Published in final edited form as:
J Psychiatr Res. 2010 November ; 44(15): 1075–1081. doi:10.1016/j.jpsychires.2010.03.014.

Tryptophan Hydroxylase 2 haplotype association with borderline personality disorder and aggression in a sample of patients with personality disorders and healthy controls

M. Mercedes Perez-Rodriguez[1], **Shauna Weinstein**[1,2], **Antonia S. New**[1,2], **Laura Bevilacqua**[3], **Qiaoping Yuan**[3], **Zhifeng Zhou**[3], **Colin Hodgkinson**[3], **Marianne Goodman**[1,2], **Harold W. Koenigsberg**[1,2], **David Goldman**[3], and **Larry J. Siever**[1,2]

[1] Department of Psychiatry, Mount Sinai School of Medicine, Psychiatry Box # 1230 One Gustave L. Levy Place, New York, NY 10029

[2] The Mental Health Patient Care Center, James J. Peters Veterans Affairs Medical Center, 130 West Kingsbridge Road, Bronx, NY 10468

[3] Laboratory of Neurogenetics, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, 5625 Fishers Lane, Room 3S-32: MSC 9412 Bethesda MD 20892-9412

Abstract

Background—There is decreased serotonergic function in impulsive aggression and borderline personality disorder (BPD), and genetic association studies suggest a role of serotonergic genes in impulsive aggression and BPD. Only one study has analyzed the association between the tryptophan-hydroxylase 2 (TPH2) gene and BPD. A TPH2 “risk” haplotype has been described that is associated with anxiety, depression and suicidal behavior.

Corresponding author: Larry J. Siever, James J Peters Veteran Administration Medical Center, 3rd Floor, Room 3B-20, 130 West Kingsbridge Road, Bronx, NY 10468 larry.siever@mssm.edu; larry.siever@med.va.gov.

Financial Disclosures

M. Mercedes Perez-Rodriguez reports no biomedical financial interests or potential conflicts of interest.
Shauna Weinstein reports no biomedical financial interests or potential conflicts of interest.
Antonia S. New reports no biomedical financial interests or potential conflicts of interest.
Laura Bevilacqua reports no biomedical financial interests or potential conflicts of interest.
Qiaoping Yuan reports no biomedical financial interests or potential conflicts of interest.
Zhifeng Zhou reports no biomedical financial interests or potential conflicts of interest.
Colin Hodgkinson reports no biomedical financial interests or potential conflicts of interest.
Marianne Goodman reports no biomedical financial interests or potential conflicts of interest.
Harold W. Koenigsberg reports no biomedical financial interests or potential conflicts of interest.
David Goldman reports no biomedical financial interests or potential conflicts of interest.
Larry J. Siever reports no biomedical financial interests or potential conflicts of interest.

Contributors

Authors Larry J. Siever, Antonia S. New and David Goldman designed the study and wrote the protocol, assisted by authors M. Mercedes Perez-Rodriguez, Laura Bevilacqua, Qiaoping Yuan, Zhifeng Zhou, Colin Hodgkinson, Marianne Goodman, and Harold W. Koenigsberg. Author Shauna Weinstein performed the statistical analyses. Author M. Mercedes Perez-Rodriguez managed the literature searches and assisted with the analyses. Author M. Mercedes Perez-Rodriguez wrote the first draft of the manuscript. Authors Shauna Weinstein, Laura Bevilacqua, Qiaoping Yuan, Zhifeng Zhou, Colin Hodgkinson, Marianne Goodman, Harold W. Koenigsberg, Larry J. Siever, Antonia S. New and David Goldman contributing to drafting and critical revision of the manuscript. All authors contributed to and have approved the final manuscript.

Methods—We assessed the relationship between the previously identified "risk" haplotype at the TPH2 locus and BPD diagnosis, impulsive aggression, affective lability, and suicidal/parasuicidal behaviors, in a well-characterized clinical sample of 103 healthy controls (HCs) and 251 patients with personality disorders (109 with BPD). A logistic regression including measures of depression, affective lability and aggression scores in predicting "risk" haplotype was conducted.

Results—The prevalence of the "risk" haplotype was significantly higher in patients with BPD compared to HCs. Those with the "risk" haplotype have higher aggression and affect lability scores and more suicidal/parasuicidal behaviors than those without it. In the logistic regression model, affect lability was the only significant predictor and it correctly classified 83.1% of the subjects as "risk" or "non-risk" haplotype carriers.

Conclusions—We found an association between the previously described TPH2 "risk" haplotype and BPD diagnosis, affective lability, suicidal/parasuicidal behavior, and aggression scores.

Keywords

Borderline personality disorder; TPH2; suicidal behavior; affective instability; impulsive aggression

Introduction

Borderline personality disorder (BPD) is a complex and serious mental disorder characterized by emotional dysregulation and aggressive behavior (New et al., 2007). Impulsive aggression and affective dysregulation/instability are core traits of BPD (McGlashan et al., 2005; Siever et al., 2002; Skodol et al., 2002), and contribute substantially to the morbidity and mortality associated with BPD. Impulsive aggression can manifest in a variety of behaviors, including destruction of property, assault, domestic violence, self-injurious and suicidal behavior, or substance abuse (New et al., 1998).

Impulsive aggression has consistently been associated with measures of reduced central serotonergic activity, such as decreased cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA) (Coccaro et al., 1990a; Lidberg et al., 2000; Linnoila et al., 1989; Linnoila et al., 1994; Roy et al., 1988; Stanley et al., 2000; Virkkunen et al., 1994), decreased platelet serotonin content (Goveas et al., 2004), and decreased hormone responses to serotonergic agonists (Coccaro et al., 1990a; Coccaro et al., 1996; Coccaro et al., 1990c; Coccaro et al., 1997a; Coccaro et al., 1995; Coccaro et al., 1997b; Coccaro et al., 1989; New et al., 2004b; O'Keane et al., 1992; Reist et al., 1996; Sher et al., 2003); tryptophan depletion enhanced and tryptophan augmentation decreased laboratory-provoked aggression in healthy women (Marsh et al., 2002). Moreover, aggressive children with a blunted prolactin response to fenfluramine were more likely to have relatives with aggression than those with a normal responses (Halperin et al., 2003). Furthermore, among personality disordered (PD) patients, a reduction in serotonergic function measured by reduced prolactin response to fenfluramine appears to be specifically associated with impulsive aggression but not with other personality traits or depression (Coccaro et al., 1989; Paris et al., 2004). In summary, the link between decreased serotonergic function and impulsive aggression across psychiatric diagnoses is one of the most robust findings in biological psychiatry, consistently replicated and supported by a broad range of studies, including metabolite, endocrine challenge, peripheral marker, genetic and brain imaging studies (New et al., 1998; Siever, 2008). In addition, selective serotonin reuptake inhibitors appear to improve anger and mood instability in non-depressed BPD patients (Coccaro et al., 1990b; Cornelius et al., 1991; New et al., 2004a; New et al., 2008; Rinne et al., 2002).

