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ORIGINAL RESEARCH

Higher *FKBP5*, *COMT*, *CHRNA5*, and *CRHR1* allele burdens are associated with PTSD and interact with trauma exposure: implications for neuropsychiatric research and treatment

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Joseph A Boscarino[1,2]
Porat M Erlich[1,3]
Stuart N Hoffman[4]
Xiaopeng Zhang[5]

[1]Center for Health Research, Geisinger Clinic, Danville, PA, [2]Department of Psychiatry, [3]Department of Medicine, Temple University School of Medicine, Philadelphia, PA, [4]Department of Neurology, [5]Department of Anesthesiology, Geisinger Clinic, Danville, PA, USA

Objective: The study aim was to assess the cumulative burden of polymorphisms located within four genetic loci previously associated with posttraumatic stress disorder (PTSD) among outpatients at risk for PTSD.

Methods: Diagnostic interviews were completed and DNA samples collected among 412 pain patients to determine if *FKBP5* (rs9470080), *COMT* (rs4680), *CHRNA5* (rs16969968), and *CRHR1* (rs110402) single nucleotide polymorphisms were cumulatively associated with increased risk for PTSD.

Results: In bivariate analyses, it was found that a count of specific PTSD risk alleles located within *FKBP5*, *COMT*, *CHRNA5*, and *CRHR1* genetic loci (allele range = 0–6, mean count = 2.92, standard deviation = 1.36) was associated with lifetime (t [409] = 3.430, $P = 0.001$) and early onset PTSD (t [409] = 4.239, $P = 0.000028$). In logistic regression, controlling for demographic factors, personality traits, and trauma exposures, this risk allele count remained associated with both lifetime (odds ratio = 1.49, $P = 0.00158$) and early onset PTSD (odds ratio = 2.36, $P = 0.000093$). Interaction effects were also detected, whereby individuals with higher risk allele counts and higher trauma exposures had an increased risk of lifetime PTSD (allele count × high trauma, $P = 0.026$) and early onset PTSD (allele count × high trauma, $P = 0.016$) in these logistic regressions. Those with no or few risk alleles appeared resilient to PTSD, regardless of exposure history.

Conclusion: A cumulative risk allele count involving four single nucleotide polymorphisms located within the *FKBP5*, *COMT*, *CHRNA5*, and *CRHR1* genes are associated with PTSD. Level of trauma exposure interacts with risk allele count, such that PTSD is increased in those with higher risk allele counts and higher trauma exposures. Since the single nucleotide polymorphisms studied encompass stress circuitry and addiction biology, these findings may have implications for neuropsychiatric research and treatment.

Keywords: posttraumatic stress disorder, genetic association study, single nucleotide polymorphism, risk alleles, trauma exposure, neuroticism, childhood adversity

Introduction

While studies suggest that most adults have experienced lifetime traumatic events, relatively few of them develop posttraumatic stress disorder (PTSD).[1–3] Available twin and family studies indicate that PTSD is at least moderately heritable, with approximately 30% of variance accounted for by genetic factors.[4] To date several genetic components for PTSD have been identified that may explain this risk.[5–7] These include biologic pathways involving the hypothalamic-pituitary-adrenal (HPA), locus

Correspondence: Joseph A Boscarino
Center for Health Research, Geisinger Clinic, 100 N. Academy Avenue, Danville, PA 17822-4400, USA
Tel +1 570 214 9622
Fax +1 570 214 9451
Email jaboscarino@geisinger.edu

coeruleus-noradrenergic, and the limbic systems, among others.[6,8–11] In the current study, genetic risk factors for PTSD were assessed among outpatients with chronic, nonmalignant pain, a condition often associated with PTSD.[12]

For the current study, four genetic markers were assessed using a cumulative risk allele model to test for an association with PTSD among outpatients, similar to what has been undertaken to predict complex genetic associations in other clinical areas.[13] To assess PTSD, a validated questionnaire based on the *Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition* was used.[2,14–17] Extending previous research,[9] single nucleotide polymorphisms (SNPs) located within the *FK506 binding protein-5* (*FKBP5*), *catechol-O-methyltransferase* (*COMT*), *cholinergic receptor nicotinic alpha-5* (*CHRNA5*), and the *corticotropin-releasing hormone receptor-1* (*CRHR1*) gene clusters were specifically genotyped and these markers were assessed for cumulative risk for PTSD.

