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Association of the rs2242446 polymorphism in the norepinephrine transporter gene *SLC6A2* and anxious arousal symptoms of posttraumatic stress disorder

Robert H. Pietrzak, Ph.D., M.P.H.[a,b], **Jennifer A. Sumner, Ph.D.**[c], **Allison E. Aiello, Ph.D.**[d], **Monica Uddin, Ph.D.**[e,f], **Alexander Neumeister, M.D.**[g], **Guia Guffanti, Ph.D.**[c], and **Karestan C. Koenen, Ph.D.**[c]

[a]United States Department of Veterans Affairs, National Center for Posttraumatic Stress Disorder, Clinical Neurosciences Division, VA Connecticut Healthcare System, West Haven, CT, USA

[b]Department of Psychiatry, Yale School of Medicine, New Haven, CT, USA

[c]Department of Epidemiology, Columbia University Mailman School of Public Health, New York, NY, USA

[d]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, Chapel Hill, NC, USA

[e]Center for Molecular Medicine and Genetics, Wayne State University School of Medicine, Detroit, MI, USA

[f]Department of Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine, Detroit, MI, USA

[g]Departments of Psychiatry and Radiology, New York University School of Medicine, New York, NY, USA

Recently, we found that greater norepinephrine transporter (NET) availability in the locus coeruleus of trauma survivors with posttraumatic stress disorder (PTSD) was associated with increased severity of anxious arousal (i.e., hypervigilance and exaggerated startle) symptoms, but not any of the other empirically-derived symptom clusters that characterize this disorder.[1] This finding suggests that greater NET availability in the locus coeruleus may serve a compensatory function of clearing elevated synaptic norepinephrine and maintaining anxious arousal symptoms in persons with PTSD.

A single nucleotide polymorphism (SNP) found in the promoter region of the NET gene *SLC6A2* (rs2242446) has been associated with panic disorder.[2,3] Given similarities in the clinical presentation of panic disorder and anxious arousal symptoms of PTSD,[4] and data linking NET availability in the locus coeruleus to anxious arousal,[1] it is reasonable to hypothesize that this SNP might be linked to anxious arousal in trauma survivors. We evaluated this possibility using data from the Detroit Neighborhood Health Study (DNHS),

Correspondence: Robert H. Pietrzak, Ph.D., M.P.H., National Center for Posttraumatic Stress Disorder, VA Connecticut Healthcare System, Department of Psychiatry, Yale School of Medicine, 950 Campbell Avenue / 151E, West Haven, CT 06516, USA; Phone: 860-638-7467; Fax: 203-937-3481; robert.pietrzak@yale.edu.

an epidemiologic study of trauma-related psychopathology in a representative sample of predominantly African-American adults from urban Detroit.[5]

Methods

Data were analyzed from 580 participants who provided information regarding trauma exposure and PTSD, and had valid data for rs2242446 from blood or saliva samples.[5] Although some additional SNPs have been significantly associated with panic disorder in prior studies,[2,3] only rs2242446 was genotyped in the DNHS; thus, we focused on this SNP. The DNHS was approved by the University of Michigan Institutional Review Board, and all participants provided written informed consent.

PTSD symptom dimension scores from the PTSD Checklist (PCL) were computed by: 1) summing item responses to create scale scores for each symptom cluster, and 2) counting the number of symptoms endorsed at a "moderate" or greater level for each symptom cluster. Linear regressions predicting scores on the five PTSD symptom dimensions were conducted using Plink version 1.07,[6] with age, sex, and number of traumatic event types entered as covariates; the first two principal components from a multidimensional scaling analysis of genome-wide data were additionally included as covariates to adjust for population stratification. Alpha was set to .01 to reduce the likelihood of Type I error when testing associations between number of minor (G) alleles and the different symptom dimensions.

Results

Table 1 shows sample characteristics and results of regression analyses, which revealed that rs2242446 genotype, coded additively as the number of minor (G) alleles, significantly predicted both scale scores and count of anxious arousal symptoms but none of the other symptom clusters or severity or probable diagnosis of PTSD. Participants with two G alleles reported the highest level of anxious arousal symptoms ($M_{scale\ score}$=5.27; M_{count}=1.00), followed by those with one G allele ($M_{scale\ score}$=4.74; M_{count}=0.81), and those with zero G alleles ($M_{scale\ score}$=4.58; M_{count}=0.73). No significant interactions between rs2242446 genotype and the number of traumatic event types emerged for either anxious arousal outcome, all βs<0.17, all ps>.01.

