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Serotonin Polymorphisms and Posttraumatic Stress Disorder in a Trauma Exposed African American Population

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Abstract

Background—Genetic polymorphisms that influence serotonin (5-hydroxytryptamine, 5HT) neurotransmission are candidates for contributing to susceptibility to posttraumatic stress disorder (PTSD). The objective of our study was to determine if a variable length polymorphism for the promoter regions of the 5HT transporter (5HTTLPR), and/or a substitution polymorphism in the promoter region for the 5HT2A receptor, would be associated with PTSD in a trauma exposed population of adult African-Americans.

Methods—Using a case control design, 118 participants recruited from the primary care clinics and the campus of a historically black university who met inclusion criteria including trauma exposure provided blood samples for genomic DNA. PTSD criteria were determined by the Clinician Assessment of PTSD Scale (CAPS) and criteria for other psychiatric disorders by the Structured Clinical Interview for DSM-IV (SCID). 5HTTLPR and 5HT2A-1438A/G were genotyped using established methods. Associations of genotypes with lifetime PTSD, and models testing associations of allele "dose", were analyzed.

Results—Fifty-five (47%) participants met lifetime criteria for PTSD and 26 (22%) met criteria for (mostly comorbid) major depression. The 5HT2A (lower expressing) G allele was significantly associated with PTSD. We did not find significant associations with 5HTTLPR.

Conclusions—Our findings suggest a relationship between genetic variation in the 5HT2A promoter region and PTSD.†

Keywords

Trauma; 5HT2A; 5HTTLPR; genetic variation; African American

Posttraumatic stress disorder (PTSD) is a potentially debilitating disorder that has been estimated to occur in 8% of the nongeriatric adult population of the United States.[1] Findings that a significant minority of individuals exposed to trauma develop PTSD have focused the

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field on identifying risk factors for developing the disorder. Family and twin studies implicate a contribution of genetic factors.[2] Estimates of heritability from twin studies indicate that genetic influences account for approximately one third of the variance in PTSD outcomes.[3] Despite these findings, to date, molecular genetic studies of PTSD have been limited.

Genes that affect serotonin (5-hydroxytryptamine, 5HT) neurotransmission are candidates for contributing to PTSD risk. Medications that block the reuptake of 5HT are considered "first-line" interventions for the disorder though the extent of their efficacy is controversial.[4] 5HT2 receptor antagonism is one of the defining neuropharmacological characteristics of second generation antipsychotic medications (SGAs).[5] SGAs have been found to have therapeutic effects as adjunctive medications for treatment refractory cases of PTSD and appear to target sleep disturbances in the disorder.[6,7] Observations from uncontrolled studies suggest benefit from antidepressants that feature 5HT2 antagonism (e.g. nefazodone, trazodone) for PTSD sleep disturbances.[8,9]

In cell lines that express 5HTR2A, the 5HTR2A-1438 A/G SNP demonstrated greater promoter activity in the presence of the A allele.[10] This and another polymorphism thought to be in complete linkage disequilibrium with 1438 A/G, have been associated with mood disorders, [11,12] schizophrenia, and response to the antipsychotic medication clozapine.[13] A meta-analysis of published findings indicated an association of suicidality with the lower expressing G allele.[14] PTSD has been found to be among the leading psychiatric diagnoses for elevating suicide risk.[15]

The short (lower expressing) allele of a functional length polymorphism in the promoter region of the gene coding for the 5HT transporter protein (5HTTLPR) was found to be associated with an increased risk for developing depression after stressful life events.[16] This finding stimulated considerable attention to 5HTTLPR in subsequent psychiatric research. A recent meta-analysis, however, concluded, that the available evidence was not supportive of a main effect of 5HTTLPR on depression or for an interaction with the effect of stressful life events. [17] Findings from another recent meta-analysis provided provisional support for an association between 5HTTLPR and amygdala activation in functional brain imaging studies. [18] Amygdala activation is central to current neurocircuitry theories of PTSD.[19] A recent study of a Korean population found a modest, albeit statistically significant association between PTSD and the short allele for 5HTTLPR.[20] Kilpatrick et al.[21] found an association of the low expressing alleles (short and L_G, see next paragraph) with PTSD but only in the subgroup with high Hurricane exposure and low social support, and the number of PTSD cases was small ($N = 19$). In another analysis of this population the "s" allele was associated with PTSD among those who lived in "high risk environments".[22] In contrast to both of these findings, Grabe et al.[23] found a relationship between the L allele and increased risk of PTSD that was explained by cases with three or more trauma exposures.

