Serotonin transporter polymorphism and borderline or antisocial traits among low-income young adults

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Objectives The short allele of the serotonin transporter linked polymorphic region, 5HTTLPR has been associated with anxiety, major depressive disorder and suicidality. The impulsive self- and other-damaging behaviors seen in borderline personality disorder and antisocial personality disorder also have substantial comorbidity with depression but are associated with more severe environmental stressors. This study tested the hypothesis of an association between the short allele of the 5HTTLPR and borderline or antisocial traits in young adulthood.

Methods The 5HTTLPR was genotyped among 96 young adults from low to moderate income families (62 adults without and 34 adults with borderline personality disorder or antisocial personality disorder traits). Traits of borderline and antisocial personality disorders were assessed with the Structured Clinical Interview for Diagnosis-Axis II.

Results The number of short 5HTTLPR alleles were significantly related to incidence of borderline personality disorder or antisocial personality disorder traits and also to each set of traits independently. Male sex and quality of care in infancy were also associated with incidence of borderline personality disorder and antisocial personality disorder traits but did not account for the association with the short allele. Depressive disorders were not associated with the short allele in this sample.

Conclusions Young adults of lower socioeconomic status who carry the short 5HTTLPR allele may be especially vulnerable to developing antisocial or borderline traits by young adulthood. *Psychiatr Genet* 17:339–343 © 2007 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Impulsive self-damaging behaviors constitute the core features of borderline personality disorder (BPD) whereas impulsive other-damaging behaviors are criteria for antisocial personality disorder (APD) (American Psychiatric Association, 1994). Their underlying phenotypic commonalities, however, are acknowledged in that both BPD and APD are grouped together as part of Cluster B 'dramatic/erratic' personality disorders. These two variants of impulse disorders are strongly associated with sex, with men more likely to be diagnosed with antisocial disorder and women more likely to be diagnosed with borderline disorder. Therefore, the combined borderline/antisocial symptom phenotype may describe a common core predisposition to engage in disregulated and destructive behaviors when under stress, a phenotype that is expressed somewhat differently by men and women. While both antisocial and self destructive behaviors have considerable comorbidity with dysphoric symptoms of anxiety and depression, they have also been associated with more adverse life events than anxiety and depression alone (Blanz *et al.*, 1991; Zanarini *et al.*, 1997).

Disruption in the serotonin neurotransmitter system has been linked to suicidal behavior and impulsive aggression toward others by a variety of methods. Low levels of the serotonin metabolite (5-hydroxyindoleacetic acid) were detected in the cerebrospinal fluid of BPD patients and nonsuicidal aggressive psychiatric patients (Brown *et al.*, 1982; Stanley *et al.*, 2000). In one study, low 5-hydroxyindoleacetic acid levels were characteristic of impulsive violent offenders (Linnoila *et al.*, 1983). In addition, tryptophan (the precursor of serotonin) depletion has been reported to increase aggressive behaviors in healthy men (Moeller *et al.*, 1996). Another determinant of serotonin metabolism, the monoamine oxidase-A (MAO-A) enzyme, has been associated with aggressive forms of impulsive behavior. In a large Dutch family study, aggressive and violent behavior was reported in MAO-A deficient men (Brunner *et al.*, 1993). Mice lacking this enzyme also showed enhanced aggression in adulthood (Cases *et al.*, 1995).

The genetic background of personality disorders, including APD and BPD, was assessed by a twin study

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demonstrating that genetic factors accounted for about 60% of the variance in liability (Torgersen *et al.*, 2000). Using a candidate-gene approach, meta-analyses of data on serotonin-related genes supported the role of the short allele of the serotonin transporter linked polymorphic region (5HTTLPR) as a genetic risk factor for suicide, whereas other polymorphisms in the serotonin receptor genes were not shown to play a role (Anguelova *et al.*, 2003). Moreover, Caspi *et al.* (2003) demonstrated the importance of gene–environment interaction in that stressful life events predicted increased suicidal ideation or attempts among those who had at least one short 5HTTLPR allele but not among those with the long/long genotype. The 5HTTLPR is located in the promoter region of the serotonin transporter gene (*SLC6A4*) and the short (44 basepair deletion) variant showed reduced transcription activity in reporter gene systems (Lesch *et al.*, 1996; Heils *et al.*, 1997). Therefore, this risk allele may account for reduced serotonin uptake in the serotonergic synapses.

