

Original Investigation

Genome-wide Association Studies of Posttraumatic Stress Disorder in 2 Cohorts of US Army Soldiers

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IMPORTANCE Posttraumatic stress disorder (PTSD) is a prevalent, serious public health concern, particularly in the military. The identification of genetic risk factors for PTSD may provide important insights into the biological foundation of vulnerability and comorbidity.

OBJECTIVE To discover genetic loci associated with the lifetime risk for PTSD in 2 cohorts from the Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS).

DESIGN, SETTING, AND PARTICIPANTS Two coordinated genome-wide association studies of mental health in the US military contributed participants. The New Soldier Study (NSS) included 3167 unique participants with PTSD and 4607 trauma-exposed control individuals; the Pre/Post Deployment Study (PPDS) included 947 unique participants with PTSD and 4969 trauma-exposed controls. The NSS data were collected from February 1, 2011, to November 30, 2012; the PPDS data, from January 9 to April 30, 2012. The primary analysis compared lifetime *DSM-IV* PTSD cases with trauma-exposed controls without lifetime PTSD. Data were analyzed from March 18 to December 27, 2015.

MAIN OUTCOMES AND MEASURES Association analyses for PTSD used logistic regression models within each of 3 ancestral groups (European, African, and Latino American) by study, followed by meta-analysis. Heritability and genetic correlation and pleiotropy with other psychiatric and immune-related disorders were estimated.

RESULTS The NSS population was 80.7% male (6277 of 7774 participants; mean [SD] age, 20.9 [3.3] years); the PPDS population, 94.4% male (5583 of 5916 participants; mean [SD] age, 26.5 [6.0] years). A genome-wide significant locus was found in *ANKRD55* on chromosome 5 ([rs159572](#); odds ratio [OR], 1.62; 95% CI, 1.37-1.92; $P = 2.34 \times 10^{-8}$) and persisted after adjustment for cumulative trauma exposure (adjusted OR, 1.64; 95% CI, 1.39-1.95; $P = 1.18 \times 10^{-8}$) in the African American samples from the NSS. A genome-wide significant locus was also found in or near *ZNF626* on chromosome 19 ([rs11085374](#); OR, 0.77; 95% CI, 0.70-0.85; $P = 4.59 \times 10^{-8}$) in the European American samples from the NSS. Similar results were not found for either single-nucleotide polymorphism in the corresponding ancestry group from the PPDS sample, in other ancestral groups, or in transancestral meta-analyses. Single-nucleotide polymorphism-based heritability was nonsignificant, and no significant genetic correlations were observed between PTSD and 6 mental disorders or 9 immune-related disorders. Significant evidence of pleiotropy was observed between PTSD and rheumatoid arthritis and, to a lesser extent, psoriasis.

CONCLUSIONS AND RELEVANCE In the largest genome-wide association study of PTSD to date, involving a US military sample, limited evidence of association for specific loci was found. Further efforts are needed to replicate the genome-wide significant association with *ANKRD55*—associated in prior research with several autoimmune and inflammatory disorders—and to clarify the nature of the genetic overlap observed between PTSD and rheumatoid arthritis and psoriasis.

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Posttraumatic stress disorder (PTSD) is a common consequence of exposure to extreme, life-threatening events.^{1,2} Posttraumatic stress disorder is also frequently associated with other mental health problems such as major depressive disorder,³ substance abuse,⁴ and suicidality^{5,6}; with other adverse health sequelae such as obesity,⁷ cardiovascular disease,⁸⁻¹⁰ and type 2 diabetes mellitus^{11,12}; and with immune-related disorders, such as rheumatoid arthritis.¹³

Although most Americans (50%-85%) experience traumatic events during their lifetime, the lifetime prevalence of PTSD is approximately 7%,¹⁴ suggesting differential vulnerability to the disorder. Rates of trauma exposure and PTSD are higher among US military personnel and veterans,¹⁵ particularly those exposed to combat.^{16,17} Much of the research on the risk for PTSD has focused on the differential impact of type,¹⁸ frequency, duration, and consequences (eg, extent of physical injury) of trauma exposures.¹⁹ Pretrauma risk factors, including personality characteristics and early life experiences, have also been scrutinized extensively,^{18,20,21} as have post-trauma factors, such as social support.²²

Twin studies have long established that genetic variation contributes to risk for PTSD symptoms, with heritability estimates in the range of 0.28 to 0.46.²³⁻²⁶ Genetic association studies have focused on a limited set of candidate genes and have been largely underpowered to detect loci of modest effect.²⁷ More recently, several genome-wide association studies (GWAS) of PTSD have been reported in civilian^{28,29} and military or veteran³⁰⁻³³ samples, yielding several genome-wide significant associations that have yet to be widely replicated.