The *COMT* gene is associated with anxiety disorders, psychosis, depression, and other conditions involving catecholamine pathway regulation and has recently been associated with PTSD.[9,18,19] The *FKBP5* gene regulates glucocorticoid receptor sensitivity, is functionally involved in HPA axis activity, and is associated with PTSD.[5,6,9,20] The *CHRNA* gene cluster, which encodes components of the nicotinic acetylcholine receptor, is associated with nicotine dependence and cigarette smoking,[21,22] substance misuse,[23] and recently PTSD.[9] The *CRHR1* gene is a polypeptide hormone and neurotransmitter involved in corticotropin-releasing hormone activity associated with the stress response. Studies suggest that this gene also regulates HPA axis function and is associated with the impact of traumatic stress exposure and PTSD.[20,24]

Methods

Subjects

Study subjects were adult outpatients (≥18 years old) who were prescribed pain medications for nonmalignant pain for ≥4 months.[14,23] Chronic pain patients typically have a high prevalence of PTSD.[25,26] The mean age of patients was 55 years old (standard deviation = 13.4) and the prevalence of lifetime PTSD was 15% (95% confidence interval [CI] = 11.7–18.1). The sample was randomly selected from among a population of chronic pain outpatients identified by query of the electronic health records of the Geisinger Clinic, an integrated health system that serves residents of 40 central and northeastern Pennsylvania counties.[14] Geisinger's ambulatory clinics have used the Epic (Epic Systems Corporation, Verona, WI) outpatient electronic health record system since 2001. With patient consent, trained and supervised interviewers administered structured diagnostic telephone interviews from August 2007 through November 2008.

Phenotypic and confounding measures

Study interviewers administered diagnostic surveys using instruments used in past research.[2,16,17] To meet criteria for lifetime PTSD, patients had to meet the full diagnostic criteria for PTSD, known as the "A through F" criteria.[2,15] These criteria include experiencing intense fear (criterion A), re-experiencing the event (criterion B), avoidance of stimuli associated with the event (criterion C), experiencing increased arousal (criterion D), experiencing symptoms for a month or more (criterion E), and experiencing psychological distress or impairment (criterion F). To be diagnosed with early onset PTSD, the patient had to meet the A–F diagnostic criteria for PTSD before the age of 35 years. Research typically suggests that early onset PTSD likely has greater impact on trauma victims.[27,28] Over half (53%) of the PTSD cases in the current study met this early onset definition. Research instruments relevant to childhood adversity, lifetime trauma exposure, and self-esteem were also administered.[17,29–31] To assess neuroticism, also a risk factor for PTSD,[32] the NEO Five-Factor Inventory was used.[33]

The childhood adversity scale used was the Adverse Childhood Experiences scale, a widely used measure of childhood adversity with good reported reliability and validity.[29,30,34] Cronbach's alpha for the Adverse Childhood Experiences scale in the current study was 88. The trauma scale used was a measure that has been extensively used in past trauma research and has been shown to have excellent predictive validity.[16,17,35] In the current study, this measure consisted of a count of the number of traumatic events (eg, combat exposure, sexual assault, major disaster) that the person experienced in his/her lifetime (range 0–9, mean = 2.19, standard deviation = 2.0). Self-esteem was measured by the Rosenberg Self-Esteem Scale, a widely used construct to measure self-esteem.[31,36] In the current study, Cronbach's alpha was 80 for this scale. The NEO Five-Factor Inventory is a personality measure widely used in neuropsychiatric research.[33,37,38] This scale is reported to have good reliability and validity.[37,38] Cronbach's alpha for the scales used in the NEO are good, typically between 0.76–0.89.[39]