Impulsive aggressive behaviors also show genetic underpinnings. Research involving children and adolescents typically find that both shared rearing environments and genetic factors account for variation in aggressive behaviors (Edelbrock *et al.*, 1995; Miles and Carey, 1997). A retrospective twin study demonstrated a substantial genetic influence on the risk for conduct disorder with a heritability estimate of 71% (Slutske *et al.*, 1997). In a later review, Slutske (2001) points out the developmental changes in heritability of antisocial behaviors. In a population-based sample of 6806 adult twins, Jacobson and colleagues (2002) found that heritability increased from childhood to adolescence and adulthood but the genetic and environmental influences on the development of antisocial behavior were similar for men and women. Demonstrating the potential importance of gene-environment interaction, Caspi *et al.* (2002) found that maltreated men with the low MAO-A activity genotype were more likely to develop conduct disorder than nonmaltreated men with the same genotype.

Consistent with the Caspi *et al.* (2003) findings that environmental stressors may interact with the presence of the 5HTTLPR short allele to produce depressive symptoms and suicidality, we hypothesized that genetically mediated vulnerability to dysphoric affect may potentiate not only anxiety or depression but also more impulsive self or other damaging behaviors. In particular, genetic vulnerability to such impulsive behaviors may be more evident when environmental conditions are less favorable. Here we examine the contribution of the serotonin transporter promoter polymorphism to antisocial and borderline traits among young adults from low to moderate income families.

Method

Participants

Study participants were 96 young adults aged 18–22 from low-to-moderate income families participating in a study of adolescent–parent relationships. Forty percent of the families ($n = 38$) had been participating in a longitudinal case–control study of attachment relationships since the first year of the child's life. Longitudinal families were recruited at child age 0–18 months and all families were at or below federal poverty level at intake (Lyons-Ruth *et al.*, 1990). Fifty-eight additional cross-sectional families were recruited as part of the young adult follow-up study and matched to the longitudinal sample on socioeconomic status. Among the longitudinal families, 53% had been referred to clinical services during the young adult's infancy for concerns about the quality of care provided and 47% were socioeconomically-matched controls. Problems in early care were further validated by an 1-hour observation at home by study clinicians and laboratory assessments (Lyons-Ruth *et al.*, 1987, 1990; Lyons-Ruth and Melnick, 2004). The study was conducted in compliance with the Code of Ethics of the World Medical Association and with the requirements of the Hospital Institutional Review Board and the National Institute of Mental Health. All young adults and their mothers provided written informed consent for their participation.

Procedure

Structured Clinical Interviews for Diagnosis (SCID) were administered in the laboratory by trained interviewers to assess borderline and antisocial traits. The SCID yields psychiatric diagnoses for both Axis I and Axis II disorders (First *et al.*, 1997a, b). Reliability analyses for the SCID have yielded κ values of 0.61 for current diagnosis and 0.68 for lifetime diagnoses. These figures are comparable with other structured diagnostic interviews. Borderline and antisocial traits were coded as present if two or more features of the disorder were endorsed.

Noninvasive sampling and DNA isolation were performed as described by Boor *et al.*, 2002, except that Purgene DNA Purification kits (Gentra Systems; Minneapolis, Minnesota, USA) were used for DNA isolation. Schleicher & Schuelle IsoCode ID kits (Schleicher & Schuelle; Keene, New Hampshire, USA) were used for samples collected by mail. Genotyping of the 5HTTLPR was performed as described elsewhere (Nemoda *et al.*, 2001). Genotype frequencies (s/s, s/l, and l/l) did not show significant deviation from the Hardy–Weinberg equilibrium ($P = 0.76$). No relation between sex and genotype [χ^2 (2, 896) = 1.03, n.s.] existed, with 61% of men and 66% of women carrying one or more short alleles.

Racial/ethnic characteristics of the sample were as follows: 73% Caucasian; 27% one or two parents African–American; no Asian participants. The possibility of spurious association due to sample heterogeneity was assessed by genomic control (Devlin and Roeder, 1999), analyzing 40 random marker polymorphisms distributed evenly along the human genome (1–3 markers per chromosome). No significant association ($P < 0.05$) was found for the marker polymorphisms with either borderline or antisocial traits. Further analysis of potential racial subpopulations is presented below.

Statistical analyses

SPSS 14.0 for Windows (SPSS; Chicago, Illinois, USA) was used for data analysis. Binary logistic regression models were calculated for prediction of borderline/antisocial traits.