Unlike major depression which has been reported to be lower in African-Americans than in whites in several multi-site epidemiological studies,[24–26] the prevalence of PTSD in African-Americans has been found to equal or exceed rates of the disorder in whites. Rates have not been found to be increased, however, after controlling for variables related to exposure.[27,28] 5HTTLPR alleles have been reported to occur at different frequencies in black versus white populations.[29,30] In addition, recent reports indicate that the L allele has a low expressing variant (L_G) and that the L_G variant is more common in black than white populations.[30,31] It is therefore important to determine the genetic background that contributes to PTSD susceptibility in African-Americans and for studies of 5HTTLPR to account for functional long allele variants. In this study we tested the hypotheses that the lower functioning polymorphisms for HT2A and 5HTTLPR would be associated with PTSD in African-American adults who were exposed to significant trauma.

Methods

Participants

Participants were recruited from 1 of 2 primary studies. In the first, African-American patients were recruited for the adult primary care clinics of Howard University and were screened for trauma exposure using procedures described in more detail in our previous publication.[32] Six hundred and seventeen patients signed consent forms and completed forms that included an inventory of lifetime trauma exposure, the Life Event Checklist (LEC).[33] Of the 403 found to have unambiguous trauma exposure, 279 agreed to and were able to receive the diagnostic interview. Obtaining blood samples was initiated approximately midway through the study. This study analyses excluded participants who met criteria for psychotic and bipolar disorders, or current alcohol and substance dependence.

The second recruitment procedure involved posting flyers around the campus of Howard University (a historically black university) and the nearby community advertising for volunteers to participate in a study evaluating the relationship of posttraumatic stress and blood pressure. Thirty of 110 participants screened participated in the laboratory evaluation that included a blood drawing to extract DNA samples. Selection of these participants involved over-sampling for PTSD and balancing the number of men and women. They were also screened to be African-American based on self-report, to have had unambiguous trauma exposure, and to not have met the psychiatric exclusion criteria described above.

Both studies were conducted in compliance with the Code of Ethics of the World Medical Association and had IRB approval with consent forms that required separate signatures for drawing blood for DNA. All participants signed consent forms after receiving explanation of study procedures.

One hundred eighteen participants (94 from the primary care study and 24 from the University based recruitment) met the inclusion criteria and provided DNA samples that were viable for analysis. All participants were trauma exposed, they had an average age of 40, and 65% were female. Traumatic incidents included violent assault in 52% and sexual assault in 34%. (see Table 1)

Screening and Evaluation

Diagnostic interviews were conducted by trained research staff who had achieved adequate reliability on training interviews and were reviewed and supervised by 1 of 2 board certified psychiatrists (TA and TAM). Assessments included the Clinician Assessed PTSD Scale (CAPS)[33] for diagnosing PTSD, and the Structured Clinical Interview for DSM-IV (SCID) [34] to evaluate major depression and the psychiatric exclusion criteria.

Genotyping

Genomic DNA was isolated from using standard protocols. The 5HT2A receptor SNP, rs6311 [A-1438G], was obtained as a Taqman Assay-on-Demand (Applied Biosystems, Foster City, CA). Genotyping was performed according to the manufacturer's protocol and genotype was determined at end-point using an ABI 7900HT Sequence Detection System. Genotyping accuracy was determined empirically by duplicate genotyping of 25% of the samples selected randomly. The error rate was <.005, and the completion rate was >.95.

Genotyping for SLC6A4 promoter (5HTTLPR) was accomplished in two stages using size discrimination accompanied by HpaII restriction enzyme digestion for SNP rs25531. The 5HTTLPR region was PCR amplified with the primers; ATCGCTCCTGCATCCCCCATTAT (forward), and GAGGTGCAGGGGGATGCTGGAA (reverse). For product detection one of