Given that the current study population was drawn from a sample of pain patients, the study results were also adjusted for prescription opioid dependence, level of pain impairment, and the number of opioid prescriptions received as

potential confounders. Opioid dependence was based on whether the subject met criteria for *Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition* drug dependence and was based on a diagnostic interview.[14] Pain assessment was based on the Brief Pain Inventory, a widely used and validated instrument.[40,41] The number of opioid prescriptions received over the past 3 years was based on electronic health record data. Finally, to potentially account for population stratification, the study results were also adjusted for ancestry status, based on country of origin, coded as Northern European, Eastern European, Southern European, and other. Non-Caucasians were excluded from these analyses. This study was approved by the Geisinger Clinic's Institutional Review Board.

DNA collection and genotyping

Following the study interview, buccal swab kits were mailed to consenting adults. Altogether, 412 returned the buccal swab kit with adequate DNA for the current analyses. Two subjects were identified as non-Caucasian and were not included in the current study analyses, as noted. The candidate genes studied (and corresponding SNPs) were: *COMT* (rs4680), *FKBP5* (rs9470080), *CHRNA5* (rs16969968), and *CRHR1* (rs110402). The SNPs for the four target loci were originally selected using linkage disequilibrium tagging with consideration of prior evidence and functional annotation.[42] For each gene, the location of the main association signals related to PTSD were determined from the relevant literature. The linkage disequilibrium structure of the gene in the HapMap Caucasian sample (release 23a; http://www.hapmap.org) was then examined using the Gabriel algorithm.[43] The algorithm of de Bakker implemented in the software HaploView 4.0 (Daly Lab, Broad Institute, Cambridge, MA) was then used to select tagged SNPs for the target block in each gene.[44] The Gabriel algorithm delineates boundaries of genomic markers identified as haplotype blocks with little evidence for historical recombination, within which only a few common haplotypes are observed and that can be tagged for association analysis using unsaturated SNP subsets.[43] The de Bakker approach selects tags from empirical data based on linkage disequilibrium to maximize the cost-effectiveness of using a limited number of typed SNPs in a locus.[44]

Genotyping was performed on an Applied BioSystems® 7500 Real-Time Polymerase Chain Reaction System using TaqMan® kits (Applied BioSystems, Foster City, CA), following the manufacturer's protocols. Quality control measures included visual inspection of the allelic discrimination plots, monitoring concordance of cross-plated duplicate pairs, monitoring the overall call rate, and monitoring agreement with Hardy–Weinberg expectations.[45]

Statistical analyses

Based on previous research,[9] a bivariate association with PTSD was tested for the four target SNPs in the current study and each of these was found to be significant ($P < 0.05$). A cumulative risk allele model that included these four SNPs was then developed, as has been done in other clinical areas.[13,46] As suggested, each of these target SNPs had been associated with PTSD in previous reports. For each SNP studied, as previously discussed, an additive coding scheme (ie, subjects assigned zero, one, or two according to the number of copies of the minor allele) was tested followed by a dominant/recessive coding scheme (ie, carriers and homozygotes for the tested allele assigned a value of one, versus homozygotes for the alternate allele assigned a value of zero) if the additive model was not significant. Only one SNP tested was reduced to a dominant/recessive model (Table 1).[9] A count of alleles across these loci resulted in a risk score ranging from 0–6 (mean = 2.92, standard deviation = 1.36). For descriptive analyses, chi-squared tests were used to assess the associations between the main variables of interest and PTSD status (Table 2). In addition, independent t-tests were also used to assess the bivariate association between risk allele counts and key exposure variables, which included trauma exposure,

