

The association between serotonin-related gene polymorphisms and susceptibility and early sertraline response in patients with panic disorder

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Abstract

Background: A number of studies have shown that genetic factor plays an important role in etiology of panic disorder (PD). The aim of the present study was to examine the association of serotonin-related gene polymorphisms with PD risk. Then, we analyzed the correlation between these gene polymorphisms and response to sertraline drug.

Methods: 233 patients with PD and 231 healthy controls were enrolled in the study. Panic Disorder Severity Scale (PDSS) were administered to all subjects, and all patients in the study were also assessed after 4 weeks of treatment. The SLC6A4(rs140701, rs3813034, 5-HTTLPR and STin2), 5-HTR1A rs6295, 5-HTR2A rs6313 and COMT rs4680 gene polymorphisms were genotyped and assessed for the potential association.

Results: The allelic model showed that the SLC6A4 rs140701 polymorphism variant was significantly associated with increased risk of PD ($OR = 0.624$, 95 % CI 0.450-0.864, $p<0.05$), and a significant result was found in the dominant model ($OR = 0.546$; 95% CI, 0.371-0.804, $p<0.05$). There was a significant difference in allele and genotype frequency between responders and nonresponders in the 5-HTTLPR polymorphism ($OR = 0.205$, 95 % CI 0.128-0.328; $OR = 0.249$, 95 % CI 0.155-0.401, both $p <0.001$), indicating the PD patients with S-allele had a poorer response to sertraline than L-allele carriers.

Conclusions: The present study suggests that the SLC6A4 rs140701 polymorphism variant may be associated with susceptibility to PD, and 5-HTTLPR polymorphism may be a predictor of response to sertraline in the treatment of PD.

Background

Panic disorder is a common anxiety disorder characterized by sudden and unexpected panic attacks and accompany with obviously anticipatory anxiety. The estimated lifetime prevalence of PD is 3.4 to 4.7% [1,2]. It typically occurs in young adults, and women are more likely to be affected than men[3]. However, the etiology of PD is complex and unclear. A meta-analysis showed genetic factors explain approximately 43% of the variance in the PD[4], indicating an important role in the pathological PD. Previous studies have consistently demonstrated serotonin involvement in the neurobiology of PD[5,6]. Clinical studies also demonstrated that selective serotonin-reuptake inhibitors (SSRIs) increasing the synaptic availability of 5-HT and are effective in the treatment of PD[7]. Therefore, the certain variants in the serotonin-related genes, such as serotonin transporter (5-HTT), 5-HT1A receptor (5-HTR1A), 5-HT2A receptor (5HTR2A) and catechol-O-methyltransferase (COMT) genes, may influence 5-HT neurotransmission, and they are good candidates for the study of PD. A few studies have investigated the association between the 5-HTT linked polymorphic region (5-HTTLPR), 5-HTR1A rs6295, 5-HTR2A rs6313, COMT rs4680 polymorphisms and PD[8-16]. However, the results were hardly replicable and the pathogenesis of PD remains to be clarified. It is important to note that previous studies have been conducted in different ethnic groups, few of them have examined the relationship between these gene polymorphisms and PD in Chinese population.

SSRIs are recommended as the first-line treatment for PD. However, not all patients benefit from these antidepressants. With the advancement of pharmacogenomic technologies, genetic variation has been identified to contribute to individual response to antidepressants. Pharmacogenomic studies focusing on candidate gene polymorphisms implicated in antidepressant response, especially in the serotonergic pathway. Abundant evidence has shown that serotonin-related gene polymorphisms played an important role in the clinical effects of antidepressants. For example, a few studies investigated that 5-HTTLPR, intron 2 (STin2), 5-HTR1A rs6295, 5-HTR2A rs6313 and COMT rs4680 polymorphisms associated with antidepressant response[17-26]. However, these findings are inconsistent and do not completely explain the predictive effects of antidepressants. To our knowledge, many previous studies have been conducted in other psychiatric disorders, such as major depressive disorder [27-30], and few of them have conducted in PD. In addition, the different results of these studies might also be partly attributable to the differences in the type of antidepressant drug[31,32]. Sertraline, a SSRI which has been used widely to treat PD for its prominent therapeutical effects and low incidence of adverse events [33], was the first-line treatment treatment for PD. Hence, the first aim of this study was to investigate the association of serotonin-related gene polymorphisms including SLC6A4 (rs140701, rs3813034, 5-HTTLPR and STin2), 5-HTR1A rs6295, 5-HTR2A rs6313 and COMT rs4680 with PD risk, and the second aim was to examine the association between these single nucleotide polymorphisms (SNPs) and early response to sertraline treatment in PD.