While early theories predominantly ascribed an environmental etiology, growing evidence demonstrates a genetic vulnerability for BPD (Kendler et al., 2008; Siever et al., 2002).

Evidence for this includes the tendency for BPD to run in families (Loranger et al., 1982; White et al., 2003) and its higher prevalence among biological than among adoptive relatives of BPD patients (New et al., 2008; Pally, 2002). More importantly, twin studies of BPD show substantial heritability scores of 0.65–0.76 (Coolidge et al., 2001; Ji et al., 2006; Torgersen et al., 2000), and the heritability of core dimensions of BPD such as affective instability or impulsive aggression may be more robustly heritable than the diagnosis itself (Siever et al., 2002).

Evidence of decreased serotonergic function in impulsive aggression and BPD along with the evidence for heritability (New et al., 2008; Siever, 2008) led to candidate gene association studies of genes involved in serotonin functioning for this disorder. Although the relationship between impulsive aggression and decreased serotonergic function extends beyond BPD, BPD is prototypic diagnosis for severe affective lability and impulsive aggression, and so serotonergic genes are appropriate candidate genes for both BPD diagnosis and impulsive aggression. Genetic association studies suggest a role of serotonergic genes, such as the serotonin transporter gene (5-HTT) (Lyons-Ruth et al., 2007; Ni et al., 2006b), the monoamine oxidase A gene (MAO-A) (Ni et al., 2007), or the 5-HT2C gene (Ni et al., 2008) in BPD; other serotonergic genes, such as the 5-HT2A, seem to be associated with personality traits, but not with the diagnosis of BPD (New et al., 2008; Ni et al., 2006a).

The tryptophan-hydroxylase 2 (TPH2) gene, which codes for the first enzyme in serotonin synthesis in the brain (Walther et al., 2003), is of particular interest because altered serotonin synthesis has been reported in BPD (Leyton et al., 2001). Surprisingly, only one study (Ni et al., 2009) has analyzed the association between TPH2 single nucleotide polymorphism (SNP) alleles and genotype variants and BPD, finding that the TPH2 and 5-HT2C genes and their interactions are associated with BPD (Ni et al., 2009). The TPH2 gene has also been associated with early-onset obsessive-compulsive disorder (Mossner et al., 2006), attention-deficit/hyperactivity disorder (Sheehan et al., 2005; Walitza et al., 2005), autism (Coon et al., 2005), major depression (Zhou et al., 2005; Zill et al., 2004a), and suicide (Lopez de Lara et al., 2007; Zhou et al., 2005; Zill et al., 2004b).

Using 15 SNPs spanning a 106-kb TPH2 region, Zhou and colleagues (Zhou et al., 2005) identified a “risk” haplotype associated with anxiety, depression, and suicidal behavior, and moderately predictive of lower CSF 5-HIAA concentrations in a Finnish white sample. By using haplotype analysis, they (Zhou et al., 2005) attempted to overcome the shortcomings of single marker analyses in case-control studies, which often yield inconsistent results (Zaboli et al., 2006). Haplotype analysis provides more power than single locus analysis in gene-disease, case-control association studies since it avoids the need to analyze the association between the target variable and many individual SNPs (Clark, 2004). The haplotype approach also takes into account the linkage phase (ignored by most SNP association tests) assessing the interaction of two SNPs and addresses the fact that the SNPs are not independent. There is an intrinsic dependency of one SNP with another due to the history of their entry into the population (Clark, 2004). Thus, the focus of genetic studies is currently shifting towards the use of haplotypes (Clark, 2004). The goal of the present study was to replicate Zhou’s findings by assessing the relationship between the previously identified “risk” haplotype (Zhou et al., 2005) at the TPH2 locus and impulsive aggression, affect lability, suicidal and parasuicidal behavior and BPD diagnosis in a well-characterized clinical sample of controls and patients with PDs. Since trauma appears to play a role in the genesis of BPD, and gene-environment interactions have been shown to induce enduring biological changes in animal and human studies (Goodman et al., 2004; Pally, 2002), we also explored the influence of trauma on the relationship between TPH2 variants, BPD, and impulsive aggression.

We tested the following hypotheses: 1) the "risk" haplotype will be significantly more common among BPD patients than among controls; 2) those individuals carrying the "risk" haplotype, regardless of diagnosis, will score higher on measures of impulsive aggression and affect lability; 3) trauma will increase the likelihood of having a diagnosis of BPD among those with the "risk" haplotype; 4) trauma will amplify the difference between aggression scores among those carrying the "risk" haplotype compared to those not carrying it; 5) those carrying the "risk" haplotype will have higher rates of suicidal and parasuicidal behaviors than those carrying the "non-risk" haplotype.

Materials and Methods

Participants

Participants (healthy controls [HC], patients with BPD, and with other PDs [OPD]) were recruited by advertisements in local newspapers, the internet and from referrals from mental health professionals. All subjects were assessed by an experienced psychologist for Axis I diagnosis using the Structured Clinical Interview for DSM-IV (First et al., 1995;), and for Axis II diagnoses using the Structured Interview for DSM-IV PDs (Pfohl et al., 1997). Consensus diagnoses were reached and interrater reliability for BPD diagnosis was 0.81. Participants were excluded for a substance abuse or dependence disorder within the last 6 months, for present or past bipolar I disorder, schizophrenia, schizoaffective disorder, organic mental syndromes, head trauma, neurological disease or significant medical illness likely to affect the central nervous system. Those with active suicidal ideation or currently taking psychotropic medication were also excluded. Healthy controls were excluded if they had any current or past personal Axis I or II disorder or a first degree family history of significant Axis I disorders (except social phobia, specific phobia, past substance use disorder and adjustment disorder). The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. All participants signed informed consent forms after the nature of the study had been fully explained in accordance with the Institutional Review Boards at Mount Sinai Medical Center and/or the James J. Peters VAMC.

The full data set (N=354) included 103 HC and 251 subjects with one or more PD (135 females, 219 males). Of the subjects with one or more PDs, 109 met criteria for BPD. Table 1 shows the distribution of self-reported ethnicities.

The European white subsample (53 females and 70 males, 38 HC and 85 PD patients, 38 with BPD, see Table 1) was accurately confirmed by a European ancestry informative marker (AIM) score at or above 0.5. This total is smaller than the sample of self-reported whites of European origin due to differences between self-reported and AIM-score determined ethnicity and missing AIM scores for several subjects. We did not analyze patients and/or controls from other ancestry informative marker groups separately due to small sample sizes, but we did analyze data from the full sample.