Table 1 Single nucleotide polymorphisms included in risk allele model

SNP	Gene	Chromosome (map location)	MAF (minor/common)	Functional annotation	HWE *P* value
Marker specifications (NCBI build 37.1)					
rs16969968*	*CHRNA5*	15 (78882925)	35.0% (A/G)	Missense (D⇔N)	0.0279
rs9470080**	*FKBP5*	6 (35646435)	33.0% (T/C)	Intron	0.7404
rs4680*	*COMT*	22 (19951271)	49.5% (G/A)	Missense (V⇔M)	0.9709
rs110402*	*CRHR1*	17 (43880047)	42.4% (A/G)	Intron	0.4333

Notes: *Additive model coded 0, 1, 2 for risk allele; **dominant model coded 0, 1 for the risk allele.
Abbreviations: HWE, Hardy–Weinberg equilibrium; MAF, minor allele frequency; NCBI, National Center for Biotechnology Information (Bethesda, MD); SNP, single nucleotide polymorphism.

Table 2 Lifetime posttraumatic stress disorder and early onset posttraumatic stress disorder by study variables

Study variables	% total (N)	Lifetime PTSD			Early onset PTSD		
		% yes (N)	% no (N)	*P* value	% yes (N)	% no (N)	*P* value
Sex							
Male	30.2 (152)	9.9 (15)	90.1 (137)	0.044	4.6 (7)	95.4 (145)	0.082
Female	68.9 (351)	16.8 (59)	83.2 (292)		9.1 (32)	90.9 (319)	
Age (years)							
18–44	17.3 (87)	25.3 (22)	74.7 (65)	<0.0001	24.1 (21)	75.9 (66)	<0.0001
45–64	58.3 (293)	15.4 (45)	84.6 (248)		5.5 (16)	94.5 (277)	
65+	24.5 (123)	5.7 (7)	94.3 (116)		1.6 (2)	98.4 (121)	
Married							
No	38.2 (192)	19.8 (38)	80.2 (154)	0.011	10.9 (21)	89.1 (171)	0.036
Yes	61.8 (311)	11.6 (36)	88.4 (275)		5.8 (18)	94.2 (293)	
High school education or less							
No	50.1 (252)	15.5 (39)	84.5 (213)	0.628	9.5 (24)	90.5 (228)	0.137
Yes	49.9 (251)	13.9 (35)	86.1 (216)		6.0 (15)	94.0 (236)	
Income less than $30,000							
No	57.5 (289)	11.4 (33)	88.6 (256)	0.015	5.5 (16)	94.5 (273)	0.031
Yes	42.5 (214)	19.2 (41)	80.8 (173)		10.7 (23)	89.3 (191)	
High trauma exposure							
No	78.5 (395)	10.9 (43)	89.1 (352)	<0.0001	4.3 (17)	95.7 (378)	<0.0001
Yes	21.5 (108)	28.7 (31)	71.3 (77)		20.4 (22)	79.6 (86)	
High childhood adversity							
No	73.2 (368)	10.1 (37)	89.9 (331)	<0.0001	3.8 (14)	96.2 (354)	<0.0001
Yes	26.8 (135)	27.4 (37)	72.6 (98)		18.5 (25)	81.5 (110)	
High neuroticism							
No	78.3 (394)	10.4 (41)	89.6 (353)	<0.0001	6.1 (24)	93.9 (370)	0.008
Yes	21.7 (109)	30.3 (33)	69.7 (76)		13.8 (15)	86.2 (94)	
High self-esteem							
No	80.1 (403)	17.4 (70)	82.6 (333)	0.001	8.9 (36)	91.1 (367)	0.047
Yes	19.9 (100)	4.0 (4)	96.0 (96)		3.0 (3)	97.0 (97)	

Abbreviation: PTSD, posttraumatic stress disorder.