Methods

Participants

233 patients with PD were recruited from inpatient and outpatient populations in the Department of Psychosomatic, Sichuan Provincial People's Hospital between May 2015 and December 2018(see recruitment flow chart in Figure S1). Diagnosis of PD was conducted according to the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) (SCID-1) [34], which was performed by trained psychiatrists. Patients with neurological diseases, and/or past or current episodes of major depression disorder, generalized anxiety disorder, manic disorder, bipolar disorder, schizophrenia or any other psychiatric disorders were excluded. In addition, 231 healthy controls were recruited from the Center of Health Examination, Sichuan Provincial People's Hospital. The SCID was also administered by a trained clinical psychiatrist to exclude a lifetime or current diagnosis of PD, major depression, generalized anxiety disorder, among others.

All subjects in this study were Han Chinese in China, and all subjects were free of acute or chronic somatic disorders. All patients were free of antidepressants or other psychotropic medications intake within 2 weeks before their examination. Demographic data and clinical presentations were obtained from medical records or qualified interviews. A 3-mL EDTA-anticoagulated peripheral blood sample was collected from every individual.

Measures

Panic Disorder Severity Scale(PDSS)

The Panic Disorder Severity Scale comprises 7 items, and participants are instructed to rate each item from 0-4 based on the severity of each symptom, with possible responses ranging from «none» to «extremely severe» [35]. The scale was translated into Chinese by Xiong HF [36], and the Panic Disorder Severity Scale-Chinese Version has good internal consistency (Cronbach's alpha) with the overall score (0.83).

Treatment

All patients received treatment for a 4-week period with sertraline(100-200 mg qd)), other psychotropic medications were not permitted during the study except for benzodiazepine, which was prescribed occasionally for insomnia with a minimal dosage at bedtime. PD severity was assessed using the PDSS at baseline and after 4 weeks of treatment. The response of PD was defined as a reduction of the pre-treatment PDSS score of at least 40%[37].

SNP Selection and Genotyping

The SNP selected was based on literature search and minor allele frequency(MAF) >0.05 of east Asian population from public databases. The references were listed in the Table S1. SNP genotyping was performed using an improved multiplex ligation detection reaction (iMLDR) technique which developed by Genesky Biotechnologies Inc. (Shanghai, China). The primer information of the reaction mixtures is described in Tables S2 and S3. The multiplex polymerase chain reaction(PCR) reaction volume(20 μ l) included 1 x GC-I buffer (Takara), 3.0 mM Mg 2+, 0.3 mM dNTP, 1 U HotStar Taq Polymerase (Qiagen Inc., Hilden, Germany), 1 μ l genomic DNA(5-10ng/ μ l), and 1 μ l Multiplex-PCR primermix. In addition, The 5-HTT of PCR reaction volume(10 μ l) included 10 x buffer I (Qiagen Inc), Q Solution(Qiagen Inc.), 0.2 mM Mg 2+, 1 U HotStarTaq polymerase (Qiagen Inc.), 1 μ l genomic DNA, and 1 μ l PCR primermix. The cycling program for PCR was 95 °C for 2 min, followed by 11 Cycles of 94 °C for 20 s, 65 °C for 40 s and 72 °C for 1.5 min, and each cycle decreased 0.5°C. The third step, 24 cycles of 94°C for 20s, 59°C for 30 s, finally, 72 °C for 2 min and 4 °C and a hold at 4°C. In addition, the 5-HTT of cycling program for PCR was 95 °C for 2 min, 35 cycles of amplification consisted of 94 °C for 20 s and 72 °C for 1.5 min, and final extension at 68 °C for 60 min and a hold at 4°C. The PCR product was purified with 5 U SAP and 2 U Exonuclease I at 37 °C for 1 h and then 15 min of 75 °C inactivation. The ligation reaction contained 1 μ l of 10 \times ligation buffer, 0.25 μ l Tag DNA ligase, 5' ligationprimer(1 μ M) 0.4 μ l, 3' ligationprimer (2 μ M) 0.4 μ l, 2 μ l purified multiplex PCR product, and 6 μ l ddH 2 O mixture. The ligation cycling program was 38 cyclesx (94 °C for 1.5 min and 56 °C for 4 min), and a hold at 4°C. Sequencing was conducted on 0.5 μ l ligation product, 0.5 μ l Liz500 Size Standard, and 9 μ l Hi-Di mixture (ABI3730XL). The raw data were analyzed by Gene Mapper v4.1 software (AppliedBiosystems, Foster City,CA USA). All primers, probes and labeling oligos were designed by and ordered from Genesky Biotechnologies Inc.