The present investigation uses data from the Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS),³⁴ a large, coordinated set of study components intended to improve understanding of suicide, PTSD, and related mental health risk and resilience in the US Army. Blood samples for DNA were provided by participants in the following 2 components of Army STARRS: a study of new soldiers during their first week of basic training (New Soldier Study [NSS]), and a study of 3 brigade combat teams before their deployment to Afghanistan (Pre/Post Deployment Study [PPDS]). Each of these studies has, to our knowledge, a larger PTSD-affected sample than any previously published genetic study of PTSD. We report herein results from within-ancestral-group and within-study genome-wide analyses, followed by meta-analyses across studies.

Methods

Participants

Detailed information about the design and conduct of Army STARRS is available in a separate report³⁴ and in the eMethods in the Supplement. The recruitment, consent, human participant, and data protection procedures were approved by the Uniformed Services University of the Health Sciences, Harvard University, University of Michigan, and University of California, San Diego. Written informed consent was obtained from all participants.

Key Points

Question Are genome-wide significant risk loci associated with posttraumatic stress disorder (PTSD) in a US military sample?

Finding In a genome-wide association study, 2 genome-wide significant loci were associated with PTSD in a cohort of new soldiers, but these findings were not replicated in a separate sample of soldiers. We also found significant evidence of genetic pleiotropy between PTSD and rheumatoid arthritis and psoriasis.

Meaning These findings should encourage further study of the association of the risk for immune-related disorders and PTSD.

New Soldier Study

The NSS was performed among new soldiers at the start of their basic training at 1 of 3 army installations from February 1, 2011, to November 30, 2012. Of 39 784 NSS participants who completed the computerized, self-administered questionnaire, 33 088 (83.2%) provided blood samples. Genotyping was conducted on samples from the first half of the cohort, from which 7999 samples were selected based on phenotype and case-control status (NSS1). When the remaining half of the cohort collection was completed, we selected an informative subset of 2835 samples for genotyping (NSS2) (eMethods in the Supplement).

Pre/Post Deployment Survey

The PPDS is a multiple-wave panel survey that collected baseline data (time 0) from US Army soldiers in 3 brigade combat teams from January 9 to April 30, 2012, within approximately 6 weeks of their deployment to Afghanistan. Seven thousand nine hundred twenty-seven PPDS soldiers with eligible self-administered questionnaire responses underwent genotyping for the GWAS.

Demographics and Case-Control Status

The population, sex, and age composition of our analyzed sample of cases and controls is shown in Table 1. Most of the participants were male, and we analyzed male and female participants together. A total of 3167 unique PTSD cases and 4607 trauma-exposed controls from NSS1 and NSS2 as well as 947 unique PTSD cases and 4969 trauma-exposed controls from PPDS entered the statistical analysis.

Measures

The self-administered questionnaire included a computerized version of the Composite International Diagnostic Interview Screening Scales³⁵ and a screening version of the PTSD Checklist (PCL) (range, 17-85, with higher scores indicating worse symptoms).³⁶ Trauma exposure was assessed from answers pertaining to childhood, adulthood civilian, and, for PPDS participants, military traumatic events (eMethods in the Supplement). A diagnosis of PTSD was assigned using multiple imputation methods that relied on the PCL and Composite International Diagnostic Interview Screening Scales data; our clinical reappraisal study found satisfactory concordance with independent clinical diagnoses based on blinded Struc-