Genotyping

Twenty- two tag SNPs designed to capture maximum haplotype information were selected for the TPH2 gene, which was one of the 130 candidate genes genotyped on a custom-designed Illumina 1536 SNP array, including 186 ancestry informative SNP markers (Hodgkinson et al., 2008). The selection of the tag SNPs were based on HapMap project Genotype data for the African Yoruban population since Africans generally present greatest haplotype diversity. Genotyping was carried out following Illumina GoldenGate assay protocols and the arrays were imaged on an Illumina Beadstation GX500. Details of the data analysis and quality controls have been described previously (Hodgkinson et al., 2008). Zhou et al. (Zhou et al., 2005) identified a "risk" haplotype in their Finnish sample. A corresponding haplotype was

identified in our sample including four of the 22 TPH2 SNPs in the addiction array (Hodgkinson et al., 2008). Mediated by the haplotypes from similar HapMap populations with many other SNP makers, a haplotype GGTG in chromosome forward strand with SNP markers rs2171363, rs1386491, rs6582078, and rs1352250 was found to be the corresponding previously identified "risk" haplotype (Zhou et al., 2005).

The number of participants genotyped successfully varied by SNP; 285 of the 354 total participants, and all 123 of the accurately confirmed European white participants were genotyped successfully on the four SNPs identified in the haplotype and therefore were included in haplotype analyses.

Measures

The primary measure of aggression was a composite of two self-report instruments assessing trait aggression: the Buss Durkee Hostility Inventory (BDHI) (Buss et al., 1957) and the Buss Perry Aggression Questionnaire (BPAQ) (Buss et al., 1992). The total scores were standardized and converted to T scores, and a mean score was calculated (tBUSS). A secondary state measure of aggression was used, the Overt Aggression Scale-Modified (OAS-M) (Sorgi et al., 1991); an aggregated mean aggression score from two OAS-M ratings gathered at different time points was used. Rates of lifetime suicidal and parasuicidal behaviors were measured with the Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott et al., 1978) and the Parasuicide History Interview-2 (PHI-2) (Linehan et al., 1983).

In addition to aggression, affect lability, using the Affect Lability Scale (ALS) (Harvey et al., 1989), and depression, using the Beck Depression Inventory (BDI) (Beck et al., 1961) were measured.

Trauma was analyzed both as categorical and continuous variables using the Childhood Trauma Questionnaire 28-item Short Form (CTQ) (Bernstein et al., 2003). The categorical variable was derived using cutoffs for four of the five subscales: emotional abuse (≥30), physical abuse (≥12), sexual abuse (≥9), and physical neglect (≥12) (Bernstein et al., 2003). The fifth subscale, emotional neglect, was not used since there is no established cutoff for this subscale. If an individual met any of the four cutoff scores, he/she was included in the "trauma" group; if the individual did not meet any of the four cutoff scores, he/she was included in the "no trauma" group. The continuous trauma variable was total CTQ score.

Statistical Analyses

Primary analyses focused on the European white subsample because the evidence for an a priori "risk" haplotype in TPH2 was reported in a Finnish white sample (Zhou et al., 2005). Since the haplotype was described in a Caucasian sample, we could not assume that it would be distributed similarly among individuals from other races. In Zhou et al.'s study, significant interpopulation differences in allele frequencies were observed for most markers. Zhou et al. found different frequencies for the yin haplotype, 212121, across populations from different races. Those carrying one or two copies of the "risk" haplotype (GGTG) were categorized in the "risk" haplotype group; those not carrying a copy of this haplotype comprised the "non-risk" haplotype group.

The prevalence of BPD diagnosis among those carrying the "risk" haplotype (GGTG) was compared to those carrying the "non-risk" haplotype (non-GGTG) using chi-square tests. There were not enough subjects in each cell to run a statistical test for a 2 × 2 × 2 table (BPD, HC; "risk"; "non-risk" haplotype; trauma, non-trauma). However, the effect of the presence or absence of trauma on the prevalence of BPD in those carrying the "risk" haplotype was examined with a chi-square test. Independent samples t-tests were used to compare aggression

(tBUSS) and affect lability (ALS) scores and the rate of suicidal/parasuicidal behaviors among those with and without the "risk" haplotype. A factorial ANOVA was used to analyze the effect of trauma on aggression scores among carriers of the "risk" and "non-risk" haplotypes. A secondary analysis using stepwise logistic regression was used to investigate the predictive importance of aggression compared to affective lability and depression on the presence of the risk haplotype.

Follow-up analyses for all the SNPs explored, including the four individual "risk" alleles within the "risk" haplotype were conducted comparing scores on the OAS-M and tBUSS across genotypes in the European white subsample. 17 of the 18 individual TPH2 SNPs outside the "risk" haplotype were included since one of them failed to yield enough data.

We do not have AIM scores on all 354 subjects so we cannot confirm the proportions of ethnic groups; however, for the 288 subjects with AIM scores, the distributions of these scores did not differ significantly across patients and HC. Therefore, given the suggested genetic homogeneity in our full sample, we ran these additional analyses on all subjects (including all ethnic groups) and present the findings as exploratory.

Results

European white subsample

Haplotype Analysis—Our primary finding is that the prevalence of the "risk" haplotype (Zhou et al., 2005) was significantly higher in patients with a BPD diagnosis (89.5%) compared to HCs (71.1%) (χ^2=4.07, df=1, p<0.05).

In addition, those with the "risk" haplotype have higher aggression (mean=57.0, standard deviation [SD]=17.8) than those without the "risk" haplotype (mean=47.6, SD=20.5) (tBUSS, t=−1.95, df= 106, p=0.05). Those with the "risk" haplotype (mean=1.1, SD=0.6) also score higher on measures of affective lability than those without the "risk" haplotype (mean=0.6, SD=0.6) (ALS, t=−2.77, df=105, p<0.01). See Table 2. A logistic regression including measures of depression, affective lability and tBUSS scores in predicting "risk" haplotype was conducted. Overall model accounts for between 10.0 and 16.8% of the variance (χ^2 =8.78, df=1, p<0.01). Affect lability was the only significant predictor (Wald's statistic=6.49, df=1, p=0.01), and it correctly classified 83.1% of the subjects as "risk" or "non-risk" haplotype carriers. Finally, those carrying the "risk" haplotype had significantly more suicidal/parasuicidal behaviors and significantly higher depression (BDI) scores than those not carrying the "risk" haplotype (Table 2).

We also examined the association between the risk haplotype, aggression (tBUSS), and affect lability (ALS) scores among healthy controls, but we found no significant differences in aggression and affect lability among controls carrying the risk haplotype compared with those not carrying it.