Results

As both antisocial and borderline features are rare and may represent gendered variants of a similar impulsive response to the dysphoric effect, in the first set of analyses a single variable indexing the presence of either antisocial or borderline traits was used. Thirty-five percent of young people in the sample displayed borderline or antisocial traits. An initial binary logistic regression analysis was conducted predicting presence of borderline or antisocial traits from male gender, race (Caucasian/African–American), and number of short 5HTTLPR alleles (l/l, s/l, s/s). Number of short 5HTTLPR alleles was significantly associated with presence of APD/BPD traits, Wald = 4.23, d.f. = 1, $P < 0.04$, Odds ratio (OR) = 2.0. Follow-up contrasts indicated that, with race and sex controlled, the incidence of borderline or antisocial traits was significantly different for young adults with the s/s genotype compared to those with the l/l genotype, Wald = 4.27, d.f. = 1, $P = 0.04$, OR = 4.1. Comparison of l/l and s/l genotypes did not reach significance, Wald = 1.34, d.f. = 1, $P = 0.25$. The data are presented in Table 1.

No effect of race on presence of APD/BPD traits existed, Wald = 0.36, d.f. = 1, $P < 0.55$. Consistent with the literature, with allele frequencies and race controlled, men independently conferred significant added risk for APD/BPD traits (primarily APD traits, see below), Wald = 4.24, d.f. = 1, $P < 0.04$, OR = 2.6 (28% of women; 47% of men displayed traits). Given limited statistical power to assess a genotype by race interaction term, data for Caucasian ($n = 70$) and African–American ($n = 26$) participants were also analyzed separately. Genotype distribution for Caucasians was 25.7% (l/l), 54.3% (s/l), and 20% (s/s); for African–Americans, 61.5% (l/l), 27% (s/l), and 11.5% (s/s). These descriptive data suggest that African–Americans are less likely to carry the short allele than Caucasians (38.5 vs. 74.3%). Furthermore, with gender controlled, the association between the short allele and BPD/APD traits was robust among Caucasians, Wald = 6.00, d.f. = 1, $P = 0.01$, OR = 2.8, but there was no similar trend among the small group of African–American families, Wald = 0.32, $P = 0.57$ (see Table 1). Clearly, then, results should be generalized only to Caucasian populations.

Table 1 **Serotonin transporter genotype frequencies among young adults with and without borderline or antisocial traits**

		Serotonin transporter genotype		
Borderline or antisocial traits	*n*	l/l genotype	s/l genotype	s/s genotype
Absent	62	0.42 (26)	0.45 (28)	0.13 (8)
Caucasian	42	0.33 (14)	0.54 (23)	0.11 (5)
African–American	20	0.60 (12)	0.25 (5)	0.15 (3)
Present	34	0.24 (8)	0.50 (17)	0.27 (9)
Caucasian	28	0.14 (4)	0.53 (15)	0.32 (9)
African–American	6	0.66 (4)	0.33 (2)	0
Total	96	34	45	17

Analyses were then conducted for borderline traits and antisocial traits separately in relation to genotype. Among the sample as a whole, borderline traits were associated linearly with the number of short alleles, Wald = 4.23, d.f. = 1, $P = 0.04$, OR = 2.2. Antisocial traits were also independently associated with the number of short alleles, Wald = 4.66, d.f. = 1, $P = 0.03$, OR = 2.7. In addition, men had a higher incidence of antisocial traits, Wald = 5.46, d.f. = 1, $P = 0.02$, OR = 4.0.

The nine features that define borderline personality disorder and the seven features that define antisocial personality disorder are heterogeneous. Given this heterogeneity, the particular BPD and APD features reported were examined to better characterize the phenotype related to the short allele. All those displaying borderline traits exhibited one of the two following behavioral features: two or more forms of impulsive self-damaging behaviors (71%) or intense and unstable relationships (64%). One half reported reactive mood changes. All other features were less frequently noted. Those with antisocial traits also displayed the more impulsive, reactive features of the disorder, with 90% reporting repeated illegal acts, 65% displaying aggressiveness, and 55% exhibiting reckless disregard for safety of self or others. All other features were less frequent. Therefore the phenotype expressed by young adults in this cohort was one of impulsive self- or other-damaging behaviors.

Further logistic regression analysis evaluated whether the association between the 5HTTLPR short allele and APD/BPD traits might be derivative of an association between APD/BPD traits and depressive disorders. Consistent with the lack of a main effect in the Caspi *et al.* (2003) data, no significant effect for number of short alleles was found on either major depressive disorders or all depressive disorders, Wald = 0.13, d.f. = 1, NS; all depressive disorders Wald = 0.52, d.f. = 1, NS. In addition, entering depressive disorders first into the logistic regression equation did not reduce the significant relation between number of short alleles and prevalence of borderline/antisocial traits, Wald = 4.21, d.f. = 1, $P = 0.04$, OR = 2.0. Results were the same for Caucasians only, Wald = 5.30, d.f. = 1, $P = 0.02$, OR = 2.6.

