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Identification of Novel, Replicable Genetic Risk Loci for Suicidal Thoughts and Behaviors Among US Military Veterans

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IMPORTANCE Suicide is a leading cause of death; however, the molecular genetic basis of suicidal thoughts and behaviors (SITB) remains unknown.

OBJECTIVE To identify novel, replicable genomic risk loci for SITB.

DESIGN, SETTING, AND PARTICIPANTS This genome-wide association study included 633 778 US military veterans with and without SITB, as identified through electronic health records. GWAS was performed separately by ancestry, controlling for sex, age, and genetic substructure. Cross-ancestry risk loci were identified through meta-analysis. Study enrollment began in 2011 and is ongoing. Data were analyzed from November 2021 to August 2022.

MAIN OUTCOME AND MEASURES SITB.

RESULTS A total of 633 778 US military veterans were included in the analysis (57 152 [9%] female; 121 118 [19.1%] African ancestry, 8285 [1.3%] Asian ancestry, 452 767 [71.4%] European ancestry, and 51 608 [8.1%] Hispanic ancestry), including 121 211 individuals with SITB (19.1%). Meta-analysis identified more than 200 GWS ($P < 5 \times 10^{-8}$) cross-ancestry risk single-nucleotide variants for SITB concentrated in 7 regions on chromosomes 2, 6, 9, 11, 14, 16, and 18. Top single-nucleotide variants were largely intronic in nature; 5 were independently replicated in ISGC, including rs6557168 in *ESR1,* rs12808482 in *DRD2,* rs77641763 in *EXD3*, rs10671545 in *DCC*, and rs36006172 in *TRAF3.* Associations for *FBXL19* and *AC018880.2* were not replicated. Gene-based analyses implicated 24 additional GWS cross-ancestry risk genes, including *FURIN, TSNARE1,* and the *NCAM1-TTC12-ANKK1-DRD2* gene cluster. Cross-ancestry enrichment analyses revealed significant enrichment for expression in brain and pituitary tissue, synapse and ubiquitination processes, amphetamine addiction, parathyroid hormone synthesis, axon guidance, and dopaminergic pathways. Seven other unique European ancestry–specific GWS loci were identified, 2 of which (*POM121L2* and *METTL15*/*LINC02758*) were replicated. Two additional GWS ancestry-specific loci were identified within the African ancestry (*PET112/GATB*) and Hispanic ancestry (intergenic locus on chromosome 4) subsets, both of which were replicated. No GWS loci were identified within the Asian ancestry subset; however, significant enrichment was observed for axon guidance, cyclic adenosine monophosphate signaling, focal adhesion, glutamatergic synapse, and oxytocin signaling pathways across all ancestries. Within the European ancestry subset, genetic correlations ($r > 0.75$) were observed between the SITB phenotype and a suicide attempt-only phenotype, depression, and posttraumatic stress disorder. Additionally, polygenic risk score analyses revealed that the Million Veteran Program polygenic risk score had nominally significant main effects in 2 independent samples of veterans of European and African ancestry.

CONCLUSIONS AND RELEVANCE The findings of this analysis may advance understanding of the molecular genetic basis of SITB and provide evidence for *ESR1*, *DRD2*, *TRAF3*, and *DCC* as cross-ancestry candidate risk genes. More work is needed to replicate these findings and to determine if and how these genes might impact clinical care.

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Supplemental content

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Worldwide, suicide accounts for over 700 000 deaths annually and is the fourth leading cause of death among individuals aged 15 to 29 years of both sexes.[1] Whereas the global rate of suicide has decreased by 36% during the past 20 years,[1] the rate of suicide within the US has increased by 35%.[2] The fastest increase has occurred among US military veterans, where the rate has increased by nearly 50% since 2005.[3] Suicide attempts and suicidal ideation (ie, suicidal thoughts and behaviors [SITB]) are robust longitudinal predictors of death by suicide[4] and are also rapidly increasing among US adults[5] and military veterans.[6] While twin studies indicate that heritability for SITB is between 30% and 55%,[7] understanding of the molecular genetic basis of SITB remains limited.[8,9] Whereas recent large-scale genome-wide association studies (GWAS) of suicide attempts only have identified a few replicable, genome-wide significant (GWS) loci,[8,10,11] there has only been 1 large-scale GWAS of the broader SITB phenotype to date (N = 122 935, including 39 265 individuals with SITB).[12] While this study identified several GWS loci, none were independently replicated.[12] The objective of the present study was to address this critical gap in the literature by conducting the largest and most diverse GWAS of SITB to date within the Million Veteran Program (MVP) cohort[13,14] with the goal of identifying novel, replicable genomic risk loci for SITB.

Key Points

Question Is there a genetic basis for suicidal thoughts and behaviors (SITB)?

Findings This genome-wide association study of SITB including 633 778 US military veterans identified 7 genome-wide significant cross-ancestry risk loci through meta-analysis, and top loci were independently replicated in a large international cohort.

Meaning This study identified multiple novel cross-ancestry candidate risk genes for SITB; however, more work is needed to replicate these findings and determine whether these genes might impact clinical care.