The examination of the interaction of trauma and haplotype in predicting BPD diagnosis and symptoms of aggression was limited by the presence of only three individuals with the "non-risk" haplotype and a trauma history (HC=2, BPD=1). Therefore, we will not include the trauma analyses in the present paper.

Exploratory Analysis of Individual SNPs—Three of the four individual "risk" alleles from the "risk" haplotype are also significantly associated with a diagnosis of BPD. The statistics for rs2171363 and rs6582078 are identical to those of the "risk" haplotype because all subjects within the European white subsample who carry any of these "risk" alleles also carry the entire "risk" haplotype. The rs1352250 allele was also significantly associated with

BPD diagnosis (χ^2=4.55, df=1, p<0.05); within the BPDs, 92.1% have the "risk" allele while 7.9% have the "non-risk" allele. Within the HCs, 73.7% have the "risk" allele while 26.3% have the "non-risk" allele.

Exploratory Analysis of Full Sample Uncorrected for Ethnic Differences

Analyses of the "risk" haplotype were negative; no significant differences for prevalence of risk haplotype across diagnosis (BPD or HC), for mean aggression, or for mean rates of suicide/parasuidal behavior were found.

Twenty-one of the 22 TPH2 SNPs genotyped in our sample yielded enough data to be analyzed. No significant differences for BPD diagnosis or tBUSS by genotype were found. However, we found a significant difference by genotypes on the OAS-M aggression score for seven of the 21 individual TPH2 SNPs.

Discussion

Hypothesis 1: The "risk" haplotype will be significantly more common among BPD patients than among controls

Ours is the first study to show an association between the previously described TPH2 "risk" haplotype (Zhou et al., 2005) and BPD diagnosis. The well-identified haplotype in the TPH2 gene (Zhou et al., 2005) previously associated with depression, suicide attempts and decreased CSF concentrations of 5-HIAA, was significantly more common among BPD patients than among controls in the European white subsample. This finding supports a role for this gene in the risk for BPD.

Surprisingly, the TPH-2 gene has not yet been the subject of extensive research in BPD. Only one study (Ni et al., 2009) has analyzed the association between TPH2 SNP alleles and genotype variants and BPD, and found an association between BPD diagnosis and TPH2 allele variants, compared to HC. Of note, SNP variants in the TPH2 gene and its 5′ upstream region have been reported to be associated with major depression (Zill et al., 2004a), and suicide (Lopez de Lara et al., 2007; Zhou et al., 2005; Zill et al., 2004b), which are commonly associated with BPD (Oldham, 2006). Moreover, in rodent studies it has been reported that the C1473G SNP of the TPH2 gene was associated with brain TPH activity and aggressive behavior (Kulikov et al., 2005), which is one of the core symptoms of BPD (Siever, 2008).

Hypothesis 2: Those carrying the "risk" haplotype will score higher on measures of aggression and affect lability than those carrying the "non-risk" haplotype

Our findings support this hypothesis, showing that those carrying the "risk" haplotype scored higher on aggression than those without the "risk" haplotype in the European white subsample. This is consistent with rodent studies showing that the C1473G SNP of the TPH2 gene is associated with brain TPH2 activity and aggressive behavior (Kulikov et al., 2005). Only one human study has analyzed the relation between TPH2 SNP variants and aggression (Oades et al., 2008), reporting an association between the TPH2 rs6582071 SNP and impulsive aggression in ADHD patients. However, other authors have found that TPH2 SNP variants were associated with suicide (Lopez de Lara et al., 2007; Zhou et al., 2005; Zill et al., 2004b), which is a form of self-directed aggression (Siever, 2008). Those with the "risk" haplotype also scored higher on affect lability than those without the "risk" haplotype. This is consistent with prior findings of increased affective instability associated with polymorphisms affecting serotonergic function in other populations including an association between the s allele of the 5-HTT gene in women with bulimia (Steiger et al., 2005), and perhaps in association with affective instability in anxiety disorders, violent suicidal behavior, seasonal affective disorder and rapid cycling (Rousseva et al., 2003).

Hypothesis 3: Trauma will increase the likelihood of having a diagnosis of BPD among those with the "risk" haplotype and Hypothesis 4: Trauma will amplify the difference between aggression scores among those carrying the "risk" haplotype compared to those not carrying it

We were not able to perform a statistical test of a gene by environment interaction, since we had only very few subjects with the "non-risk" haplotype who had had a history of trauma.

Hypothesis 5: Those carrying the "risk" haplotype will have higher rates of suicidal/ parasuicidal behaviors than those carrying the "non-risk" haplotype

The rates of suicidal/parasuicidal behaviors were significantly higher among those carrying the "risk" haplotype compared to those carrying the "non-risk" haplotype in the European white subsample. This is a replication of prior findings of an association between the "risk" haplotype and suicide attempts (Zhou et al., 2005) and between SNP variants of TPH2 and suicide (Lopez de Lara et al., 2007; Zill et al., 2004b). However, other studies have not found an association between variants of the TPH2 gene and suicidal behaviors in bipolar disorder (De Luca et al., 2004), and schizophrenia (De Luca et al., 2005).

Secondary Specificity Analyses

In a logistic regression, affect lability was the only significant predictor of haplotype (correctly classifying 83.1% of subjects). Thus, it is possible that other phenotypic manifestations of the "risk" haplotype, including impulsive aggression and depression, may be mediated by affective lability. Impulsive aggression may be driven by the component of affect lability encompassing increased reactivity to environmental stimuli (Gurvits et al., 2000). This finding supports the specificity of the haplotype for the core dimension of BPD, affective lability; impulsive aggression and affect lability are very closely related in BPD (ALS score correlated strongly with tBUSS, $r=0.77$, $p<0.001$). ALS score also correlated significantly with other symptoms of BPD, including depression (BDI, $r=0.71$, $p<0.001$), impulsivity (tBIS, $r=0.21$, $p<0.05$), and anger (STAXI State, $r= 0.45$, $p<.0001$, and STAXI Trait, $r= 0.61$, $p<0.001$).

The results in the full sample, while supportive at least in part of the results in the European white subsample, should be interpreted with caution given that the full sample includes several different ethnic groups. However, for the 288 subjects with available AIM scores, the distributions of these scores did not differ significantly across patients and HC. These results suggest that other SNPs outside the "risk" haplotype may be of interest for future studies.

Strengths

This study has several strengths. We used a well-characterized clinical sample. The haplotype is well-defined, and the ethnicity was defined by European ancestry informative markers. This study replicates and extends the finding of Zhou and colleagues that the "risk" haplotype (previously associated with suicide attempts) is associated with suicidal behavior in BPD but also the BPD diagnosis itself and other core symptoms of BPD, building on the already strong association between serotonergic genes, reduced serotonin function and impulsive aggression.