the amplification primers was FAM-labeled. PCR was performed in a 20 μl reaction containing 10 ng genomic DNA, 1 × Optimized buffer A (Invitrogen Corp, Carlsbad, CA), 1 × PCR enhancer (Invitrogen Corp), 0.25 μM PCR primers (each primer), 0.125 μM dNTP, 1.25 units Platinum Taq polymerase (Invitrogen Corp), using the amplification conditions: 95°C (5 min), 40 cycles of 94°C (30 sec), 52°C (30 sec), 68°C (1 min), followed by a final elongation step of 68°C (10 min). For distinguishing the S and L alleles, 25 μl of the PCR reaction mix was added to 8 μl loading mix (7.5 μl formamide, 0.5 μl GeneScan™-500 ROX Size Standard (Applied Biosystems, Foster City, CA). For SNP rs25531 genotyping, 10 μl of the PCR mix was added to a restriction digest mix and made up to a final volume of 20 μl, containing 50 units HpaII (New England Biolabs, Ipswich, MA), 1 × NEB restriction buffer 1, incubated at 37°C for 1 hr, and 2 μl of reaction mix added to 8 μl loading mix (see above). Allelic discrimination for S (103 bp) and L (146 bp) alleles, and for L_A (146 bp) and L_G (61 bp post-digestion, if forward primer is labeled) alleles was performed by size determination on a 3730 DNA Analyzer (Applied Biosystems), with data analyzed using GeneMapper 4.0 software (Applied Biosystems).

In order to analyze for possible racial/ethnic stratification of the sample, Ethnic Factor Scores were derived for each individual from 175 unlinked loci genotyped by Illumina, Inc. (San Diego, CA) that had been previously determined to be ancestrally informative.[30] Proportion of membership of each subject in each of 7 geographic clusters was estimated, and these scores sum to 1.

Analysis

Possible differences between cases with and without PTSD were evaluated using grouped *t*-tests for age, and the ethnic factor score for the African geographic cluster, and χ^2 for other demographic and diagnostic characteristics, assault and sexual assault histories, and associations with genotypes. Adjustment for multiple testing was made using Bonferroni correction.

The independent contribution of 5HTT functional low expression (LE) alleles (S or L_G) and the -1438A/G 5-HT2A G allele on predicting PTSD were modeled utilizing logistic regression incorporating the variables that were significantly or at a trend level different between PTSD positives and negatives as covariates (female sex, sexual assault history, and depression). The models utilized a value of 0 for high expression (HE)/HE, and A/A genotypes; 1 for HE/LE and A/G, and 2 for LE/LE and G/G. Separate models were calculated for the 5HTT LE alleles and the 5-HT2A G allele. Findings were considered significant at $P<.01$ due to multiple comparisons.

Results

Demographic and genetic variables and their associations with a lifetime diagnosis of PTSD are presented in the Table 1. Forty-five percent of the study participants had a lifetime diagnosis of PTSD ($n = 55$) and 23% had a lifetime diagnosis of major depression. All but 6 of the 27 cases of major depression were comorbid with PTSD. In the univariate analyses there were trend acossiations for female sex ($\chi^2 = 5.5$, $df = 2$, $P = .02$) and sexual assault ($\chi^2 = 4.4$, $df = 2$, $P = .04$), and major depression ($\chi^2 = 12.0$, $df = 2$, $P = .001$) was significantly more frequent among the participants with PTSD. The mean African ethnic factor score was .76 ($SD = .14$) and was similar for cases and controls.

In the total population, 13 (11%) were homozygous for the short allele of the 5HTTLPR, 56 (45%) for the long allele, and the remaining 55 (44%) were heterozygous. Sixty-three (57%) of the long alleles were L_G and were therefore classified with S alleles as low expression (LE). The functional genotype distribution is presented in the Table 1. PTSD was not significantly

associated with 5HTTLPR functional genotypes ($\chi^2 = 1.0$, $df = 2$, NS). There was a significant association of PTSD with 5HT2A genotypes ($\chi^2 = 9.8$, $df = 2$, $P = .008$). The regression model revealed a significant association of the G allele with PTSD (OR = 2.7, 95% CI = 1.3–5.6, $P = .006$). The relationship of 5HTTLPR LE alleles to PTSD was not significant (OR = 1.3, 95% CI = 0.8–2.3, NS). Lifetime history of major depression was the only other significant covariate in these models ($P<.004$, all models).