As noted, 22% of families in the study were referred during the young adult's infancy to clinical services for problems in caregiving. No relation existed between problems in early care and child genotype, Wald = 0.15, d.f. = 1, NS. Problems in early care were, however, related to borderline or antisocial traits, Wald = 6.03, d.f. = 1, $P = 0.01$, OR = 3.95. With sex, race, and effects associated with problems in early care accounted for in the model, the effect of the number of short alleles on BPD/APD traits was still robust, both in the whole data set, Wald = 3.98, d.f. = 1, $P = 0.05$, OR = 2.0; and among Caucasians only, Wald = 5.43, d.f. = 1, $P = 0.02$, OR = 2.7. Given the limited cell sizes, the interaction between genotype and problems in early care could not be tested.

Overall, among low-to- moderate-income families, the OR indicated that the relative risk of antisocial or borderline traits was increased by a factor of two for each short allele in the genotype. Among individuals possessing only short alleles 53% reported borderline or antisocial traits by young adulthood, whereas 38% (s/l) and 24% (l/l) did so in the presence of one or no short alleles. For Caucasians only, corresponding rates were 64, 39 and 22% (see data in Table 1).

Discussion

These results suggest a relation between the short 5HTTLPR allele and borderline and antisocial traits. A recent case–control study did not find association with the 5HTTLPR or the A/G single nucleotide polymorphism within this repeat sequence among individuals meeting full criteria for BPD (Ni *et al.*, 2006). Only the 10-repeat allele of the intron 2 VNTR and its combination with the short 5HTTLPR allele showed significant association with the full syndrome of BPD. These results suggest that the short 5HTTLPR allele may confer a broader endophenotype for impulsive self- and other-damaging behaviors that, in turn, contributes to the more complex APD and BPD disorders described in the *Diagnostic and Statistical Manual of Mental Disorders*.

Limitations of the study include the relatively small sample size and the predominantly low-income nature of the sample. The main effect of the short allele found here may represent a gene–environment interaction in that the short form of the 5HTTLPR polymorphism may be related to internalizing symptoms of depression and anxiety in more advantaged environments, whereas in more stressful low-income environments genetic vulnerability may be expressed through more impulsive self- and other-damaging behaviors, consistent with the relation between BPD/APD and cumulative family adversity (Blanz *et al.*, 1991; Zanarini *et al.*, 1997). Given demonstrations of environmental potentiation of genetic effects on stress-responsiveness in animal models (Francis *et al.*, 1999; Barr *et al.*, 2003), future work should include careful assessment of environmental stressors as potential regulators of the relation observed here.

The consistency of the genetic association with BPD/APD traits over sex, symptom type and quality of early care points to the potential stability of the finding for Caucasian populations. Further work is in progress to increase sample size, assess parental genotype, and test the possibility of gene–environment interaction.

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References

American Psychiatric Association (1994). *Diagnostic and statistical manual of mental disorders*. 4th ed. Washington, DC: American Psychiatric Press.

Anguelova M, Benkelfat C, Turecki G (2003). A systematic review of association studies investigating genes coding for serotonin receptors and the serotonin transporter: II. Suicidal behavior. *Mol Psychiatry* **8**:646–653.

Barr CS, Newman TK, Shannon C, Parker C, Dvoskin RL, Becker ML, *et al.* (2003). Rearing condition and rh5-HTTLPR interact to influence limbic-hypothalamic-pituitary-adrenal axis response to stress in infant macaques. *Biol Psychiatry* **55**:733–738.

Blanz B, Schmidt MH, Esser G (1991). Familial adversities and child psychiatric disorder. *J Child Psychol Psychiatry* **32**:939–950.

Boor K, Ronai Z, Nemoda Z, Gaszner P, Sasvari-Szekely M, Guttman A, Kalasz H (2002). Noninvasive genotyping of dopamine receptor D4 [DRD4] using nanograms of DNA from substance-dependent patients. *Curr Med Chem* **9**:793–797.

Brown GL, Ebert MH, Goyer PF, Jimerson DC, Klein WJ, Bunney WE, *et al.* (1982). Aggression, suicide, and serotonin: relationships to CSF amine metabolites. *Am J Psychiatry* **139**:741–746.

Brunner HG, Nelen MR, van Zandvoort P, Abeling NG, van Gennip AH, Wolters EC, *et al.* (1993). X-linked borderline mental retardation with prominent behavioral disturbance: phenotype, genetic localization, and evidence for disturbed monoamine metabolism. *Am J Hum Genet* **52**:1032–1039.

