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Serotonin 2A receptor gene is associated with personality traits, but not to disorder, in patients with borderline personality disorder

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Abstract

Borderline personality disorder (BPD) is a chronic, disabling, and high-risk mental disorder characterized by a pervasive pattern of instability in regulation of emotion, interpersonal relationships, self-image, and impulse control beginning in early adulthood. BPD affects about 1%–2% of the general population and has a high mortality rate as a result of suicide and impulsive behaviour. The serotonin 2A receptor gene (HTR2A) is considered a candidate gene for BPD because multiple lines of evidence suggest that it plays an important role in suicide, impulsivity and emotional liability. To test for an association between HTR2A and BPD, we genotyped four polymorphisms, rs6313 (T102C), rs4941573, rs2296972 and rs6314 (His452Tyr), in 111 Caucasian patients with BPD and 287 Caucasian healthy controls. The program UNPHASED was used to compare allele and haplotype frequencies between cases and controls. We did not find a significant association between HTR2A and BPD based on allele, genotype or haplotype analyses. However, there were significant associations between HTR2A and personality traits in the BPD patients. The C allele of rs6313 and the A allele of rs4941573 associated with a higher Extraversion score. Our results suggest that the serotonin 2A receptor gene may not play a major role in the aetiology of borderline personality disorder, but may have a role in personality traits.

Keywords: Borderline personality disorder; Personality trait; Genetics; Candidate gene; Serotonin 2A receptor gene; Association study

Borderline personality disorder (BPD) is a chronic, disabling, and high-risk mental disorder characterized by a pervasive pattern of instability in regulation of emotion, interpersonal relationships, self-image, and impulse control beginning in early adulthood. It affects about 1%–2% of the general population, up to 10% of psychiatric outpatients and 20% of psychiatric inpatients [49]. The disease has a high mortality rate as a result of suicide and impulsive behaviour—up to 10% of patients commit suicide [2]. The cause of BPD is complex and likely includes genetic factors and adverse childhood experience [27]. The morbidity risk of BPD in first-degree relatives is 11.5%, much higher than 1%–2% in the general population [34]. One twin study showed a heritability of 69%, suggesting a strong genetic effect in the development of BPD [49].

It has been suggested that the serotonin 2A receptor gene (HTR2A) is associated with suicidal and/or impulsive aggressive behavior. Several studies, though not all, report a elevated serotonin 2A receptor binding in the brain of suicide victims, particularly in the prefrontal cortex [3,4,14,18,19,28,41,51,54,56]. Also, HTR2A receptors were increased on platelets of suicidal patients [41]. This anatomically diverse distribution of receptor change raised the possibility of a genetic origin. The T102C and His452Tyr polymorphisms in HTR2A are suggested to be functional markers [39,54]. The first studies examining the role of HTR2A in suicidal behavior were published in 1999 [12,54]. Du et al. [12] did not find any association between the T102C variant and suicide, but the 102C allele associated with major depression [11]. Several other studies have subsequently failed to find an association between HTR2A and suicide [6,37,44]. A recent meta-analysis of suicide association studies found no association in combining nine studies of the T102C variant [1].

Aggressive behavior is reported to be independently associated with low or impaired serotonergic function [55]. Low cerebrospinal fluid 5-HIAA has been observed in aggressive patients with no history of suicide attempt [50]. Coccaro et al. [8] studied the relationship between platelet serotonin 2A recep-

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tor binding and aggressive behavior, and found both density and affinity values correlated positively with Buss-Durkee Hostility Inventory (BDHI) Assault scores in patients with personality disorder, but not in healthy controls. Oquendo and Mann reported a significant correlation between lifetime aggression scores and serotonin 2A receptor binding in suicide subjects, but not in nonsuicide subjects [38]. The T102C polymorphism in HTR2A has been reported to be associated with neuropsychiatric symptoms including aggression in patients with Alzheimer's disease [5,24].

As for its role in aggression, suicide and mood liability [38], HTR2A can be considered a functional candidate in BPD. Studies of patients with alcohol dependence found no association between a subgroup of subjects with BPD and HTR2A though alcohol dependence with high impulsivity showed a significant association with the -1438A allele [45]. Extracting data from Nishiguchi et al.'s study in Japanese patients with eating disorders, we can find that BPD tended to be associated with increased frequency of the -1438G allele [35]. To our knowledge, there is still a lack of well-designed genetic association studies on HTR2A and BPD. To test for this hypothesis we genotyped four HTR2A polymorphisms in 111 Caucasian BPD patients and 287 Caucasian healthy controls and performed association analyses using individual marker and haplotype data. A number of studies showed a significant relationship between HTR2A and personality traits, but with conflicting results [15,21,47,53]. Moreover, personality traits have been considered to be endophenotypes in aggression and suicidal behavior [46,48]. Therefore, we also carried out an association analysis between HTR2A and personality traits in a subgroup of the BPD patients ($n = 72$).