Statistical analysis

The data were analyzed using SPSS version 18.0 software (SPSS Inc., Chicago, IL, USA). Student's *t*-tests were used for inter group comparisons of continuous variables, with Pearson's chi-square tests

utilized for categorical variables. P values for the Hardy-Weinberg equilibrium (HWE) were tested by Pearson's chi-square test, and $P > 0.05$ indicated no significant deviation in allele and genotype frequencies among subjects. Associations between SNPs and disease status were determined based on the distributions of allelic frequencies and genetic models (additive, dominant, and recessive model), and odds ratios (ORs) and 95% confidence intervals (CIs) were performed in unconditional logistic regression analysis using PLINK v1.07,²⁰ adjusting for age, gender, educational level and resident location. To protect from Type I error, a Bonferroni correction was conducted. For all analyses, statistical tests were two-tailed and an alpha level of 0.05 was used to define statistical significance. Power calculation ($\alpha = 0.05$) was performed using Power and Sample Size Calculation Software (3.6.1).

Results

Demographic data and clinical manifestations

A total of 233 patients with PD (92 men, 141 women) and 231 controls (98 men, 133 women) were selected. The average age of the study sample was (35.65 ± 9.77) years, and the mean age of the control group was (36.96 ± 7.82) years. 53.6 percent of the patients ($n = 125$) were residing in urban locations, and 46.4 percent of the patients ($n = 108$) were residing in rural locations. No statistically significant differences were noted between cases and controls in terms of sex, age, education level and resident location($p > 0.05$). In addition, the mean total duration of panic disorder was (2.49 ± 1.45) years. The PDSS score was 15.47 ± 3.82 before medication and 9.51 ± 3.81 after 4 weeks of medication, and the score was significantly reduced after medication ($p < 0.05$). According to the definition of remission, the response rate was 42.1%(n=98). The demographic details of the sample are given in Table 1.

Association of serotonin-related gene polymorphisms with PD risk

To determine whether the sample size of this study has power to detect the real difference, a power analysis was performed. From the result of Table S4, the sample size of 233 vs 230 ensured that a two-sided test with $\alpha = 0.05$ had 80% power to detect an relative risk of 2.0 ($\Psi = 2.0$). All selected SNPs fulfilled the HWE in both cases and controls($p > 0.05$). To determine the extent of linkage disequilibrium (LD) between the two polymorphisms (rs140701, rs3813034) in SLC6A4 gene, standardized LD coefficient $D\bar{}$ was calculated for this pair of polymorphisms. The R^2 and $D\bar{}$ was 0.510 and 0.717 respectively, indicating weak LD between these two polymorphisms.

The allele distributions of SLC6A4 (rs140701 and rs3813034) were significantly different between PD cases and the controls($OR = 0.624$, 95 % CI 0.450-0.864, $p = 0.004$; $OR = 0.705$, 95 % CI 0.509-0.975, $p = 0.034$; respectively), and only SLC6A4 rs140701 remained significant after adjusting for Bonferroni's multiple testing($p = 0.028$). After adjustment for age, gender, educational level and resident location, the dominant model of SLC6A4 rs140701 showed the relative risk of PD for genotype CC+CT was lower than for genotype TT ($OR = 0.546$; 95% CI, 0.371-0.804, $p = 0.004$), and after Bonferroni correction for multiple comparisons, the significance remained ($p = 0.028$).

In addition, the dominant model of rs3813034 showed the relative risk of PD for genotype CA+AA was lower than for genotype CC (OR = 0.636; 95% CI, 0.432-0.935, p = 0.025). For serotonin-transporter-linked polymorphic region (5-HTTLPR) polymorphism, the relative risk of PD for genotype LL+LS was lower than for genotype SS (OR = 0.632; 95% CI, 0.436-0.916; p = 0.021). The additive model of rs140701 and rs3813034 showed similar association with PD(OR = 0.638, 95 % CI 0.463-0.879, p =0.009; OR = 0.721, 95 % CI 0.526-0.988, p =0.048; respectively). However, these correlations were no longer significant after adjusting for Bonferroni's multiple testing (p >0.05). Also, there were no significant associations of other SNPs with PD in allelic or other models (p >0.05) (Table 2).