Table 1. Ancestry, Sex, and Age Distributions in the Case-Control Samples^a

Characteristic	NSS1 Participants			NSS2 Participants			All NSS Participants			PPDS Participants		
	Case	Control	All	Case	Control	All	Case	Control	All	Case	Control	All
Ancestry, No. of participants												
European American	1245	2291	3536	895	618	1513	2140	2909	5049	672	3335	4007
African American	306	664	970	191	151	342	497	815	1312	97	570	667
Latino American	306	697	1003	224	186	410	530	883	1413	178	1064	1242
Male sex, No. (%)	1446 (77.8)	3052 (83.5)	4498 (81.6)	1038 (79.2)	741 (77.6)	1779 (78.5)	2484 (78.4)	3793 (82.3)	6277 (80.7)	876 (92.5)	4707 (94.7)	5583 (94.4)
Age, mean (SD), y	20.7 (3.0)	21.3 (3.5)	21.1 (3.3)	20.1 (3.1)	20.6 (3.4)	20.3 (3.2)	20.4 (3.0)	21.1 (3.5)	20.9 (3.3)	27.1 (5.9)	26.4 (6.0)	26.5 (6.0)
Total No. of participants	1857	3652	5509	1310	955	2265	3167	4607	7774	947	4969	5916

Abbreviations: NSS, New Soldier Study; PPDS, Pre/Post Deployment Study.

^a Cases with posttraumatic stress disorder (PTSD) are identified through information provided by the PTSD Checklist and Composite International Diagnostic Interview Screening Scales. Controls were exposed to at least 1

nondeployment trauma (NSS1, NSS2, and PPDS) or deployment trauma (PPDS). Cohorts are described in the Participants subsection of the Methods section.

tured Clinical Interviews for *DSM-IV* (area under the curve, 0.70-0.79; κ , 0.4-0.6).³⁷

DNA Collection and Genotyping

Whole-blood samples were shipped to Rutgers University Cell and DNA Repository, where they were frozen for later DNA extraction using standard methods. The NSS1 and PPDS samples underwent genotyping using the OmniExpress and Exome array (Illumina) with additional custom content. The NSS2 samples were genotyped on the PsychChip array (Illumina) (eMethods in the Supplement). Imputation, population assignment, and principal component analysis are described in the eMethods and eFigures 1 to 5 in the Supplement.

Statistical Analysis

Data were analyzed from March 18 to December 27, 2015. Lifetime PTSD cases and controls (ie, individuals without lifetime PTSD) reporting at least 1 traumatic event were included in the association analyses. We used PLINK (version 1.9)³⁸ to perform association tests on imputed single-nucleotide polymorphism (SNP) dosage with logistic regression adjusted for the top 10 within-population principal components. The meta-analysis of NSS1 and NSS2 is the primary analysis. The analysis of the PPDS sample is our internal attempt at replication analysis. We sought external replication with other published military-relevant data sets (described in the Results section below).

Single-nucleotide polymorphism-based heritability was estimated using the GCTA (genome-wide complex trait analysis) software tool.³⁹ We tested the genetic correlation (proportion of variance that phenotypes share owing to genetic causes, which considers only causal variants with the same directionality of effects) and pleiotropy (effect of the same gene on multiple phenotypes, which considers causal variants with the same and opposite effects) of PTSD in all European American samples with psychiatric disorders (including schizophrenia,⁴⁰ bipolar disorder,⁴¹ attention-deficit/hyperactivity disorder,⁴² major depressive disorder,⁴³ autism spectrum disorder, and a

cross-disorder phenotype⁴⁴) and with immune-related disorders (including Crohn disease,⁴⁵ ulcerative colitis,⁴⁶ multiple sclerosis,⁴⁷ psoriasis,⁴⁸ rheumatoid arthritis,⁴⁹ systemic lupus erythematosus,⁵⁰ celiac disease,⁵¹ primary biliary cirrhosis,⁵² and type 1 diabetes mellitus⁵³) using linkage disequilibrium (LD) score regression⁵⁴ and the GPA (Genetic Analysis Incorporating Pleiotropy and Annotation) R package,⁵⁵ respectively.

We followed up the significant pleiotropic outcomes with enrichment analysis using DEPICT (Data-driven Expression Prioritized Integration for Complex Traits), version 1⁵⁶ and DAVID (Database for Annotation, Visualization and Integrated Discovery), version 6.7.⁵⁷ Further details are available in the eMethods in the Supplement.