Limitations

The findings should be interpreted in light of several limitations. First, results are based on a European white sample, and may not be generalizable to other populations. Second, Zhou et al. (Zhou et al., 2005) acknowledged that they did not know whether any of the SNPs included in the haplotype were functional. Third, a complex illness such as BPD likely involves multiple genes related to brain organization and development (thus far not widely explored) and other neurotransmitter systems, such as the cholinergic system, which appears to mediate affective instability (New et al., 2008; Silverman et al., 1991) and were not analyzed in the present report.

In fact, the serotonergic abnormalities in BPD appear to be specifically associated with affective instability but not with other symptoms (Coccaro et al., 1989). Finally, our sample size is large for a clinical sample of well-characterized PD subjects, but is relatively small for genetic association studies.

Conclusion

In summary, the major findings of this study are an association between the previously described TPH2 “risk” haplotype and BPD diagnosis, affective instability, suicidal/parasuicidal behavior, and aggression scores.

It has been suggested that the genetic basis may be stronger for dimensions of BPD than for the diagnosis itself (Siever et al., 2002). According to this model, BPD is conceptualized as a PD resulting from the interaction of these underlying traits, which may represent heritable endophenotypes that increase the likelihood of developing BPD (Siever et al., 2002). The present study supports the heritability of BPD and BPD traits of impulsive aggression.

The results of the present study require replication in other samples, preferably of different origin, and studies on the role of these SNPs will be required to evaluate the functional consequences on brain and behavior. Further research is needed to shed light on the complex interplay of genetic and environmental factors in BPD.

Acknowledgments

Acknowledgement

None.

Role of funding sources

This research was supported by Grants MH56140 & MH63875 from the National Institute of Mental Health to Larry J. Siever; by a Veterans Affairs Merit Review Grant (7609-028) to Larry J. Siever; and by the Veterans Affairs VISN 3 Mental Illness Research, Education & Clinical Center.

This publication was made possible by Grant Number MO1-RR-00071 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of NCRR or NIH.

This work was supported in part by a VA Merit award to Dr. New (9001-03-0051 New (PI)-“Intermediate Phenotypes for Borderline Personality Disorder” and a VA Career Development Award to Dr. Goodman.

The funding sources had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

References

Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561–71. [PubMed: 13688369]

Bernstein DP, Stein JA, Newcomb MD, Walker E, Pogge D, Ahluvalia T, Stokes J, Handelsman L, Medrano M, Desmond D, Zule W. Development and validation of a brief screening version of the Childhood Trauma Questionnaire. Child Abuse Negl 2003;27:169–90. [PubMed: 12615092]

Bierer LM, Yehuda R, Schmeidler J, Mitropoulou V, New AS, Silverman JM, Siever LJ. Abuse and neglect in childhood: relationship to personality disorder diagnoses. CNS Spectr 2003;8:737–54. [PubMed: 14712172]

Buss AH, Durkee A. An inventory for assessing different kinds of hostility. J Consult Psychol 1957;21:343–9. [PubMed: 13463189]

Buss AH, Perry M. The aggression questionnaire. J Pers Soc Psychol 1992;63:452–9. [PubMed: 1403624]

Clark AG. The role of haplotypes in candidate gene studies. Genet Epidemiol 2004;27:321–33. [PubMed: 15368617]

Coccaro EF, Astill JL. Central serotonergic function in parasuicide. Prog Neuropsychopharmacol Biol Psychiatry 1990a;14:663–74. [PubMed: 1981394]

Coccaro EF, Astill JL, Herbert JL, Schut AG. Fluoxetine treatment of impulsive aggression in DSM-III-R personality disorder patients. J Clin Psychopharmacol 1990b;10:373–5. [PubMed: 2258454]

Coccaro EF, Berman ME, Kavoussi RJ, Hauger RL. Relationship of prolactin response to d-fenfluramine to behavioral and questionnaire assessments of aggression in personality-disordered men. Biol Psychiatry 1996;40:157–64. [PubMed: 8830948]

Coccaro EF, Gabriel S, Siever LJ. Buspirone challenge: preliminary evidence for a role for central 5-HT1a receptor function in impulsive aggressive behavior in humans. Psychopharmacol Bull 1990c; 26:393–405. [PubMed: 2274641]

Coccaro EF, Kavoussi RJ, Cooper TB, Hauger RL. Central serotonin activity and aggression: inverse relationship with prolactin response to d-fenfluramine, but not CSF 5-HIAA concentration, in human subjects. Am J Psychiatry 1997a;154:1430–5. [PubMed: 9326827]

Coccaro EF, Kavoussi RJ, Hauger RL. Physiological responses to d-fenfluramine and ipsapirone challenge correlate with indices of aggression in males with personality disorder. Int Clin Psychopharmacol 1995;10:177–9. [PubMed: 8675971]

Coccaro EF, Kavoussi RJ, Trestman RL, Gabriel SM, Cooper TB, Siever LJ. Serotonin function in human subjects: intercorrelations among central 5-HT indices and aggressiveness. Psychiatry Res 1997b; 73:1–14. [PubMed: 9463834]

Coccaro EF, Siever LJ, Klar HM, Maurer G, Cochrane K, Cooper TB, Mohs RC, Davis KL. Serotonergic studies in patients with affective and personality disorders. Correlates with suicidal and impulsive aggressive behavior. Arch Gen Psychiatry 1989;46:587–99. [PubMed: 2735812]

Coolidge FL, Thede LL, Jang KL. Heritability of personality disorders in childhood: a preliminary investigation. J Pers Disord 2001;15:33–40. [PubMed: 11236813]

Coon H, Dunn D, Lainhart J, Miller J, Hamil C, Battaglia A, Tancredi R, Leppert MF, Weiss R, McMahon W. Possible association between autism and variants in the brain-expressed tryptophan hydroxylase gene (TPH2). Am J Med Genet B Neuropsychiatr Genet 2005;135B:42–6. [PubMed: 15768392]

Cornelius JR, Soloff PH, Perel JM, Ulrich RF. A preliminary trial of fluoxetine in refractory borderline patients. J Clin Psychopharmacol 1991;11:116–20. [PubMed: 2056138]

De Luca V, Mueller DJ, Tharmalingam S, King N, Kennedy JL. Analysis of the novel TPH2 gene in bipolar disorder and suicidality. Mol Psychiatry 2004;9:896–7. [PubMed: 15197398]

De Luca V, Voineskos D, Wong GW, Shinkai T, Rothe C, Strauss J, Kennedy JL. Promoter polymorphism of second tryptophan hydroxylase isoform (TPH2) in schizophrenia and suicidality. Psychiatry Res 2005;134:195–8. [PubMed: 15840421]

Endicott J, Spitzer RL. A diagnostic interview: the schedule for affective disorders and schizophrenia. Arch Gen Psychiatry 1978;35:837–44. [PubMed: 678037]

First M, Spitzer R, Gibbon M, Williams J, Davies M, Borus J, Howes M, Kane J, Pope H, Rounsaville B. The Structured Clinical Interview for DSM-III-R Personality Disorders (SCID-II). Part II: Multi-site Test-retest Reliability Study. Journal of Personality Disorders 1995;9:92–104.