Association between serotonin related gene polymorphisms and early response to sertralines in the treatment of PD

Finally, we investigated whether variations of gene could predict response to sertraline in Han Chinese population with PD. There was a significant difference in allele and genotype frequency between responders and nonresponders in the 5-HTTLPR polymorphism (OR = 0.205, 95 % CI 0.128-0.328; OR = 0.249, 95 % CI 0.155-0.401, all p ^{corr} =0.000; respectively), and the dominant and recessive model of 5-HTTLPR showed significant association with therapeutic response, indicating the PD patients with S-allele had a poorer response to sertraline than L-allele carriers. However, genotype and allele frequencies of the other gene polymorphisms were not significantly different between responders and nonresponders (p >0.05). (Table 3).

Discussion

In this present study, a significant relationship was found between the SLC6A4 rs140701 polymorphism and PD. The patients with PD possessed significantly higher frequencies of the TT genotype compared to the controls. This result is consistent with the previous study reported that only SNP rs140701 was associated with PD in a 163 sample of African American [9]. Similar studies have found a nominally significant association of rs140701 with social anxiety disorder[38]. The serotonin transporter (5-HTT) is encoded by the α solute carrier family 6 β (neurotransmitter transporter) member 4 (SLC6A4) gene, at locus 17q11.2. SNP rs140701 is located in intron 9 of the serotonin transporter gene SLC6A4. SLC6A4 is involved in the transport of serotonin from synaptic spaces to presynaptic neurons, and the pool of available serotonin for subsequent release [39].Collective evidence suggests the involvement of the serotonin system in the neurobiology and pharmacotherapy of PD[5-7]. Specific SLC6A4 variants may be associated with PD. In addition, previous studies have found 5-HTT knockout mice showed increased anxiety-like behaviour. Such cases have been shown in an animal experiment which found homozygous 5-HTT knockout mice were more anxious [40,41], while 5-HTT overexpressing mice displayed reduced anxiety-like behaviour[42]. These findings suggest that the importance of the SLC6A4 gene polymorphisms in genetic association studies of PD. However, the SNP rs140701 of function is unclear and remains to be clarified in future studies.

However, we did not find any significant association evidence within the promoter region (5-HTTLPR), rs3813034 and STin2 polymorphisms of the SLC6A4 gene, which is consistent with findings from other studies and meta-analysis demonstrating that the 5-HTTLPR and STin2 were not associated with PD[43,44]. However, inconsistent with previous research which has found the rs3813034 of SLC6A4 is a putative risk factor for PD and other behavioral disorders that involve dysregulation of serotonergic neurotransmission[45]. Additionally, we found no significant statistical differences in the genotype distributions or allele frequencies of the SNPs (5-HTR1A rs6295, 5-HTR2A rs6313 and COMT rs4680) between PD and control groups. In a study comprised of 119 PD patients and 119 healthy controls from Japanese population, no significant differences were found in the allele frequencies or genotype distributions of the COMT rs4680 or the 5-HT1A (rs6295) between PD patients and controls [10], but other studies have found significant relationship between the COMTVal158Met (rs4680) polymorphism and PD [14,15]. In a meta analysis, the COMT gene Val158Met polymorphism has been found to be associated with PD in European ancestry, but not Asian ancestry[46]. Previous studies also found pure PD was associated with HTR2A 102T-C (rs6313) polymorphism [47], but not in other study [14]. The above findings of genetic association studies are limited and inconsistent. These mixed results of studies might be attributable to different samples, sex, races, agoraphobia co-morbidity or severity of PD. For example, previous study showed that the HTR2A rs6311 polymorphism was associated with the severity of PD [43]. Above all, these conflicting findings indicate that the contribution of genetic factors to PD may involve a complex network of variants.