Results

Genome-wide Association Analyses

The NSS population was 80.7% male (6277 of 7774 participants; mean [SD] age, 20.9 [3.3] years); the PPDS population, 94.4% male (5583 of 5916 participants; mean [SD] age, 26.5 [6.0] years). The λ_{GC} and the QQ plot showed negligible inflation of association *P* values in the NSS (meta-analysis of NSS1 and NSS2) and PPDS samples (eFigure 6 in the Supplement). An SNP on chromosome 19 was significantly associated with PTSD in the NSS results in European American samples (**rs11085374**; odds ratio [OR], 0.77; 95% CI, 0.70-0.85; $P = 4.59 \times 10^{-8}$). A SNP on chromosome 5 was significantly associated with PTSD in the NSS results in African American samples (**rs159572**; OR, 1.62; 95% CI, 1.37-1.92; $P = 2.34 \times 10^{-8}$) and persisted after adjustment for cumulative trauma exposure (adjusted OR, 1.64; 95% CI, 1.39-1.95; $P = 1.18 \times 10^{-8}$). We did not find similar results for either SNP in the corresponding ancestry groups from the PPDS sample. The individual study and meta-analysis results are presented in Table 2, and the Manhattan plots in NSS African American and European American samples are shown in Figure 1. We further created

Table 2. Genome-wide Significant Loci in the NSS1, NSS2, and PPDS Individual Analyses and Meta-analyses From the Standard GWAS Analysis

Population	Study Sample	FRQ	INFO	P Value	OR (95% CI)
Chr 5/SNP rs159572^a					
European American	NSS1	0.75	1.00	.93	1.00 (0.89-1.12)
	NSS2	0.73	0.98	.045	0.84 (0.71-0.997)
	NSS-MA	NA	NA	.23	0.94 (0.86-1.04)
	PPDS	0.73	1.00	.36	0.94 (0.82-1.07)
	All-MA	NA	NA	.13	0.94 (0.87-1.02)
African American	NSS1	0.46	1.04	4.91×10^{-6}	1.57 (1.29-1.91)
	NSS2	0.44	0.95	1.16×10^{-3}	1.74 (1.25-2.43)
	NSS-MA ^b	NA	NA	2.34×10^{-8}	1.62 (1.37-1.92)
	PPDS	0.47	1.03	.28	1.18 (0.87-1.60)
	All-MA	NA	NA	6.13×10^{-8}	1.51 (1.30-1.75)
Latino American	NSS1	0.68	1.03	.52	1.07 (0.87-1.31)
	NSS2	0.67	0.96	.21	0.82 (0.60-1.12)
	NSS-MA	NA	NA	.88	0.99 (0.83-1.17)
	PPDS	0.69	1.09	.07	0.81 (0.65-1.02)
	All-MA	NA	NA	.23	0.92 (0.80-1.05)
Chr 19/SNP rs11085374^c					
European American	NSS1	0.32	0.98	3.67×10^{-6}	0.77 (0.69-0.86)
	NSS2	0.30	0.81	3.62×10^{-3}	0.77 (0.65-0.92)
	NSS-MA ^b	NA	NA	4.59×10^{-8}	0.77 (0.70-0.85)
	PPDS	0.31	0.97	.50	1.05 (0.91-1.21)
	All-MA	NA	NA	5.40×10^{-5}	0.86 (0.80-0.93)
African American	NSS1	0.51	0.90	.63	0.95 (0.77-1.17)
	NSS2	0.50	0.67	.62	1.10 (0.75-1.61)
	NSS-MA	NA	NA	.85	0.98 (0.82-1.18)
	PPDS	0.51	0.85	.79	0.96 (0.68-1.34)
	All-MA	NA	NA	.77	0.98 (0.83-1.15)
Latino American	NSS1	0.27	0.92	.08	1.23 (0.98-1.54)
	NSS2	0.25	0.76	.65	1.09 (0.74-1.61)
	NSS-MA	NA	NA	.08	1.19 (0.98-1.45)
	PPDS	0.26	0.93	.34	0.87 (0.66-1.16)
	All-MA	NA	NA	.38	1.08 (0.92-1.26)

Abbreviations: All-MA, meta-analysis of NSS1, NSS2, and PPDS results; Chr, chromosome; FRQ, allele frequency; GWAS, genome-wide association study; INFO, imputation quality score; NA, not applicable; NNS, New Soldier Study; NSS-MA, meta-analysis of NSS1 and NSS2 results; OR, odds ratio; PPDS, Pre/Post Deployment Study; SNP, single-nucleotide polymorphism.