Goodman M, New A, Siever L. Trauma, genes, and the neurobiology of personality disorders. Ann N Y Acad Sci 2004;1032:104–16. [PubMed: 15677398]

Goveas JS, Csernansky JG, Coccaro EF. Platelet serotonin content correlates inversely with life history of aggression in personality-disordered subjects. Psychiatry Res 2004;126:23–32. [PubMed: 15081624]

Gurvits IG, Koenigsberg HW, Siever LJ. Neurotransmitter dysfunction in patients with borderline personality disorder. Psychiatr Clin North Am 2000;23:27–40. vi. [PubMed: 10729929]

Halperin JM, Schulz KP, McKay KE, Sharma V, Newcorn JH. Familial correlates of central serotonin function in children with disruptive behavior disorders. Psychiatry Res 2003;119:205–16. [PubMed: 12914892]

Harvey PD, Greenberg BR, Serper MR. The affective lability scales: development, reliability, and validity. J Clin Psychol 1989;45:786–93. [PubMed: 2808736]

Hodgkinson CA, Yuan Q, Xu K, Shen PH, Heinz E, Lobos EA, Binder EB, Cubells J, Ehlers CL, Gelernter J, Mann J, Riley B, Roy A, Tabakoff B, Todd RD, Zhou Z, Goldman D. Addictions biology: haplotype-based analysis for 130 candidate genes on a single array. Alcohol Alcohol 2008;43:505–15. [PubMed: 18477577]

Ji WY, Hu YH, Huang YQ, Cao WH, Lv J, Qin Y, Pang ZC, Wang SJ, Li LM. A twin study of personality disorder heritability. Zhonghua Liu Xing Bing Xue Za Zhi 2006;27:137–41. [PubMed: 16749995]

Kendler KS, Aggen SH, Czajkowski N, Roysamb E, Tambs K, Torgersen S, Neale MC, Reichborn-Kjennerud T. The structure of genetic and environmental risk factors for DSM-IV personality disorders: a multivariate twin study. Arch Gen Psychiatry 2008;65:1438–46. [PubMed: 19047531]

Kulikov AV, Osipova DV, Naumenko VS, Popova NK. Association between Tph2 gene polymorphism, brain tryptophan hydroxylase activity and aggressiveness in mouse strains. Genes Brain Behav 2005;4:482–5. [PubMed: 16268992]

Leyton M, Okazawa H, Diksic M, Paris J, Rosa P, Mzengeza S, Young SN, Blier P, Benkelfat C. Brain Regional alpha-[11C]methyl-L-tryptophan trapping in impulsive subjects with borderline personality disorder. Am J Psychiatry 2001;158:775–82. [PubMed: 11329401]

Lidberg L, Belfrage H, Bertilsson L, Evenden MM, Asberg M. Suicide attempts and impulse control disorder are related to low cerebrospinal fluid 5-HIAA in mentally disordered violent offenders. Acta Psychiatr Scand 2000;101:395–402. [PubMed: 10823300]

Linehan, M.; Wagner, A.; Cox, G. Parasuicide History Interview: comprehensive assessment of parasuicidal behavior [unpublished manuscript]. Seattle: University of Washington; 1983.

Linnoila M, DeJong J, Virkkunen M. Family history of alcoholism in violent offenders and impulsive fire setters. Arch Gen Psychiatry 1989;46:613–616. [PubMed: 2472125]

Linnoila, M.; Virkkunen, M.; George, T.; Eckardt, M.; Higley, JD.; Nielsen, D.; Goldman, D. Serotonin, behavior and alcohol. In: Jansson, B.; Jornvall, H.; Rydberg, U.; Terenius, L.; Vallee, L., editors. Toward a Molecular Basis of Alcohol Use and Abuse. Switzerland: Birkhauser Verlag Base; 1994.

Lopez de Lara C, Brezo J, Rouleau G, Lesage A, Dumont M, Alda M, Benkelfat C, Turecki G. Effect of tryptophan hydroxylase-2 gene variants on suicide risk in major depression. Biol Psychiatry 2007;62:72–80. [PubMed: 17217922]

Loranger AW, Oldham JM, Tulis EH. Familial transmission of DSM-III borderline personality disorder. Arch Gen Psychiatry 1982;39:795–9. [PubMed: 7165479]

Lyons-Ruth K, Holmes BM, Sasvari-Szekely M, Ronai Z, Nemoda Z, Pauls D. Serotonin transporter polymorphism and borderline or antisocial traits among low-income young adults. Psychiatr Genet 2007;17:339–43. [PubMed: 18075474]

Marsh DM, Dougherty DM, Moeller FG, Swann AC, Spiga R. Laboratory-measured aggressive behavior of women: acute tryptophan depletion and augmentation. Neuropsychopharmacology 2002;26:660–71. [PubMed: 11927191]

McGlashan TH, Grilo CM, Sanislow CA, Ralevski E, Morey LC, Gunderson JG, Skodol AE, Shea MT, Zanarini MC, Bender D, Stout RL, Yen S, Pagano M. Two-year prevalence and stability of individual DSM-IV criteria for schizotypal, borderline, avoidant, and obsessive-compulsive personality disorders: toward a hybrid model of axis II disorders. Am J Psychiatry 2005;162:883–9. [PubMed: 15863789]

Mossner R, Walitza S, Geller F, Scherag A, Gutknecht L, Jacob C, Bogusch L, Remschmidt H, Simons M, Herpertz-Dahlmann B, Fleischhaker C, Schulz E, Warnke A, Hinney A, Wewetzer C, Lesch KP. Transmission disequilibrium of polymorphic variants in the tryptophan hydroxylase-2 gene in children and adolescents with obsessive-compulsive disorder. Int J Neuropsychopharmacol 2006;9:437–42. [PubMed: 16146581]

New AS, Buchsbaum MS, Hazlett EA, Goodman M, Koenigsberg HW, Lo J, Iskander L, Newmark R, Brand J, O'Flynn K, Siever LJ. Fluoxetine increases relative metabolic rate in prefrontal cortex in impulsive aggression. Psychopharmacology (Berl) 2004a;176:451–8. [PubMed: 15160265]