adversity exposure, neuroticism level, self-esteem, as well as PTSD status (Table 3). Next, multivariate logistic regressions were used to test for an association of genetic risk allele count with PTSD status, controlling for potential confounding (Table 4).[42,47] Gene × environmental exposure interaction effects were specifically tested for (Table 5), since these have been previously reported for some of these loci.[5,20] For these interaction assessments, lifetime trauma and childhood adversity were classified as high versus not, based on the upper quintile or quartile range for lifetime trauma and childhood adversity, respectively. Specific gene × environment interaction effects were statistically evaluated by use of a cross-product term for risk allele-count × trauma exposure (or childhood adversity) in multivariate logistic regressions that included the main effects (ie, risk allele count and the respective environmental exposure) and predicted PTSD status. As suggested, given the current study population, prescription opioid dependence, pain impairment, and the number of opioid prescriptions received were also assessed as potential confounders as a final regression step. For data analyses, Stata® version 11.2 (StataCorp LP, College Station, TX) was used.

Results

The bivariate analysis confirmed that all four target SNPs were associated with lifetime PTSD ($P < 0.05$), including *FKBP5* (rs9470080), *COMT* (rs4680), *CHRNA5* (rs16969968), and *CHRR1* (rs110402) SNPs. For each of these target SNPs, Table 1 shows the chromosomal location, minor allele frequency, functional annotation, and Hardy–Weinberg equilibrium results. All four SNPs studied met expectations for Hardy–Weinberg equilibrium ($P > 0.025$). Table 2 shows the association between lifetime and early onset PTSD and the main study variables. As can be seen, lifetime PTSD is associated with female sex, younger age, being unmarried, having lower household income, having higher trauma exposure, having higher childhood adversity, having higher neuroticism, and having lower self-esteem (all *P* values <0.05).

Table 3 shows the unadjusted risk allele count results by PTSD status and key study variables. The prevalence of lifetime PTSD in the study was 14.7% (95% CI = 11.7–18.1) and the prevalence of early onset PTSD was 7.6% (95% CI = 5.1–10.7) (Table 3). As can be seen, both lifetime ($P = 0.001$) and early onset ($P = 0.000028$) PTSD were

Table 3 Mean risk allele counts by posttraumatic stress disorder status and key study variables (mean risk allele count = 2.92, standard deviation = 1.36)

Study variables	Risk allele counts Mean (n)	t-test	Difference	P value
Lifetime PTSD*				
No	2.83 (352)	–	–	–
Yes	3.47 (59)	3.430	0.648	0.001
Early onset PTSD**				
No	2.84 (382)	–	–	–
Yes	3.93 (29)	4.239	1.09	0.000028
High trauma				
No	2.90 (324)	–	–	–
Yes	2.98 (87)	0.442	0.073	0.659
High adversity				
No	2.87 (293)	–	–	–
Yes	3.05 (118)	1.241	0.184	0.215
High neuroticism				
No	2.92 (323)	–	–	–
Yes	2.91 (88)	0.083	0.014	0.934
High self-esteem				
No	2.90 (325)	–	–	–
Yes	3.01 (86)	0.704	0.116	0.482

Notes: *Prevalence of lifetime posttraumatic stress disorder = 14.7% (95% confidence interval = 11.7–18.1); **prevalence of early onset posttraumatic stress disorder = 7.6% (95% confidence interval = 5.1–10.7).
Abbreviation: PTSD, posttraumatic stress disorder.

associated with higher risk allele counts. Trauma exposure, childhood adversity, neuroticism, and self-esteem were not associated with risk allele counts (all *P* values >0.05).

Table 4 presents the multivariate logistic regression results for lifetime and early onset PTSD. As can be seen, after controlling for demographic factors, trauma exposures and psychological traits (ie, neuroticism and self-esteem), risk allele count was significant for lifetime PTSD (odds ratio [OR] = 1.49, $P = 0.00158$). Noteworthy is that high trauma exposure ($P = 0.049$) and high neuroticism ($P = 0.0003$) were significant in this adjusted lifetime PTSD model. For early onset PTSD, the multivariate logistic regression results were highly significant (OR = 2.36, $P = 0.000093$). In contrast to lifetime PTSD, significant variables in this early onset model included high trauma exposure ($P = 0.0011$) and high childhood adversity ($P = 0.0074$). These logistic regression data suggest that those with six or more risk alleles have about nine times greater risk of lifetime PTSD ($6 \times 1.49 \approx 9$) and that those with six or more risk alleles have about 14 times greater risk of early onset PTSD ($6 \times 2.36 \approx 14$) than those with no risk alleles, respectively (Table 4).