In the present study, we only found significant correlation between 5-HTTLPR

polymorphism and treatment response to sertraline after 4-weeks treatment for PD. The results of our study indicated the PD patients with S-allele was linked to poorer response to sertraline during the early stage of treatment, suggesting that 5-HTTLPR could be a predictor of response to sertraline treatment. 5-HTTLPR is a 44 base pair insertion\deletion polymorphism which can exist as a long (L) variant of a 16 repeat sequence or a short (S) variant of 14 repeats [48]. Previous researches indicated the L allele was associated with higher levels of transcription and concentrations of 5-HTT mRNA compared to the S allele, and the short (S) allele of the 5-HTTLPR polymorphism resulted in less efficient transcription [49-51]. This may explain the fact to some extent that the SSRIs are effective in the treatment of PD with the SLC6A4 being the primary drug target. These findings may contribute to our understanding of the association between 5-HTTLPR polymorphism and antidepressant response. Consistent study found the 5-HTTLPR low-expression genotypes showed a more favorable response to exposure-based behavior therapy in PD with agoraphobia [52]. Similar findings were found in subjects with depressive disorder treated with sertraline [53]. However, previous report found no association of the 5-HTTLPR polymorphism with treatment response in a sample size of 102 PD patients treated with sertraline or paroxetine [54]. Also, there was no significant associations between the 5-HTTLPR polymorphism and sertraline responses in major depression patients [55]. On the one hand, other polymorphisms of SLC6A4 may have a combined effect with 5-HTTLPR. In addition, the variants of cytochrome P450 enzyme genes may also contribute to the pharmacokinetics. One study found the CYP2C19 genetic polymorphism is associated with Escitalopram treatment response in Chinese patients

with PD [56]. On the other hand, functional variants in SLC6A4 may be related to epigenetic mechanisms and affect gene expression. For instance, epigenetic modifications of SLC6A4 gene is showing promising results as biomarkers for prediction of antidepressant response [57]. Notably, evidence has been shown that different ethnicities responded differently to antidepressants possibly due to the variants in the SLC6A4 genes. One Meta-analysis showed 5-HTTLPR may be a predictor of antidepressant response and remission in Caucasians, while it does not appear to play a major role in Asians [58]. Last but not the least, we did not find the relationship between other gene polymorphisms and treatment response to sertraline. This is inconsistent with previous studies that found the 5-HT1A receptor -1019C/G polymorphism was strongly associated with response to treatment in PD receiving sertraline or paroxetine [54,59]. Another study suggested that the genetic variant of the COMT enzyme may be related to treatment response to paroxetine in PD [60]. Inconsistent results may be related to small sample size, short follow-up periods, definition of response, antidepressant choice and ethnic differences. In addition, gene-environment interactions may also contribute to these inconsistent findings and provide more robust predictors of treatment response.

Conclusions

The present study suggests that the SLC6A4 rs140701 variant may be associated with susceptibility to PD, and 5-HTTLPR polymorphism may be a predictor of response to sertralines in the treatment of PD. However, the results of our study should be considered in light of the following limitations: (1) The sample size was limited and only from Sichuan provinces of western China, which may not completely represent the Chinese ethnicity. (2) The etiology of PD is complex and comprises environmental and genetic factors, a potential gene-environment interaction or epigenetics study should be investigated. (3) We did not measure the relationship between plasma sertraline concentration and clinical response.

Abbreviations

COMT: Catechol-O-Methyltransferase; CIs: Confidence Intervals; CYP450: Cytochrome P450; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders fourth edition; HWE: Hardy-Weinberg Equilibrium; L: Long; LD: linkage disequilibrium; ORs: Odds Ratios; PD: Panic disorder; PDSS: Panic Disorder Severity Scale; PCR: Polymerase Chain Reaction; SCID: Structured Clinical Interview for DSM-IV; SNPs: Single Nucleotide Polymorphism; S: Short; SLC6A4: Serotonin Transporter Gene; SSRIs: Selective Serotonin-Reuptake Inhibitors; STin2: intron 2; 5-HTR1A: 1A receptor; 5-HTR2A: 5-Hydroxytryptamine 2A receptor; 5-HTT: Serotonin Transporter; 5-HTTLPR: Serotonin-Transporter-Linked Polymorphic Region.

Declarations

Ethics approval and consent to participate

The study was approved by the Sichuan Provincial People's Hospital ethics committee, reference number: (2016) Ethics Review (29). All individuals provided written informed consent prior to the initiation

of study procedures.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

ZLZ was critically involved in the study design and wrote the manuscript. YLH, JYW and WJM were involved in subject recruitment. BZ guided this research and supervised the entire project. All authors read and approved the final manuscript.

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Figures



Figure 1

Linkage disequilibrium in SLC6A4 gene polymorphisms (rs3813034 and rs140701).

Supplementary Files

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