New AS, Gelernter J, Yovell Y, Trestman RL, Nielsen DA, Silverman J, Mitropoulou V, Siever LJ. Tryptophan hydroxylase genotype is associated with impulsive-aggression measures: a preliminary study. Am J Med Genet 1998;81:13–7. [PubMed: 9514581]

New AS, Goodman M, Triebwasser J, Siever LJ. Recent advances in the biological study of personality disorders. Psychiatr Clin North Am 2008;31:441–61. vii. [PubMed: 18638645]

New AS, Hazlett EA, Buchsbaum MS, Goodman M, Mitelman SA, Newmark R, Trisdorfer R, Haznedar MM, Koenigsberg HW, Flory J, Siever LJ. Amygdala-prefrontal disconnection in borderline personality disorder. Neuropsychopharmacology 2007;32:1629–40. [PubMed: 17203018]

New AS, Trestman RF, Mitropoulou V, Goodman M, Koenigsberg HH, Silverman J, Siever LJ. Low prolactin response to fenfluramine in impulsive aggression. J Psychiatr Res 2004b;38:223–30. [PubMed: 15003426]

Ni X, Bismil R, Chan K, Sicard T, Bulgin N, McMain S, Kennedy JL. Serotonin 2A receptor gene is associated with personality traits, but not to disorder, in patients with borderline personality disorder. Neurosci Lett 2006a;408:214–9. [PubMed: 17000047]

Ni X, Chan D, Chan K, McMain S, Kennedy JL. Serotonin genes and gene-gene interactions in borderline personality disorder in a matched case-control study. Prog Neuropsychopharmacol Biol Psychiatry. 2008

Ni X, Chan D, Chan K, McMain S, Kennedy JL. Serotonin genes and gene-gene interactions in borderline personality disorder in a matched case-control study. Prog Neuropsychopharmacol Biol Psychiatry 2009;33:128–33. [PubMed: 19032968]

Ni X, Chan K, Bulgin N, Sicard T, Bismil R, McMain S, Kennedy JL. Association between serotonin transporter gene and borderline personality disorder. J Psychiatr Res 2006b;40:448–53. [PubMed: 16690085]

Ni X, Sicard T, Bulgin N, Bismil R, Chan K, McMain S, Kennedy JL. Monoamine oxidase a gene is associated with borderline personality disorder. Psychiatr Genet 2007;17:153–7. [PubMed: 17417058]

O'Keane V, Moloney E, O'Neill H, O'Connor A, Smith C, Dinan TG. Blunted prolactin responses to d-fenfluramine in sociopathy. Evidence for subsensitivity of central serotonergic function. Br J Psychiatry 1992;160:643–6. [PubMed: 1591573]

Oades RD, Lasky-Su J, Christiansen H, Faraone SV, Sonuga-Barke EJ, Banaschewski T, Chen W, Anney RJ, Buitelaar JK, Ebstein RP, Franke B, Gill M, Miranda A, Roeyers H, Rothenberger A, Sergeant JA, Steinhausen HC, Taylor EA, Thompson M, Asherson P. The influence of serotonin- and other genes on impulsive behavioral aggression and cognitive impulsivity in children with attention-deficit/hyperactivity disorder (ADHD): Findings from a family-based association test (FBAT) analysis. Behav Brain Funct 2008;4:48. [PubMed: 18937842]

Oldham JM. Borderline personality disorder and suicidality. Am J Psychiatry 2006;163:20–6. [PubMed: 16390884]

Pally R. The neurobiology of borderline personality disorder: the synergy of "nature and nurture". J Psychiatr Pract 2002;8:133–42. [PubMed: 15985870]

Paris J, Zweig-Frank H, Kin NM, Schwartz G, Steiger H, Nair NP. Neurobiological correlates of diagnosis and underlying traits in patients with borderline personality disorder compared with normal controls. Psychiatry Res 2004;121:239–52. [PubMed: 14675743]

Pfohl, B.; Blum, N.; Zimmerman, M. Structured Interview for DSM-IV® Personality (SIDP-IV). American Psychiatric Publishing, Inc; 1997.

Reist C, Helmeste D, Albers L, Chhay H, Tang SW. Serotonin indices and impulsivity in normal volunteers. Psychiatry Res 1996;60:177–84. [PubMed: 8723308]

Rinne T, van den Brink W, Wouters L, van Dyck R. SSRI treatment of borderline personality disorder: a randomized, placebo-controlled clinical trial for female patients with borderline personality disorder. Am J Psychiatry 2002;159:2048–54. [PubMed: 12450955]

Rousseva A, Henry C, van den Bulke D, Fournier G, Laplanche JL, Leboyer M, Bellivier F, Aubry JM, Baud P, Boucherie M, Buresi C, Ferrero F, Malafosse A. Antidepressant-induced mania, rapid cycling and the serotonin transporter gene polymorphism. Pharmacogenomics J 2003;3:101–4. [PubMed: 12746735]

Roy A, Adinoff B, Linnoila M. Acting out hostility in normal volunteers: negative correlation with levels of 5-HIAA in cerebrospinal fluid. Psy Res 1988;24:187–194.

Sheehan K, Lowe N, Kirley A, Mullins C, Fitzgerald M, Gill M, Hawi Z. Tryptophan hydroxylase 2 (TPH2) gene variants associated with ADHD. Mol Psychiatry 2005;10:944–9. [PubMed: 15940290]

Sher L, Oquendo MA, Li S, Ellis S, Brodsky BS, Malone KM, Cooper TB, Mann JJ. Prolactin response to fenfluramine administration in patients with unipolar and bipolar depression and healthy controls. Psychoneuroendocrinology 2003;28:559–73. [PubMed: 12689612]

Siever LJ. Neurobiology of aggression and violence. Am J Psychiatry 2008;165:429–42. [PubMed: 18346997]

Siever LJ, Torgersen S, Gunderson JG, Livesley WJ, Kendler KS. The borderline diagnosis III: identifying endophenotypes for genetic studies. Biol Psychiatry 2002;51:964–8. [PubMed: 12062879]

Silverman JM, Pinkham L, Horvath TB, Coccaro EF, Klar H, Schear S, Apter S, Davidson M, Mohs RC, Siever LJ. Affective and impulsive personality disorder traits in the relatives of patients with borderline personality disorder. Am J Psychiatry 1991;148:1378–85. [PubMed: 1897620]

Skodol AE, Siever LJ, Livesley WJ, Gunderson JG, Pfohl B, Widiger TA. The borderline diagnosis II: biology, genetics, and clinical course. Biol Psychiatry 2002;51:951–63. [PubMed: 12062878]

Sorgi P, Ratey J, Knoedler DW, Markert RJ, Reichman M. Rating aggression in the clinical setting. A retrospective adaptation of the Overt Aggression Scale: preliminary results. J Neuropsychiatry Clin Neurosci 1991;3:S52–6. [PubMed: 1687961]