^a Position 55 507 046 is in NCBI Build 37/UCSC hg19 coordinates. The nearest gene is *ANKRD55*; FRQs and ORs shown are for allele A, and allele C is the reference allele.

^b Indicates genome-wide significance ($P < 5 \times 10^{-8}$).

^c Position 20 906 220 is in NCBI Build 37/UCSC hg19 coordinates. The nearest gene is *ZNF626*; FRQs and ORs shown are for allele A, and allele T is the reference allele.

regional plots⁵⁸ for 300-kilobase regions around the 2 most significant (top-hit) SNPs (eFigure 7 in the Supplement). No significant associations were observed in the Latino NSS or PPDS samples or in any of the transethnic meta-analyses. Adjustment for lifetime trauma exposure slightly strengthened the genome-wide significant associations for the 2 lead SNPs (eTable 1 in the Supplement), whereas simultaneous adjustment for lifetime trauma exposure, sex, and age slightly attenuated the associations (eTable 2 and eFigure 8 in the Supplement).

The top SNP, *rs159572* (eFigure 7A in the Supplement), on chromosome 5 is intronic to the ankyrin repeat domain 55 gene (*ANKRD55* [NCBI Entrez Gene 79722]), and multiple other SNPs in this region were in LD with this SNP. *ANKRD55* has been associated with several autoimmune diseases, including multiple sclerosis,^{59,60} type 2 diabetes mellitus,⁶¹ celiac disease,⁶² and rheumatoid arthritis.⁶³ The top SNP, *rs11085374*, on chromosome 19 is located near the zinc finger protein 626 gene (*ZNF626* [NCBI Entrez Gene 199777]). We found minimal LD

between this SNP and surrounding SNPs (eFigure 7B in the Supplement), and no other SNPs in the region showed evidence of association.

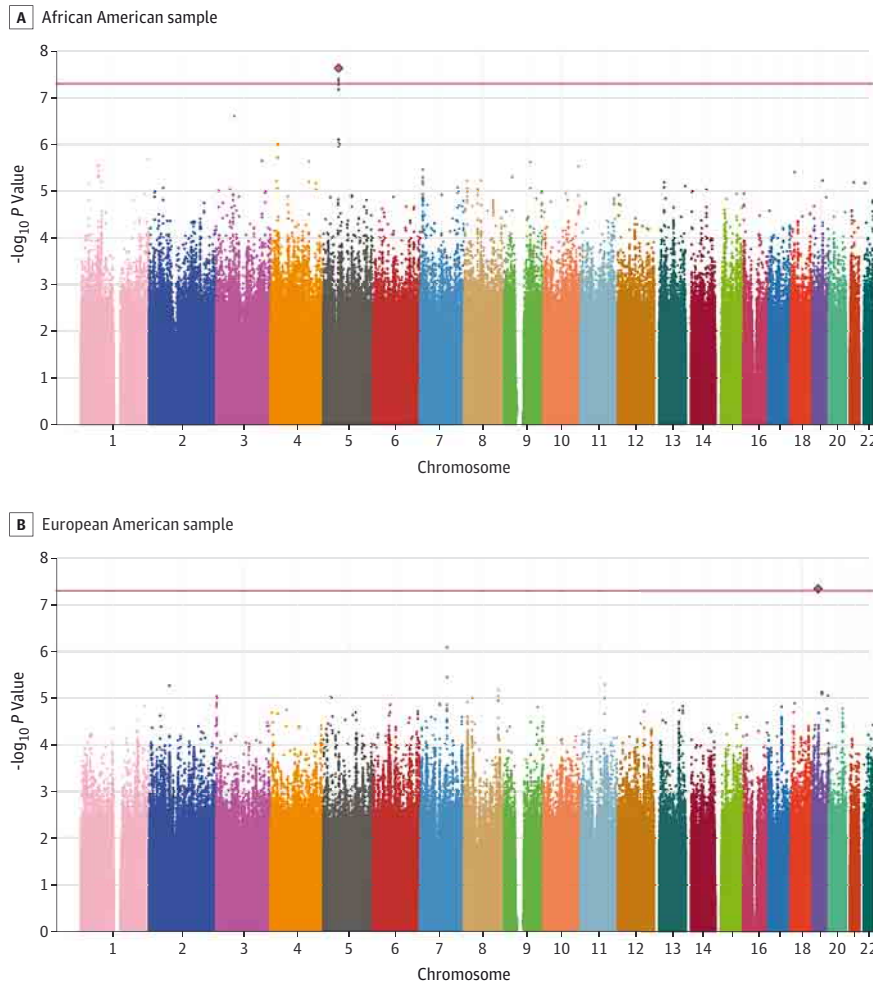
Meta-analysis With Other Military Data Sets

