Relationships Between Angry-Impulsive Personality Traits and Genetic Polymorphisms of the Dopamine Transporter

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Background: The 9-repeat variable number tandem repeat allele of the dopamine transporter has recently been associated with borderline personality disorder (BPD) in depressed patients.

Methods: We investigated the association between the 9-repeat allele of the dopamine transporter and angry-impulsive personality traits in a family study with 512 subjects on the molecular genetics of depression and personality.

Results: Across the whole sample, the 9-repeat allele of the dopamine transporter was associated with angry-impulsive personality traits ($p = .002$). This association was stronger in subjects with no history of mood disorders or BPD (odds ratio [OR] = 4.85, $p = .008$) than in subjects with a history of mood disorders (OR = 1.73, $p = .033$). Angry-impulsive traits were also associated with lifetime mood disorder diagnoses and with BPD.

Conclusions: The associations reported in this article suggest that the 9-repeat allele of the dopamine transporter is associated with angry-impulsive personality traits, independent of any link to mood disorder or BPD. This could form the basis of a dopaminergic neurobiological model of angry-impulsive personality traits.

Key Words: Angry-impulsive, borderline personality disorder, dopamine transporter

The dopamine transporter (DAT1) functions to reuptake dopamine rapidly from the synaptic cleft into the presynaptic nerve terminals and therefore acts as one of the key mechanisms in the regulation of dopamine neurotransmission. The gene for the dopamine transporter SLC6A3 contains 15 exons and is localized to chromosome 5p15.3. Genetic variation in SLC6A3 may alter the expression of DAT1 (1). A 40-bp polymorphic variable number tandem repeat (VNTR) element is present in the 3′ untranslated region of the gene and can vary from 3 to 12 repeats. The two most common alleles are the 9-repeat and the 10-repeat, and there are inconsistent studies that link these polymorphisms to attention-deficit/hyperactivity disorder, prolonged psychosis following stimulant withdrawal, and the severity of alcohol withdrawal in alcohol-dependent subjects (2–10). We have recently reported (11) that the 9-repeat allele of DAT1 is associated with a threefold increase in the rate of borderline personality disorder (BPD) across two independent samples of depressed patients (12,13). This association of the 9-repeat allele with BPD was unchanged after covarying for developmental risk factors for BPD such as childhood neglect and abuse.

BPD is a severe disorder of personality characterized by a pervasive and pathological pattern of affective instability, intense and unstable close relationships, instability of self-image, feelings of abandonment and boredom, impulsivity, and anger. Because of the intensity of emotions and the range of impulsive behaviors, patients with BPD are often seen as difficult to treat. However, an increasing number of studies has found that the long-term prognosis for BPD is not as pessimistic as previously believed (14) and that a comorbid BPD diagnosis in those with Axis I disorders such as depression or bulimia does not adversely affect the treatment of the Axis I disorder (15,16).

In an earlier study on the structure of personality disorder symptoms, we suggested that these can be reduced to four main groups, which we called the four As. These were the *antisocial,* which are the Cluster B disorders, and the prototype is borderline personality disorder; the *asocial,* which are the Cluster A personality disorders, and the prototype was schizoid personality disorder; the *anankastic* or obsessive-compulsive personality disorder; and the *asthenic,* which are the Cluster C disorders, except obsessive-compulsive personality disorder, and the prototype is avoidant personality disorder (17). We then identified the three key personality traits for each of the four groups that best loaded onto each factor. For the borderline cluster, the three identified screening questions were related to being impulsive, easily angered, and having a pattern of unstable and erratic relationships.

In this article, using data from a family study on the molecular genetics of depression and personality, we set out to examine whether our previously observed association between the 9-repeat allele of DAT1 and BPD would extend to the "normative" personality traits of anger, impulsivity, and having unstable and erratic relationships. We also sought to examine the associations of these personality traits to BPD and mood diagnoses.

Methods and Materials

Subjects

The subjects of this article were recruited for a family study on the molecular genetics of depression and personality. We initially recruited adult probands, who had been treated for depression (regardless of a history of bipolarity) and who would be willing to participate in a family study of depression. Probands were than asked to identify two first-degree relatives, preferably parents but otherwise siblings, who might also participate in the

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study. Our intentions were to recruit family trios to allow for family-based association statistical analyses.

The study was approved by the Canterbury, New Zealand, Ethics Committee.

Screening

Subjects contacted the research team in response to advertisements placed in a variety of community locations, including posters and newspapers, as well as on radio. When potential subjects contacted the research team, the details of the project were explained. A proband was identified, and potentially consenting family members were also identified. If subjects consented, they were offered the options of being interviewed in their homes or within the university department conducting the study.

Interviews

All consenting subjects were interviewed by trained interviewers/research assistants who had appropriate university degrees, usually in psychology. All interviews were reviewed by a psychiatrist (P.R.J.), and DSM-IV diagnoses were assigned. If the interview yielded insufficient information to be confident about diagnoses, we used further information obtained from family members or, with consent, from medical records.