Discussion

These results build on our prior finding that greater NET availability in the locus coeruleus is linked to increased anxious arousal[1] and previous studies linking SNPs in *SLC6A2* to panic disorder[2,3] to suggest an independent association between a polymorphism in the promoter region of *SLC6A2* (rs2242446) and anxious arousal symptoms of PTSD. The magnitude of this association ranged from small-to-moderate based on the number of risk alleles.[7] Given that the *SLC6A2* gene encodes for the NET, this polymorphism may affect NET synthesis, which in turn modulates anxious arousal symptoms in trauma survivors. This association was especially pronounced for exaggerated startle response, which suggests a role for this SNP in modulating panic-based hyperreactivity[4] in trauma survivors. Importantly, that this association was not significant for any other symptom cluster or for

total severity or probable diagnosis of PTSD, underscores the importance of evaluating how candidate genetic markers for PTSD are linked to symptom clusters that comprise this phenotype.

This study demonstrates the utility of a translational epidemiologic approach to characterizing genetic correlates of psychiatric phenotypes, as it uses the best available, empirically-derived information regarding the phenotypic expression of PTSD[4] and attempts to link candidate genetic polymorphisms to component aspects of this complex phenotype. Further research will be useful in replicating these results, assessing how other genetic markers may be linked to the phenotypic expression of PTSD, and evaluating the utility of genotyping for risk genes associated with PTSD in personalizing treatment approaches for symptomatic trauma survivors.

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Table 1

Sample characteristics and results of regression analyses examining associations between *SLC6A2* rs2242446 genotype and PTSD symptom dimensions

Sample characteristics		
	M (SD), n (%), or proportion	**Range in Sample**
Age	52.4 (16.0)	18-90
Female sex	329 (56.7%)	-
Race		-
African-American	480 (82.8%)	-
White	65 (11.2%)	-
Other	35 (6.0%)	
SLC6A2 rs2242446 minor (G) allele frequency	0.20	-
Genotype frequency		Hardy-Weinberg equilibrium, p>.99
A/A	371 (64.0%)	-
A/G	186 (32.0%)	-
G/G	23 (4.0%)	-

Results of Regression Analyses					
	Descriptive statistics		**Regression results**		
	***M* (*SD*) or *n* (%)**	**Range**	***β***	***t***	***p***
PTSD Symptoms					
PCL total severity	35.50 (15.60)	17-85	0.04	1.16	.25
Re-experiencing	11.26 (5.16)	3-25	0.01	0.17	.87
Avoidance	4.36 (2.59)	1-10	0.04	1.04	.30
Numbing	9.28 (4.89)	4-25	0.02	0.45	.65
Dysphoric Arousal	5.86 (3.43)	2-15	0.06	1.69	.09
Anxious Arousal	4.66 (2.48)	2-10	0.09	2.45	.01
Counts of Symptoms					
Re-experiencing	1.80 (1.68)	0-5	−0.00	0.01	.99
Avoidance	0.68 (0.84)	0-2	0.03	0.86	.39
Numbing	1.21 (1.55)	0-5	0.01	0.29	.78
Dysphoric Arousal	0.80 (1.10)	0-3	0.05	1.36	.17
Anxious Arousal	0.76 (0.80)	0-2	0.12	3.04	.002

Results of Regression Analyses					
	Descriptive statistics		**Regression results**		
	***M* (*SD*) or *n* (%)**	**Range**	***β***	***t***	***p***
Endorsement of Anxious Arousal Symptoms			*OR* (95% *CI*)	*t*	*p*
Hypervigilance	283 (48.8%)	0-1	1.41 (1.03, 1.95)	2.12	.03
Exaggerated Startle	160 (27.6%)	0-1	1.76 (1.25, 2.49)	3.24	.001
			OR (95% *CI*)	*t*	*p*
Probable PTSD	92 (15.9%)	–	0.97 (0.65, 1.44)	0.17	.86

rs2242446 genotype was entered as the number of minor (G) alleles.

Greater trauma exposure was significantly associated with higher symptom levels for all symptom dimensions (all *β*s>0.28, all *p*s<.01), and female sex was significantly associated with higher re-experiencing, dysphoric arousal, and anxious arousal (scale score only) symptoms (all *β*s>0.12, all *p*s<.01). The first principal component was significantly associated with anxious arousal (scale score only; *β*=0.16, p<.0001) and avoidance (*β*s=0.12, p's<.01) symptoms. No significant interactions between the number of traumatic events and rs2242446 genotype emerged for either anxious arousal outcome, all *β*s<0.17, all *p*s>.01.

OR=odds ratio; 95% *CI*=95% confidence interval.

Re-experiencing symptoms=DSM-IV B1-B5 symptoms; Avoidance symptoms=C1-C2 symptoms; Numbing symptoms=C3-C7 symptoms; Dysphoric arousal=D1-D3 symptoms; Anxious arousal=D4-D5 symptoms.[4] Formal confirmatory factor analyses in the DNHS sample revealed that the 5-factor model of PTSD symptoms provided the best fit to PCL data (data not shown, available from first author).

[a] All regression models included sex, age, number of lifetime traumatic events, and the first two principal components from a multidimensional scaling analysis of genomewide markers as covariates.