We performed a meta-analysis of the results for SNP *rs159572* on chromosome 5 between 3 GWAS of African American military samples, including data reported herein from Army STARRS (the current analysis), the Marine Resiliency Study,³¹ and a recently published genetic study of Iraq-Afghanistan US veterans³² (Figure 2). The results were directionally consistent in the Army STARRS NSS and PPDS samples as well as the Marine Resiliency Study but not in the PTSD veteran GWAS (OR for meta-analysis, 1.17; 95% CI, 1.05-1.31).

Alternate Phenotypic Characterization

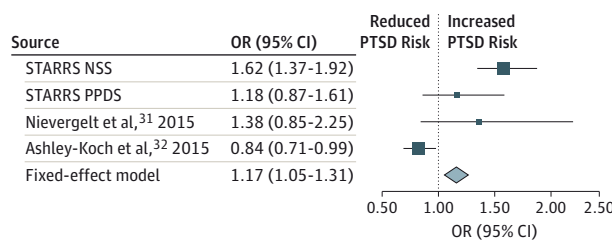
To examine the robustness of our findings, we tested for association of the top 2 SNPs at the chromosome 19 and 5 loci with an alternate phenotypic characterization of PTSD; all par-

Figure 1. Manhattan Plots of the New Soldier Study (NSS) Meta-analysis



A, The NSS meta-analysis of African American samples identifies a genome-wide significant association for posttraumatic stress disorder (PTSD) with rs159572 on chromosome 5. B, The NSS meta-analysis of European American samples identifies a genome-wide significant association for PTSD with rs11085374 on chromosome 19. Diamond indicates the single-nucleotide polymorphism with the lowest P value.

Figure 2. Meta-analysis for Single-Nucleotide Polymorphism rs159572 Between African American Samples



Different marker sizes indicate the precision of the odds ratio (OR) estimate for each study in the meta-analysis (larger means more precise). Army STARRS indicates Army Study to Assess Risk and Resilience in Servicemembers; NSS, New Soldier Study; and PPDS, Pre/Post Deployment Study.

participants in the respective ancestral groups were included. For this purpose, we chose a dimensional measure of lifetime worst PTSD severity from a 6-item version of the PCL (PCL-6) (range, 6-30, with higher scores indicating worse symptoms)⁶⁴ that has been used in other published Army STARRS research reports.⁶⁵ Among European American participants, the num-

ber of risk alleles (0-2) for rs11085374 was nominally significantly associated with lifetime PCL-6 severity in the NSS1 ($P = .007$) and NSS2 ($P < .001$) but not PPDS ($P = .82$) samples. Among African American participants, the number of risk alleles (0-2) for rs159572 was nominally significantly associated with lifetime PCL-6 severity in the NSS1 ($P = .002$) and NSS2 ($P = .03$) but not PPDS ($P = .42$) samples.

Heritability of Lifetime PTSD Phenotype

We estimated SNP-based heritability (h^2_g) using the GCTA software tool³⁹ in European American samples for the NSS1, NSS2, PPDS, and all cohorts pooled together. We found no significant h^2_g estimates in overall ($h^2_g = 0.062$ [SE, 0.049]; $P = .10$) or sex-specific analyses (eTable 3 in the Supplement).

Pleiotropy and Genetic Correlation

We tested the pleiotropy shared by PTSD and 6 psychiatric disorders and 9 immune-related disorders in the European American samples (Table 3). Significant pleiotropy was observed for PTSD and rheumatoid arthritis ($P = 3.04 \times 10^{-9}$) and psoriasis ($P = 2.41 \times 10^{-3}$). No significant pleiotropy was observed between PTSD and the other psychiatric disorders tested. No sig-

Table 3. Genetic Pleiotropy Analysis Between PTSD and Other Disorders

Disorder	P Value
Immune-related	
Crohn disease	.64
Multiple sclerosis	.96
Psoriasis	2.41×10^{-3}
Rheumatoid arthritis	3.04×10^{-9}
Systemic lupus erythematosus	.87
Type 1 diabetes mellitus	.13
Ulcerative colitis	.38
Celiac disease	.049
Primary biliary cirrhosis	.09
Psychiatric	
Schizophrenia	.12
Bipolar disorder	.78
Attention-deficit/hyperactivity disorder	.89
Major depressive disorder	.78
Autism spectrum disorder	.84
PGC cross-disorder	.29

Abbreviations: PGC, Psychiatric Genomics Consortium; PTSD, posttraumatic stress disorder.

nificant genetic correlations were found in the same data sets (eTable 4 in the Supplement).