Cases O, Seif I, Grimsby J, Gaspar P, Chen K, Pournin S, *et al.* (1995). Aggressive behavior and altered amounts of brain serotonin and norepinephrine in mice lacking MAOA. *Science* **268**:1763–1766.

Caspi A, McClay J, Moffitt TE, Mill J, Martin J, Craig IW, *et al.* (2002). Role of genotype in the cycle of violence in maltreated children. *Science* **297**:851–854.

Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, *et al.* (2003). Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* **301**:386–389.

Devlin B, Roeder K (1999). Genomic control for association studies. *Biometrics* **55**:997–1004.

Edelbrock C, Rende R, Plomin R, Thompson LA (1995). A twin study of competence and problem behavior in childhood and early adolescence. *J Child Psychol Psychiatry* **56**:775–785.

First MB, Spitzer RL, Gibbon M, Williams JBW (1997a). *Structured clinical interview for DSM-IV Axis I disorders-Clinical version [SCID-CV]*. Washington, DC: American Psychiatric Press.

First MB, Gibbon M, Spitzer RL, Williams JBW, Benjamin LS (1997b). *User's guide for the structured clinical interview for DSM-IV Axis II personality disorders [SCID-II]*. Washington, DC: American Psychiatric Press.

Francis D, Diorio J, Liu D, Meaney M (1999). Nongenomic transmission across generations of maternal behavior and stress responses in the rat. *Science* **286**:1155–1158.

Heils A, Mossner R, Lesch KP (1997). The human serotonin transporter gene polymorphism – basic research and clinical implications. *J Neural Transm* **104**:1005–1014.

Jacobson KC, Prescott CA, Kendler KS (2002). Sex differences in genetic and environmental influences on the development of antisocial behavior. *Dev Psychopathol* **14**:395–415.

Lesch KP, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S, *et al*. (1996). Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science* **274**:1527–1531.

Linnoila M, Virkkunen M, Scheinin M, Nuutila A, Rimon R, Goodwin FK (1983). Low cerebrospinal fluid 5-hydroxyindoleacetic acid concentration differentiates impulsive from nonimpulsive violent behavior. *Life Sci* **33**: 2609–2614.

Lyons-Ruth K, Connell D, Zoll D, Stahl J (1987). Infants at social risk: Relationships among infant maltreatment, maternal behavior, and infant attachment behavior. *Dev Psychol* **23**:223–232.

Lyons-Ruth K, Connell D, Grunebaum H, Botein D (1990). Infants at social risk: Maternal depression and family support services as mediators of infant development and security of attachment. *Child Dev* **61**:85–98.

Lyons-Ruth K, Melnick S (2004). Dose-response effect of mother-infant clinical home-visiting on aggressive behavior problems in kindergarten. *J Am Acad Child Psychiatry* **43**:699–707.

Miles DR, Carey G (1997). Genetic and environmental architecture of human aggression. *J Pers Soc Psychol* **72**:207–217.

Moeller FG, Dougherty DM, Swann AC, Collins D, Davis CM, Cherek DR (1996). Tryptophan depletion and aggressive responding in healthy males. *Psychopharmacology* **126**:97–103.

Nemoda Z, Ronai Z, Szekely A, Kovacs E, Shandrick S, Guttman A, Sasvari-Szekely M (2001). High-throughput genotyping of repeat polymorphism in the regulatory region of serotonin transporter gene by gel microchip electrophoresis. *Electrophoresis* **22**:4008–4011.

Ni X, Chan K, Bulgin N, Sicard T, Bismil R, McMain S, Kennedy JL (2006). Association between serotonin transporter gene and borderline personality disorder. *J Psychiatr Res* **40**:448–453.

Slutske WS (2001). The genetics of antisocial behavior. *Curr Psychiatry Rep* **3**:158–162.

Slutske WS, Heath AC, Dinwiddie SH, Madden PA, Bucholz KK, Dunne MP, *et al*. (1997). Modeling genetic and environmental influences in the etiology of conduct disorder: a study of 2682 adult twin pairs. *J Abnorm Psychol* **106**:266–279.

Stanley B, Molcho A, Stanley M, Winchel R, Gameroff MJ, Parsons B, *et al*. (2000). Association of aggressive behavior with altered serotonergic function in patients who are not suicidal. *Am J Psychiatry* **157**:609–614.

Torgersen S, Lygren S, Oien PA, Skre I, Onstad S, Edvardsen J, *et al*. (2000). A twin study of personality disorders. *Compr Psychiatry* **41**:416–425.

Zanarini MC, Williams AA, Lewis RE, Reich DB, Vera SC, Marino MF (1997). Reported pathological childhood experiences associated with the development of borderline personality disorder. *Am J Psychiatry* **154**:1101–1106.