Following assessment of main effect models, interaction effects were evaluated for allele count × high trauma and allele count × high adversity exposure for both lifetime and early onset PTSD (Table 5). These interaction effects were significant for risk allele count × high trauma exposure for both lifetime (OR = 2.05, $P = 0.026$) and early onset PTSD (OR = 3.47, $P = 0.016$) (Table 5). These interactions suggest that individuals with higher risk allele counts and higher trauma exposures had an increased risk of PTSD. However, the interaction effect for risk allele count × high childhood adversity was not significant in either the lifetime or early onset PTSD model (available upon request).

Figure 1 shows the prevalence of both lifetime and early onset PTSD by risk allele burden. As seen, those with less than two risk alleles have a low prevalence of PTSD. By comparison, those with four or more risk alleles have a prevalence of lifetime PTSD of more than 20%. These data

Table 4 Multivariate logistic regressions predicting lifetime and early onset posttraumatic stress disorder from risk allele count, controlling for key risk factors and potential confounders

Study variables	Lifetime PTSD†		Early onset PTSD†	
	OR (95% CI)	P value	OR (95% CI)	P value
Risk allele count (0–6)*	1.49 (1.16–1.90)	0.00158	2.36 (1.53–3.62)	0.000093
High trauma				
No (ref)	1.00	–	1.00	–
Yes	2.03 (1.00–4.11)	0.049	5.21 (1.93–14.09)	0.0011
High adversity				
No (ref)	1.00	–	1.00	–
Yes	1.52 (0.79–2.92)	0.209	3.90 (1.44–10.55)	0.0074
High neuroticism				
No (ref)	1.00	–	1.00	–
Yes	3.31 (1.72–6.37)	0.0003	1.74 (0.64–4.74)	0.282
High self-esteem				
No (ref)	1.00	–	1.00	–
Yes	0.23 (0.05–1.03)	0.055	0.94 (0.18–4.84)	0.939

Notes: *Risk allele count coded as a continuous variable, coded 0–6; †logistic regression model includes risk allele count, trauma exposure, childhood adversity, neuroticism, and self-esteem, plus age (in years), sex, income, and marital status as covariates.
Abbreviations: CI, confidence interval; OR, odds ratio; PTSD, posttraumatic stress disorder.

Table 5 Multivariate logistic regression interactions for lifetime and early onset posttraumatic stress disorder showing risk allele count × high trauma exposure effect

Study variables	Lifetime PTSD†		Early onset PTSD†	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Risk allele count*	1.24 (0.94–1.65)	0.131	1.51 (0.92–2.50)	0.104
High trauma**	0.19 (0.02–1.79)	0.146	0.06 (0.01–2.40)	0.132
Risk allele count × high trauma	2.05 (1.09–3.87)	0.026	3.47 (1.27–9.53)	0.016

Notes: *Risk allele count coded as a continuous variable, coded 0–6; **high trauma coded as binary variable, coded 0, 1; †logistic regression model includes risk allele count, trauma exposure, childhood adversity, neuroticism, and self-esteem, plus age (in years), sex, income, and marital status as covariates. The interaction effect (ie, risk allele count × trauma exposure) has been added to this model.
Abbreviations: CI, confidence interval; OR, odds ratio; PTSD, posttraumatic stress disorder.

suggest that those with no or few risk alleles may be resilient to PTSD, regardless of environmental exposures, since these exposures were not associated with allele burden (Table 3) or with significant confounding of the association between allele count and PTSD (Table 4). This suggests that the main exposures known to cause PTSD – psychological trauma – did not vary by risk allele count. However, those with higher risk allele counts and high trauma exposure have an increased risk of PTSD (Table 5), indicating that a gene × environmental effect is present for risk allele count by level of trauma exposure.