To further characterize the observed pleiotropy, we performed an enrichment analysis of SNPs with pleiotropy posterior probability of greater than 0.5. For pleiotropy for PTSD and rheumatoid arthritis, we observed several significant enrichments for medical subject headings for tissue and cell type annotations (eTable 5 in the Supplement) and gene ontology terms (eTable 6 in the Supplement) related to several immune systems and functions. No enrichment was present for pleiotropy for PTSD and psoriasis. Finally, we estimated that the probability for an SNP associated with PTSD to be a central nervous system SNP is 2.28 (SE, 0.24) times the probability for an SNP not associated with PTSD to be a central nervous system SNP. Similarly, the enrichment ratio for immune-related expression quantitative trait loci in PTSD is 2.36 (SE, 0.27).

Discussion

This study is, to our knowledge, the largest GWAS of PTSD conducted to date. Because the study is reflective of the US Army, the composition of the samples was ethnically diverse, obligating us to conduct initial association analyses within ancestral groups and then to attempt transancestral meta-analyses. We found no genome-wide significant loci at the level of the transancestral meta-analyses but found 2 genome-wide significant loci, one each in the African American and European American samples from the NSS.

In the African American NSS sample, we observed genome-wide significant association with PTSD for SNPs on chromosome 5 in *ANKRD55*. Inclusion of data from African American participants from additional military cohorts continued to yield

a significant result of the meta-analysis at this locus, albeit attenuated compared with that of the NSS alone (Figure 2). This gene, whose function is currently unknown, has been reported to be associated with a range of autoimmune and inflammatory disorders, including multiple sclerosis,^{59,60} type 2 diabetes mellitus,⁶¹ celiac disease,⁶² and rheumatoid arthritis.⁶³

We also found evidence of significant pleiotropy between PTSD and 2 immune-related disorders, namely, rheumatoid arthritis and, to a lesser extent, psoriasis. We may have seen this genetic overlap in European American participants (whereas the *ANKRD55* association finding was in African American individuals) because human populations can present ancestry-specific risk alleles in the context of similar underlying biological mechanisms of disease predisposition.⁶⁶ These novel findings are consistent with recent reports of pleiotropy between other mental disorders, such as schizophrenia, and immune disorders, such as rheumatoid arthritis and multiple sclerosis.^{67,68} In the context of new evidence that schizophrenia involves allelic variation in the major histocompatibility complex, these observations suggest that intensive scrutiny of immune factors, and perhaps in particular of complement component 4,⁶⁹ should be the subject of further study in other mental disorders, such as PTSD.

A hypothetical immune-related or inflammatory cause of PTSD has, in fact, gained some empirical support.⁷⁰ Two recent studies have found elevated levels of the inflammatory biomarker C-reactive protein in individuals at risk for PTSD⁷¹ or with PTSD.⁷² Other studies have found abnormal cytokine regulation⁷³ or other evidence of a proinflammatory milieu⁷⁴ in PTSD. Posttraumatic stress disorder is itself highly comorbid with several of the disorders associated with *ANKRD55*, including type 2 diabetes mellitus^{12,75} and rheumatoid arthritis.^{76,77} Moreover, a recent epidemiologic study of Iraq and Afghanistan military veterans found PTSD to be associated with a broad range of autoimmune disorders, including inflammatory bowel disease, rheumatoid arthritis, and multiple sclerosis.¹³ Further research is needed to determine whether variation in *ANKRD55*—or other genes contributing to the observed pleiotropy—accounts for these associations. Why the association of *ANKRD55* with PTSD is apparently restricted to African American individuals should also be determined, although this restriction may be explained by differing LD block structure and increased minor allele frequency.