Power to detect the association with the 5-HT2A polymorphism was estimated using the Genetic Power Calculator.[35] Sample size was estimated based on the 5-HT2A polymorphism with a risk allele (G) frequency of .755 and an estimated disease prevalence of .47. The power of our full sample (55 cases and 63 controls) at a 5% significance level to detect the observed genotypic relative risk of 2.9 for AG and 6.1 for GG, was at least 90% under the assumption of a general, allelic, or recessive model but 52% for a dominant model. In this study we fit an allelic model. Even if the relative risk were half the observed, the sample will have at least 80% power to detect such risk under an allelic model.

Discussion

Our findings provide evidence for a relationship between the lower expressing G allele of the 5HT2A promoter region and PTSD. We did not find an association with the functional expression alleles of the 5HTT promoter. In addition to associations with PTSD, our study provides additional information regarding 5HTTLPR allele frequencies in African-Americans. The frequency of L alleles in our population (67%) was somewhat lower than that reported by Lotrich et al.[29] for African-Americans residing in western Pennsylvania (77%) and South Carolina (87%). The frequency of the L_G variant (38%) is somewhat higher than that reported by Roy et al.[30] (25%). The frequency of the G allele for 5HTR2A-1438 A/G in our study (75.5%) is higher than the 59% reported for African-Americans in the National Center for Biotechnology Information website [ncbi.nlm.nih.gov].

Findings need to be considered in light of study limitations most notably a limited sample size for testing genetic associations, particularly for excluding relationships. Therefore the absence of an association of 5HTTLPR could reflect a Type II error. Our sample is efficient however, for testing contribution to susceptibility to PTSD in terms of being high risk due to inclusion having been based on trauma exposure, frequent representation of high risk traumas (physical and sexual assault), and the high rate of lifetime PTSD (45%). Thus, while the overall sample size is small, the number of PTSD cases in our study is within the range of the prior published studies associating PTSD and 5HTTLPR (*n*'s = 19, 67, 100).[20–23] An additional limitation concerns that while analyses co-varied for sex, depression, and sexual assault, the possibility remains that these variables could have confounded the results.

The association of 5HT2A G with PTSD must be considered preliminary and requires replication. There are a number of findings regarding 5HT2 receptors, however, that support the plausibility of a relationship of a lower expressing allele in the promoter region to PTSD susceptibility in addition to the association of the G allele with suicide and the role of 5HT2 in PTSD pharmacotherapy, noted in the introduction. Fetal exposure to 5HT2 antagonism resulted in visual motor impairment in an animal model.[36] Brain 5HT2 binding in vivo was reduced among 12 remitted depressed patients with high familial loading[37] and healthy males were found to have higher 5HT2 brain binding capacity than females.[38] (PTSD is commonly comorbid with depression and is more prevalent in women than in men[1]).

Prior evidence linking 5HTTLPR to PTSD is limited. In one study, the relationship depended on the presence of an adverse environmental and social context.[21] Our findings are consistent

with the recent meta-analysis findings not supporting an interaction with the effect of stressful life events on depression.[17]

Further research is indicated to exclude a relationship between PTSD and 5HTTLPR, confirm the finding of a relationship to a low expression promoter polymorphism for the 5HT2A receptor, and explore possible relationships of this polymorphism to medication treatment response. These future studies should include multi-ethnic/racial samples.

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Table 1
PTSD versus controls—demographics, diagnosis, and 5HT genotypes and alleles

	Total *N* = 118	PTSD *n* = 55	PTSD negative *n* = 63	*P* value
Age	39.9±16.3	39.5±15.8	40.3±16.8	.84
Female	78 (.65)	43 (.76)	35 (.55)	.01
Assault trauma	61 (.52)	29 (.53)	32 (.49)	.70
Sexual trauma	40 (.34)	24 (.44)	16 (.25)	.03
Depression	26 (.22)	20 (.36)	6 (.10)	.001
Ethnic Factor Score (African)	.76±.14	.77±.09	.75±.17	.45
5HTTLPR				
(Functional genotype)				
HE/HE	25 (.21)	10 (.18)	15 (.23)	
HE/LE	57 (.47)	26 (.46)	31 (.49)	.60
LE/LE	38 (.32)	20 (.36)	18 (.28)	
(Functional allele)				
LE				.34[a]
5HTR2A				
(Genotype)				
AA	12 (.10)	2 (.04)	10 (.16)	
AG	34 (.29)	11 (.21)	23 (.36)	.008[a]
GG	71 (.61)	40 (.75)	31 (.48)	
(Allele)				
G[a]				.008

[a]Significance of allele(s) in predicting PTSD in logistic regression models.