As suggested, since the study population included Caucasian pain patients on pain medications, pain status, drug dependence status, the number of prescription orders for pain medicines were also controlled for, but these variables had little impact on the final regression results. Based on previous research, since a dominant model for SNP marker rs9470080 (*FKBP5*) – and not the other three markers – was used, a risk allele model that included all four SNPs was also assessed as additive risk allele markers (ie, all four SNPs coded zero, one, or two). This additive model produced similar results in the logistic regressions. Finally, ancestry status was also entered into the final logistic regression models and this adjustment also made little difference.

Discussion

Examination of risk allele counts by PTSD status, as coded in the regression models, suggested that the "A" allele of rs16969968 (*CHRNA5*) and rs4680 (*COMT*), the "T" allele of rs9470080 (*FKBP5*), and the "G" allele of rs110402 (*CRNR1*) are more common among PTSD cases than non-PTSD cases. Thus, this study confirmed that SNP markers rs16969968(A), rs9470080(T), rs4680(A), and rs110402(G) were each individually associated with PTSD. When these SNP markers were combined into a cumulative risk allele model (Table 3), the bivariate *t*-test results were significant for both lifetime ($P = 0.001$) and early onset PTSD ($P = 0.000028$). In multivariate analyses controlling for potential confounders, both lifetime (OR = 1.49, $P = 0.00158$) and early onset PTSD (OR = 2.36, $P = 0.000093$) remained significant. Interactions were also detected for risk allele count × trauma exposure for both lifetime ($P = 0.026$) and early onset PTSD ($P = 0.016$).

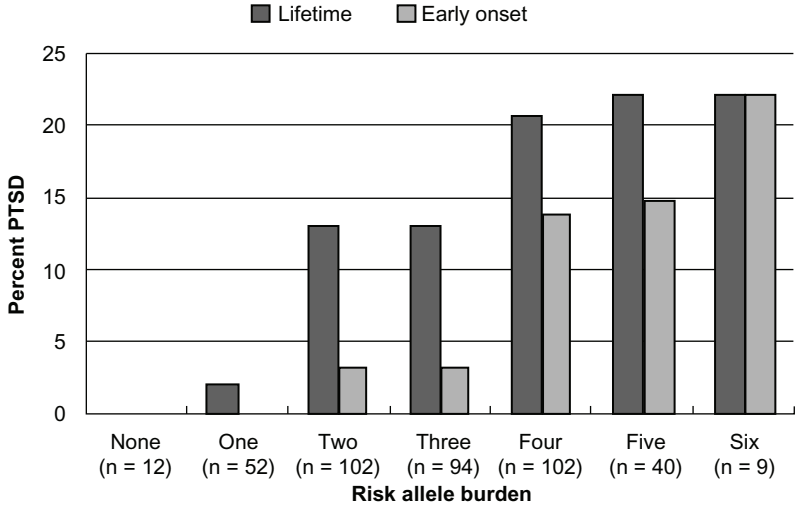

Figure 1 Prevalence of lifetime posttraumatic stress disorder and early onset posttraumatic stress disorder by risk allele burden.
Abbreviation: PTSD, posttraumatic stress disorder.

The final cumulative risk model suggests that the risk for lifetime PTSD was about nine times higher among those with six or more risk alleles ($1.49 \times 6 \approx 9$), compared to those with no risk alleles. For early onset PTSD, this risk was about 14 times higher among those with six or more risk alleles ($2.36 \times 6 \approx 14$).