We also detected in the European American NSS samples 1 genome-wide significant SNP on chromosome 19 near *ZNF626*, a gene thought to be involved in the regulation of RNA transcription. The regional plot showed no other associated SNPs in LD with this result. This finding may represent a spurious association, but it also may reflect a lack of nearby variants in LD with the index SNP, which requires further study.

Genome-wide significant results from the NSS were not replicated in the PPDS. The PPDS sample was smaller and distinct in important ways from the NSS sample. Participants in the NSS were younger (mostly 18-20 years of age), and their trauma exposure and resultant PTSD were entirely premilitary. In contrast, PPDS participants were older, their mean non-military trauma exposure was higher than in the NSS (reflect-

ing the accrual of traumatic exposures over time), and many participants had additionally experienced deployment-related traumas. This finding of consistent results in identically ascertained samples (ie, NSS1 and NSS2) but inconsistent results in a second military sample with different rates and types of trauma exposure serves as a reminder of the challenges this field will face in working across and combining data sets that include individuals with heterogeneous trauma experiences.⁷⁸

In this regard, adjustment for trauma exposure tended to increase the statistical significance of genome-wide or near-genome-wide significant SNPs. We know, however, that certain types of trauma have higher conditional risks for PTSD than others.¹⁵ Therefore, adjustment for trauma based on tallying exposure to different trauma types—without taking into account differential conditional risks for PTSD for certain trauma types—might inadequately model these relationships. Our results underscore the need for additional work to determine the appropriate metrics for trauma exposure and the optimal functional forms for modeling these outcomes in genetic data sets. For example, when these effects should be modeled by covarying for trauma exposure or when interactions—with overall trauma severity or with specific trauma types—should be considered remains unclear. Well-powered gene- and environment-wide interaction studies may be especially illuminating given observations that the interaction of PTSD susceptibility genes with early trauma (eg, childhood maltreatment) exposure may be paramount.⁷⁹

The cross-phenotype LD score regression results failed to provide evidence of genetic correlation between PTSD and the other mental disorders examined. Previous studies have reported evidence of shared genetic risk between PTSD and bipolar disorder.^{31,80} Clinical and genetic epidemiologic studies have found considerable comorbidity—at least some of which is explained by shared genetic vulnerability^{26,81,82}—between PTSD and major depressive disorder and attention-deficit/hyperactivity disorder.^{83,84} Insufficient power is a possible explanation for our study's failure to find evidence of a shared genetic risk across these disorders. However, enrichment analysis suggested that risk variants for PTSD aggregate in many of the

same biological pathways shared with other neuropsychiatric disorders, notably those involved in immune regulation.⁸⁵

Our results should be interpreted in light of several additional limitations. First, samples sizes—especially within ancestral groups—are likely to be insufficiently powered to detect loci of modest effect. Given our total sample size, we would have 80% power to detect associations for SNPs with 20% minor allele frequency with an OR of 1.2 or higher. Second, the genetic correlation of the risk for trauma exposure with risk for PTSD is well established.^{24,86,87} Therefore, although exclusion of control individuals with no trauma exposure should have improved our power to detect PTSD risk loci given trauma exposure, it may have reduced our ability to detect loci that contribute to PTSD by increasing the risk for trauma. Third, our finding of no apparent heritability emanating from the GCTA analyses may be owing to insufficient power. Fourth, the use of the GPA package to detect pleiotropy is quite novel, and heretofore unappreciated limitations in this approach may exist.

Conclusions

We found no genome-wide significant evidence that transcended ancestry and replicated across studies. We did, however, find genome-wide significant evidence of an association of *ANKRD55*, a gene previously associated with inflammatory and immune disorders, with PTSD in African American participants. This association was observed in a pre-military PTSD sample (NSS), not replicated in a mixed pre-military and military PTSD sample (PPDS), but showed similar effect size and directionality in an independent sample of Marines with PTSD (Marine Resiliency Study).³¹ This association is small in magnitude and, even if replicated, would be of no obvious clinical utility at present. Its value may lie, however, in eventual elucidation of the nature of PTSD and its association with other illnesses. The finding of pleiotropy between PTSD and rheumatoid arthritis and psoriasis should further motivate the study of immune-related factors in PTSD, their potential contribution to comorbidity with inflammatory disorders, and a possible role for anti-inflammatory treatments in PTSD.⁸⁸

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