Stanley B, Molcho A, Stanley M, Winchel R, Gameroff MJ, Parsons B, Mann JJ. Association of aggressive behavior with altered serotonergic function in patients who are not suicidal. American Journal of Psychiatry 2000;157:609–614. [PubMed: 10739421]

Steiger H, Joober R, Israel M, Young SN, Ng Ying Kin NM, Gauvin L, Bruce KR, Joncas J, Torkaman-Zehi A. The 5HTTLPR polymorphism, psychopathologic symptoms, and platelet [3H-] paroxetine binding in bulimic syndromes. Int J Eat Disord 2005;37:57–60. [PubMed: 15690467]

Torgersen S, Lygren S, Oien PA, Skre I, Onstad S, Edvardsen J, Tambs K, Kringlen E. A twin study of personality disorders. Compr Psychiatry 2000;41:416–25. [PubMed: 11086146]

Virkkunen M, Rawlings R, Tokola R, Poland RE, Guidotti A, Nemeroff C, Bisette G, Kalogera K, Karonen SL, Linnoila M. CSF biochemistries, glucose metabolism, and diurnal activity rhythms in alcoholic violent offenders, fire setters, and healthy volunteers. Arch Gen Psychiatry 1994;51:20–27. [PubMed: 7506515]

Walitza S, Renner TJ, Dempfle A, Konrad K, Wewetzer C, Halbach A, Herpertz-Dahlmann B, Remschmidt H, Smidt J, Linder M, Flierl L, Knolker U, Friedel S, Schafer H, Gross C, Hebebrand J, Warnke A, Lesch KP. Transmission disequilibrium of polymorphic variants in the tryptophan hydroxylase-2 gene in attention-deficit/hyperactivity disorder. Mol Psychiatry 2005;10:1126–32. [PubMed: 16116490]

Walther DJ, Bader M. A unique central tryptophan hydroxylase isoform. Biochem Pharmacol 2003;66:1673–80. [PubMed: 14563478]

White CN, Gunderson JG, Zanarini MC, Hudson JI. Family studies of borderline personality disorder: a review. Harv Rev Psychiatry 2003;11:8–19. [PubMed: 12866737]

Zaboli G, Gizatullin R, Nilsonne A, Wilczek A, Jonsson EG, Ahnemark E, Asberg M, Leopardi R. Tryptophan hydroxylase-1 gene variants associate with a group of suicidal borderline women. Neuropsychopharmacology 2006;31:1982–90. [PubMed: 16495936]

Zhou Z, Roy A, Lipsky R, Kuchipudi K, Zhu G, Taubman J, Enoch MA, Virkkunen M, Goldman D. Haplotype-based linkage of tryptophan hydroxylase 2 to suicide attempt, major depression, and cerebrospinal fluid 5-hydroxyindoleacetic acid in 4 populations. Arch Gen Psychiatry 2005;62:1109–18. [PubMed: 16203956]

Zill P, Baghai TC, Zwanzger P, Schule C, Eser D, Rupprecht R, Moller HJ, Bondy B, Ackenheil M. SNP and haplotype analysis of a novel tryptophan hydroxylase isoform (TPH2) gene provide evidence for association with major depression. Mol Psychiatry 2004a;9:1030–6. [PubMed: 15124006]

Zill P, Buttner A, Eisenmenger W, Moller HJ, Bondy B, Ackenheil M. Single nucleotide polymorphism and haplotype analysis of a novel tryptophan hydroxylase isoform (TPH2) gene in suicide victims. Biol Psychiatry 2004b;56:581–6. [PubMed: 15476687]

Table 1

Demographic Characteristics of the Sample: The whole sample and the European white subsample

All subjects		**Female**	**Male**	**Total**
		N (% across races)	**N (% across races)**	**N (% across races)**
Race (self report)	**European white**	66 (48,9)	116 (53,0)	182 (51,4)
	Black	33 (24,4)	48 (21,9)	81 (22,9)
	Hispanic	19 (14,1)	40 (18,3)	59 (16,7)
	Asian	14 (10,4)	15 (6,8)	29 (8,2)
	Mixed	2 (1,5)	0 (0,0)	2 (0,6)
	Indian	1 (0,7)	0 (0,0)	1 (0,3)
	Total	135 (100.0)	219 (100.0)	354 (100.0)
		Mean (SD)	**Mean (SD)**	**Mean (SD)**
Age		32.7 (10.5)	35.2 (10.5)	34.2 (10.5)
		N (% across races)	**N (% across races)**	**N (% across races)**
Race (European ancestry informative marker [AIM] score)	**European white**	53 (39.3)	70 (32.0)	123 (34.7)
		Mean (SD)	**Mean (SD)**	**Mean (SD)**
Age		39.8 (12.3)	43.1 (9.9)	41.7 (11.1)
European white subsample		**N (%)**	**N (%)**	**N (%)**
	HC	22 (57.9)	16 (42.1)	38 (100)
	BPD	19 (50.0)	19 (50.0)	38 (100)
	Other PDs	12 (25.5)	35 (74.5)	47 (100)
	Total	53 (43.1)	70 (56.9)	123 (100)

Table 2

Effect of tryptophan-hydroxylase 2 (TPH2) haplotypes and alleles on aggression and affect lability scores in the European white subsample (including 38 healthy controls, 38 patients with BPD, and 47 patients with other PDs): Aggression is measured by self-report with a composite measure of the Buss Durkee Aggression Inventory and the Buss Perry Aggression Questionnaire (tBUSS). Affect lability was measured using the Affect Lability Scale (ALS). Individuals carrying one or more copies of the "risk" haplotype are grouped together.

		"risk" haplotype or allele (1 or 2 copies)		"non-risk" haplotype or allele (0 copies)		
SNP/haplotype	**Measure**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	
Haplotype	tBUSS	91	57.0 (17.8)	17	47.6 (20.5)	t=−1.95, df= 106, p=0.05
	ALS	90	1.1 (0.7)	17	0.6 (0.6)	t=−2.77, df=105, p<0.01
2171363	tBUSS	91	57.0 (17.9)	17	47.6 (20.5)	t=−1.95, df= 106, p=0.05
6582078	tBUSS	91	57.0 (17.9)	17	47.6 (20.5)	t=−1.95, df= 106, p=0.05
1352250	tBUSS	93	57.2 (18.0)	15	45.5 (18.9)	t=−2.30, df=106, p<0.05
Haplotype	Sui/parasuicidal behaviors	45	0.89 (2.09)	15	0.13 (0.35)	*t=−2.33, df=50.64, p<0.05*
Haplotype	Depression (BDI)	70	3.71 (7.12)	14	9.94 (11.57)	t= −2.65, df=28.84, p<0.05