FKBP5 polymorphisms are known to regulate the cortisol-binding affinity and nuclear translocation of the glucocorticoid receptor and polymorphisms at the *FKBP5* locus have been reported to interact with exposure to child adversity in predicting PTSD.[5,48] *COMT* polymorphisms have been found to affect fear extinction and are thought to play a role in the etiology of anxiety disorders.[9,19,49] The *CHRNA5* gene has been associated with smoking and nicotine dependence.[21,22] PTSD is known to be associated with cigarette smoking.[50] This locus has recently been associated with PTSD and is likely involved in mammalian fear circuitry.[9] Research suggests that the *CRHR1* gene regulates HPA axis function in conjunction with exposure to early life trauma.[20] In addition, corticotropin-releasing hormone is thought to play a role in the pathophysiology of stress-related psychiatric disorders, such as major depressive disorder and PTSD.[24] It has been suggested that corticotropin-releasing hormone contributes to alterations in memory formation in PTSD cases and that this hormone influences hippocampal regulation of the HPA axis.[24] Note that the assignment of risk alleles for the SNP variants examined in the current study agree with prior findings for the *FKBP5*, *CRHR1*, and *COMT* genetic variants.[5,51–53] A 2011 paper, based on this same cohort,[9] was the first to associate a *CHRNA5* genetic variant with PTSD, so the risk allele assignment in the current paper would be consistent with that earlier paper.

It is noteworthy that research suggests that PTSD is associated with an increased prevalence of chronic health conditions, including cardiovascular disease, rheumatoid arthritis, and other chronic diseases.[54–60] Studies suggest that PTSD may result in inflammatory injuries through overactivation of the HPA and sympathetic-adrenal-medullary stress axes, subsequently followed by hypocortisolism related to molecular downregulation of these systems.[54,61,62] Epigenetic-related phenomena are also suspected.[63,64] Consistent with these findings, current research suggests that low-grade systemic inflammatory activity is common in PTSD.[65–68] This PTSD-disease link also could be related to adverse health behaviors, such as cigarette smoking and substance misuse related to self-regulation of aversive psychological states brought on by PTSD.[69,70]

Study limitations for this research include the fact that the interview data were based on self-report, the total sample size was limited, and the study participants were more often female and drawn from a pain population. Also, multiple comparisons were not adjusted for and population stratification using genetic methods were not taken into account, although final regression results were adjusted for reported ancestry and all non-Caucasians were eliminated from the analyses to control for stratification. These factors may have biased the results and could limit study generalization. Also, the total number of PTSD cases in the study was limited (n = 59). Thus, the findings will require further replication.

The current research suggests that *FKBP5*, *COMT*, *CHRNA5*, and *CRHR1* genetic loci involving biologic pathways encompassing inflammatory mechanisms, nicotine dependence, substance misuse, sleep regulation, and fear circuitry, among others, are associated with PTSD and interact with levels of trauma exposure.[9] These genetic loci seem worthy of research related to the behavioral genetics of PTSD as well as related to chronic disease onset. For example, researchers have reported that *CHRNA* gene is associated with lung cancer.[71] This gene was also recently associated with cigarette smoking and nicotine dependence.[23] Thus, the causal pathway for lung cancer involving these loci appears to involve nicotine addiction associated with alterations in nervous system molecular biology. Without this compulsive addiction behavior, there would likely be insufficient exposure to cigarette smoke to result in lung cancer for most individuals.

Similarly, the genetic components involved in PTSD, including the *FKBP5*, *COMT*, *CHRNA5*, and *CRHR1* genes, may be associated with the pathophysiology of specific diseases following PTSD onset. Recently it was reported that *CHRNA* was not only associated with lung cancer but also with peripheral arterial disease.[22] PTSD has also been associated with metabolic syndrome.[72] Since the risk alleles studied appear to encompass multiple, interrelated disease pathways, these genetic markers may have research implications for neuropsychiatric research and treatment. The absence of PTSD among those with no or few risk alleles is intriguing and also worthy of investigation. The authors suspect that genetic resilience, in this case the absence of PTSD risk alleles, may also be associated with chronic disease resilience, but further research is required to confirm this hypothesis.

Previous presentation

Preliminary results from this study were presented at: The 31st Annual Anxiety Disorders Association of America Conference, New Orleans, LA, March 25, 2011.

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Disclosure

The authors report no conflicts of interest in this work.

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