The interview for Axis I disorders was based on the mini-international neuropsychiatric interview (MINI) (18) but with expansions in the area of alcohol and drug dependence and bipolar disorder. The alcohol and drug interview was based on the Structured Clinical Interview for DSM-IV (SCID) (19). A diagnosis of any bipolar disorder was not dependent on just the MINI probe questions, in that if subjects denied a history of mania using the MINI probe, they were then asked the items in the mood disorder questionnaire (MDQ) (20); if they affirmed three or more items from the MDQ, which occurred at the same time, the nature, extent, number, duration, and impairment associated with these "manic" episodes were further inquired about. DSM-IV criteria were used for making a diagnosis of bipolar I or II disorder, whereas bipolar disorder NOS (21) was diagnosed when an individual reported recurrent 1- to 3-day hypomanic episodes plus a history of major depression. Following the depression section of the MINI there was an expanded section on suicide attempts and self mutilation. At the beginning of the MINI there was an expanded section on the use of Mental Health Services and on history of treatment, including response to specific antidepressant drugs.

After completion of the interview for Axis I disorders, subjects were then screened for personality traits and for difficulties associated with these traits. The screener consisted of 12 questions selected to screen for avoidant, obsessive-compulsive, schizoid, and borderline personality disorders. For each personality adjective or phrase, subjects were asked whether they would consider themselves to be "not at all" (score = 0), "somewhat" (score = 1), or "very much so" (score = 2). The three screening questions for BPD were: "Are you impulsive?" "Are you easily angered?" and "Do you have unstable and erratic relationships?" If identified traits were affirmed, subjects were then asked whether these had caused them significant difficulties.

Following the screening questions, the interviewer followed up on any potentially "positive" personality disorder traits by completing the Structured Clinical Interview for DSM-IV (SCID-II) (22). All diagnoses were reviewed with the supervising psychiatrist (P.R.J.).

At the time of the interview, a blood sample was obtained for DNA extraction.

Genotyping

DATI genotyping was based on the polymerase chain reaction method of Vandenbergh *et al.* (23) but with modifications as previously described (24).

Questionnaires

Around the time of the interview and the obtaining of a blood sample for DNA extraction, all subjects completed two self-report questionnaires. This included the 240-item, 5-point Likert scale version of the Temperament and Character Inventory (TCI), which assesses four dimensions of temperament and three dimensions of character, inclusive of subscales, in Cloninger's Psychobiological Model of Personality (25,26). The second questionnaire was the general behavioral inventory (GBI), which assesses depressive, manic and biphasic mood symptoms (27).

Data Management and Analysis

All data from interviews and questionnaires were entered into a relational database and then transferred to SYSTAT for statistical analyses. Analyses included *t* tests, chi-square tests, Pearson correlations, and univariate and multivariate logistic regression.

Results

The subjects for this study consisted of 512 subjects comprising 177 probands, 118 mothers, 73 fathers, 92 sisters, and 52 brothers. The mean age of the sample was 47.8 (± 16.1) years, and 67.8% were women. Of the 512 subjects included, 209 had one or more copies of the 9-repeat allele of DAT1, and 303 subjects did not have a 9-repeat allele. The genotypes were in Hardy-Weinberg equilibrium. Five subjects had genotyping completed, but because they had the rare 5-repeat or 6-repeat alleles of DAT1, they were excluded. A further 42 subjects had been interviewed, but no genotyping data were available. Thirteen probands and one relative had been participants in our earlier clinical trials in major depression in which we initially reported the association of DAT1 genotype with BPD (11). On the three BPD screening questions, the distributions of scores were as follows: angry—60% not at all, 34% somewhat, 6% very much so; impulsive—64% not at all, 31% somewhat, 5% very much so; unstable relationships—85% not at all, 10% somewhat, 5% very much so.

Table 1 shows the mean scores on a 0–2 range, for the three BPD screening questions of easily angered, impulsive, and having unstable and erratic relationships by the presence or absence of the 9-repeat allele of DAT1. As can be seen from this table, those with the 9-repeat were more easily angered (p = .029) and more impulsive (p = .025). We then created a 0–4 score of angry-impulsive, and a dichotomous angry-impulsive score with a cut-point of two or more. Subjects with a 9-repeat allele of DAT1 had higher angry-impulsive scores (p = .007) and had higher rates (29% vs. 17%) of angry-impulsive personality traits (p = .002).

From Table 2 it can be seen that 10% of the 164 subjects with no mood diagnosis (and no BPD) were classified as having angry-impulsive personality traits. In those with a lifetime history of major depression without BPD, 17% had angry-impulsive personality traits. The rates of angry-impulsive personality traits increased to 40% in those with bipolar I or bipolar II or bipolar NOS disorders (without BPD), and to more than 80% of subjects with either major depression or bipolar disorder plus BPD.