One hundred and eleven Caucasian patients with DSM-IV BPD (male = 18, female = 93), and 287 healthy Caucasian controls (male = 135, female = 152) were recruited from Toronto and central Canada. A structured interview of International Personality Disorder Examination (IPDE) was administered to each patient to establish a DSM-IV diagnosis of BPD. A Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I) was also applied. Most of the patients also participated in a clinical treatment research project supported by the Canadian Institute of Health Research (CIHR, P.I.: Dr. Shelley McMain). Patients with psychotic disorder, bipolar I disorder, dementia, current active substance dependence disorder, or organicity were excluded. A subgroup of the patients ($n = 72$, male/female = 11/61) finished a scale of personality traits with the revised NEO Personality Inventory (NEO-PI-R). The controls were screened for history of major psychiatric disorders or history of substance abuse, and excluded if either was detected, currently or in the past. Informed consent was obtained from each participant prior to investigation.

Four polymorphic markers in HTR2A [rs6313 (102T/C) [57]; rs4941573; rs2296972; and rs6314 (His452Tyr) [40]] were genotyped. The -1438 A/G polymorphism in the promoter region was not analyzed because it is in complete linkage disequilibrium (LD) with the T102C marker. Markers rs6313, rs4941573 and rs229697 were genotyped using TaqMan SNP genotyping assays [16,32]. A PCR-restriction fragment length polymorphism (RFLP) was used for the His452Tyr polymorphism [33].

The statistical power of the samples was calculated using Power Calculator on the UCLA website (http://calculators.stat.ucla.edu/powercalc/) for the case-control study. The program HaploView (Version 2.04) was used to test for concordance with Hardy-Weinberg equilibrium, calculate D' between SNP pairs and identify LD blocks. The program COCAPHASE in UNPHASED (Version 2.403) was used for an association analysis using both alleles and haplotypes [13]. Comparison of genotype frequencies between cases and controls was performed with chi-square test. The program QTPHASE in the UNPHASED was used to association study of HTR2A and personality traits in a subgroup of the BPD patients. An analysis of variance (ANOVA) was used to compare personality scores among patients grouped by genotypes.

Our case-control study had 80% power to detect a relative risk as low as 1.89 after setting significance level to 0.05. For both cases and controls, distributions of genotype frequencies of the four HTR2A polymorphisms were in Hardy-Weinberg equilibrium ($p > 0.10$). Although there was a significant difference in the sex ratio between patients with BPD and control samples ($X^2 = 32.13$, $p < 0.001$), there were no differences in allele and genotype frequencies of the four markers between males and females ($p > 0.05$). The first two markers (rs6313 and rs4941573) demonstrated a LD block in BPD patients though no LD block was found among markers in controls. Cases also showed a higher D' value between rs2296972 and rs6314 than the controls (0.86 versus 0.22).

We did not find significant differences in allele or genotype frequencies between BPD patients and controls ($p > 0.05$) (Table 1). Moreover, there was no significant association of HTR2A haplotypes and BPD using all four markers ($X^2 = 16.471$, $p = 0.125$) (Table 2). However, we found a trend toward significance in the rs2296972-rs6314 haplotypes ($p = 0.05$).

In 72 patients who took the NEO-PI-R, we found the C allele of rs6313 and the A allele of rs4941573 associated with a higher Extraversion score (LRS = 5.703 and 7.223, $p = 0.017$ and 0.007, respectively) (Fig. 1). Rs6313 genotypes showed a trend to significance with Extraversion ($F = 2.558$, $p = 0.085$). We detected significant differences of the extraversion score among patients grouped upon genotypes in rs4941573 ($F = 4.403$, $p = 0.016$) (Fig. 1). Patients with the rs4941573 A/A genotype, compared to G/G genotype, demonstrated a higher score of Extraversion after Bonferroni multiple comparisons ($p = 0.012$). Moreover, rs6313 and rs4941573 haplotypes in one LD block also associated with Extraversion (LRS = 11.834, $p = 0.008$). The C-A haplotype showed a significant high Extraversion score ($X^2 = 8.828$, $p = 0.003$) (Table 2). For other personality traits, rs6313 and rs4941573 showed a trend toward significance with Neuroticism based on allele analysis (LRS = 3.324 and 3.633, $p = 0.068$ and 0.057, respectively). We also observed a trend to significance between rs4941573 genotype and Neuroticism ($F = 2.452$, $p = 0.094$).

In this study we did not find any significant differences in HTR2A allele, genotype or haplotype frequencies between BPD patients and controls. In a subgroup of the BPD patients taking the NEO-PI-R, we found that higher Extraversion scores asso-