

Association between serotonin transporter gene and borderline personality disorder

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Abstract

Borderline personality disorder (BPD) is 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 transporter gene (5-HTT) is considered as a candidate gene for BPD as multiple lines of evidence have suggested that it plays an important role in suicide, impulsive behaviour, and emotional lability. To test for an association between 5-HTT and BPD, we genotyped three common polymorphisms: the serotonin transporter linked promoter region (5-HTTLPR); a variable number of tandem repeat (VNTR) in intron 2, and a single nucleotide variant (A/G) within the LPR region. Eighty-nine Caucasian patients with BPD and 269 Caucasian healthy controls were analyzed. The program UNPHASED was used to compare allele and haplotype frequencies between cases and controls. Significant differences in allele frequencies of the VNTR marker ($p = 0.012$) and haplotype frequencies ($p = 0.002$) between patients and controls were found. Compared with healthy controls, patients with BPD showed higher frequencies of the 10 repeat of the VNTR marker and the S-10 haplotype, and lower 12 repeat and L_A-12 haplotype. Our results suggest that the serotonin transporter gene may play a role in the aetiology of borderline personality disorder.

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1. Introduction

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 (Torgersen et al., 2001). The disease has a high mortality rate as a result of suicide and impulsive behaviour – up to 10% of patients commit

suicide, a rate almost 50 times higher than in the general population (APA, 2001). Due to substantial treatment utilization, patients with BPD require more mental-health resources than do individuals with other psychiatric disorders (Bender et al., 2001; Zanarini et al., 2001).

The cause of borderline personality disorder is complex with several factors, including genetic factors and adverse childhood experience, interacting in various ways (Lieb et al., 2004). Investigators found statistically significant increases in the rate of the disorder in relatives of BPD patients compared to relatives of controls, and observed familial transmission of BPD (Skodol et al., 2002; Torgersen, 2000). The morbidity risk of BPD in first-degree relatives is 11.5%, much higher than 1–2% in the general population (Nigg and Goldsmith, 1994). In one twin study,

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BPD concordance rates were 35% and 7% in monozygotic and dizygotic twin pairs, respectively, suggesting a moderate genetic effect in the development of the disorder (Torgersen et al., 2000).

Multiple lines of evidence suggest that the serotonin transporter gene (5-HTT) plays an important role in suicide (Bondy et al., 2000; Simeon et al., 1992), impulsive behaviour (Coccaro et al., 1996; Frankle et al., 2005; Lesch et al., 1996), and emotional lability (Collier et al., 1996; Hoefgen et al., 2005), suggesting it as a candidate gene for borderline personality disorder. It has been reported that the long A variant of the 5-HTT gene linked polymorphic region (5-HTTLPR) and rs25531 is associated with high levels of 5-HTT mRNA while the long G and short variants with lower mRNA level (Goldman et al., 2004). For a variable number of tandem repeats (VNTR) in intron 2, higher expression of the 12-repeat was found when compared to 10-repeat (MacKenzie and Quinn, 1999). Furthermore, 5-HTTLPR was shown to be associated with amygdala activation in response to emotional faces (Hariri et al., 2005), and the amygdala was reported to be dysregulated in BPD (Donegan et al., 2003; Ebner-Priemer et al., 2005). Recently, Steiger et al. (2005) studied 59 women with bulimia-spectrum disorders and found that bulimia patients with BPD ($n = 13$) showed a higher short (S) allele frequency of 5-HTTLPR (Steiger et al., 2005).

Commonly used polymorphic markers in 5-HTT are the 5-HTTLPR and the intron 2 VNTR in (Battersby et al., 1996; Heils et al., 1996). Recently, a single nucleotide variant (A to G, rs25531) was detected in the region of 5-HTTLPR and shown to create an AP2 binding site (Goldman et al., 2004). In this paper we, for the first time, tested for an association between 5-HTT and BPD in 89 Caucasian BPD patients and 269 Caucasian healthy controls.

2. Materials and methods

2.1. Subjects

Eighty-nine Caucasian patients with DSM-IV BPD (male = 13, female = 76, age = 32.0 ± 9.5), and 269 healthy Caucasian controls (male = 128, female = 141, age = 37.5 ± 12.8) were recruited from Toronto and central Canada. A structured interview of the international personality disorder examination (IPDE) was administered by trained research assistants to each patient to establish a DSM-IV diagnosis of BPD and other personality disorders. A structured clinical interview for DSM-IV Axis I disorders (SCID-I) was also applied. Two senior psychiatrists each reviewed the information packages (including IPDE, SCID-I and medical records), and made the diagnosis independently. When there was disagreement between these two diagnostic decisions, a third clinical research expert would review the patient's dossier and decide on a final diagnosis. All patients also participated in a clinical 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. Control subjects were screened for major psychiatric disorders and substance abuse, and excluded if either was detected currently or in the past. Informed consent was obtained from each participant prior to investigation, and DNA was extracted from blood samples using a high-salt extraction procedure (Lahiri and Nurnberger, 1991).

2.2. Genotyping

The 5-HTTLPR and rs25531 polymorphisms in the promoter region was amplified by the polymerase chain reaction (PCR) and digested by MspI restriction enzyme. High-resolution agarose gel was used to separate different alleles: long A (L_A) = 340bp, long G (L_G) = 166 bp + 174 bp and short (S) allele = 297 bp (Goldman et al., 2004; Heils et al., 1996). We did not find MspI cutting site in short allele in our samples. We also detected three alleles of the VNTR, the 9 repeat (345 bp), 10 repeat (360 bp) and 12 repeat (390 bp), using PCR amplification and high-resolution agarose gel electrophoresis (Battersby et al., 1996).

2.3. Statistical analysis

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 UNPHASED (version 2.403) was used to test for association of 5-HTT and BPD using both alleles and haplotypes, and to calculate the D' values between markers (Dudbridge, 2003). Comparison of genotype frequencies between cases and controls was performed with a χ^2 test. Odds ratios (OR) with 95% confidence intervals were estimated for the effects of high-risk alleles (www.hutchon.net/ConfidOR.htm) (Bland and Altman, 2000). Due to sex and age differences between cases and controls ($p < 0.001$ and $=0.007$, respectively), a backward stepwise logistic regression method was performed, with the diagnosis as the dependent variable, and the sex and age of subjects and alleles, genotypes and haplotypes as the independent variables (Luo et al., 2005).

3. Results

Our case-control study had 80% power to detect a relative risk as low as 1.99. For both cases and controls, distributions of genotype frequencies of the 5-HTT polymorphisms were in Hardy–Weinberg equilibrium. There was no strong linkage disequilibrium between the 5-HTTLPR and VNTR markers in either cases or controls ($D' = 0.54$ in total sample). Although there was a difference in the sex ratio between BPD patients and control samples ($X^2 = 30.46$, $p < 0.001$), there were no differences in allele and genotype frequencies of the markers in 5-HTT between males and females (all $p > 0.10$).

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