (Yang and YL, 1999). It has been validated in a Chinese population. Negative events include serious illness, housing, relationship, and social difficulties, relationship breakdowns, unemployment, and financial crises. The scores for positive and negative events were determined by the interviewers to yield a total life events score. The scale considers four aspects of the event: time of occurrence (absent = 1, more than one year ago = 2, within the past year = 3, chronic = 4), character (good = 1, bad = 2), influence on mood (absent = 1, mild = 2, moderate = 3, severe = 4, extreme = 5), and duration of influence (≤ 3 months = 1, 3–6 months = 2, 6–12 months = 3, > 12 months = 4). The 75% percentile (a score of 6) was used as a cutoff value for high- and low-level negative life events.

2.3. DNA extraction and genotyping

Genomic DNA was extracted from 250 μl EDTA-anticoagulated venous blood samples using the AxyPrep Blood Genomic DNA Miniprep Kit (Axygen, Union City, CA, USA). Three SNPs of the TPH2 gene were genotyped: rs4570625 (−703G/T), rs11178997 (−473T/A), and rs120074175 (1463G/A). The primers used for PCR amplification were designed using Primer 5.0 software, and the specificity of each potential primer was checked using Blast of the National Center for Biotechnology Information (Blastn Home Page).

Genotyping SNP rs4570625: PCR amplification was performed in a 25 μl reaction volume containing 2.5 μl 10 × PCR buffer (Tiangen, Beijing, China), 100 ng genomic DNA, 200 μM dNTPs, 0.2 μM of each primer, and 1.0 unit of Taq DNA polymerase (Tiangen, Beijing, China). The conditions used for PCR amplification were denaturation at 94 °C for 5 min, followed by 30 cycles of 94 °C for 1 min, 52 °C for 1 min, and 72 °C for 1 min, and final elongation at 72 °C for 10 min. The PCR products were purified and sequenced bidirectionally using an ABI 3730 DNA sequencer (Applied Biosystems, Foster City, CA, USA). The genotype of each SNP was identified by Chromas version 2.31.

Genotyping SNPs rs11178997 and rs120074175: The PCR amplification protocol for the TaqMan assays included denaturation at 95 °C for 5 min, followed by 40 cycles of 95 °C for 5 s and 60 °C for 30 s, and final elongation at 72 °C for 5 min. The TaqMan assays were then read on an ABI 7900 Fast Real-Time PCR System (Applied Biosystems). Fluorescence data files from each plate were analyzed by automated software (SDS 2.1; Applied Biosystems).

The primer sequences and lengths of the PCR products are given in Table 2.