Methods

Study Procedures and Participants

This study involved secondary analyses of the MVP cohort that were reviewed and approved by the Department of Veterans Affairs (VA) Central Institutional Review Board. MVP study procedures included providing informed consent, donating a blood sample, and agreeing to have one's genetic information linked with one's electronic health record data within the MVP biorepository.[13,14] Study participants included 633 778 US military veterans of African, Asian, European, or Hispanic ancestry (**Table 1**). Rates of SITB differed significantly by ancestry (25.0% in those of African ancestry; 21.2% in those of Asian ancestry; 16.8% in those of European ancestry; and 25.6% in those of Hispanic ancestry; $P < .00001$; eTable 1 in Supplement 1), which is consistent with prior GWAS[11] and national surveys.[5] Rates of SITB also differed by age and sex; those with SITB were younger and more likely to be female. Accordingly, age, sex, and genetic principal components were included as covariates in analyses. Study enrollment began in 2011 and is ongoing. Data were analyzed from November 2021 to August 2022.

SITB Phenotype

The codes used to phenotype individuals with SITB and control individuals are provided in eTables 2, 3, and 4 in Supplement 1. Building off of our prior GWAS of suicide attempts only,[11] 4 different data sources were used, including *International Classification of Diseases, Ninth Revision* (*ICD-9*) and *Tenth Revision* (*ICD-10*) codes from the electronic health record, suicide behavior reports from the VA's Suicide Prevention Applications Network database, mental health survey responses from the VA's Mental Health Assistant database, and cause of death codes from the National Death Index. A total of 121 211 individuals with SITB were identified, 66 344 of whom (54.7%) were identified by mental health surveys alone; 37 013 (30.5%) by more than 1 source; 16 824 (13.9%) by *ICD* codes alone; 756 (0.6%) by VA Suicide Prevention Applications Network records alone; and 274 (0.2%) by National Death Index records alone. Participants were classified as control individuals if they had no documented lifetime history of suicidal ideation, suicide attempt, or suicide death.

Genotyping and Quality Control Procedures

Samples were genotyped on a custom Axiom 1.0 array.[14] Samples of questionable identity and samples with low call rates (<98.5%) were excluded.[14] Genotyping array data were imputed with Minimac version 4[15] using the global reference panel from 1000Genomes. Markers with a minor allele frequency below 0.01 were excluded.

Replication

All GWS associations were tested for direct replication within the International Suicide Genetics Consortium (ISGC), a large, primarily civilian international consortium (N = 549 743; 29 782 individuals with suicide attempts only).[10] In cases where specific GWS single-nucleotide variants (SNVs) were not available, the best available proxy SNVs (ie, those with the highest r^2 values) were identified using LDproxy.[16,17] In all cases, the proxy SNV had an r^2 value of 0.5 or greater with the original MVP SNV. We ultimately performed 21 marker lookups in the ISGC data set to check for replication. Thus, the Bonferroni-corrected level of significance was <.002. The VA Mid-Atlantic Mental Illness Research, Education, and Clinical Center (MIRECC) cohort[18-20] was used to assess the replicability of polygenic risk scores generated from the present GWAS. This cohort was selected because it is composed entirely of US military veterans, many of whom have experienced SITB and psychiatric problems,[18-20] and because a comparable SITB phenotype could be calculated.[18-20] Individuals with SITB in MIRECC were defined as participants who self-reported a history of SITB on the Beck Scale for Suicide Ideation (BSS),[21] Beck Depression Inventory II (BDI-II),[22] or Symptom Checklist 90-R (SCL-90-R).[23] The European ancestry MIRECC subset included 331 individuals with SITB and 847 control individuals,

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Table 1. Overall Sample Characteristics (N = 633 778)

Variable	No. (%)		Standardized mean difference
	Individuals with SITB	Control individuals	
Sample size, No.	121 211	512 567	NA
Age, mean (SD), y	55.1 (13.7)	63.0 (13.8)	0.57
Age group, y			
18-29	5912 (4.9)	12 285 (2.4)	0.61
30-39	14 048 (11.6)	28 245 (5.5)	
40-49	17 002 (14.0)	40 337 (7.9)	
50-59	31 034 (25.6)	84 571 (16.5)	
60-69	39 482 (32.6)	186 217 (36.3)	
70-79	11 126 (9.2)	110 664 (21.6)	
>79	2607 (2.2)	50 248 (9.8)	
Sex			
Female	15 751 (13.0)	41 401 (8.1)	0.16
Male	105 240 (86.8)	470 548 (91.8)	
HARE-based ancestry			
African	30 283 (25.0)	90 835 (17.7)	0.24
Asian	1757 (1.4)	6528 (1.3)	
European	75 941 (62.7)	376 826 (73.5)	
Hispanic	13 230 (10.9)	38 378 (7.5)	
Military service period			
September 2001 or later	21 689 (17.9)	57 456 (11.2)	0.19
August 1990 to August 2001	40 480 (33.4)	114 166 (22.3)	0.25
May 1975 to July 1990	32 266 (26.6)	116 582 (22.7)	0.09
February 1955 to April 1975	50 725 (41.8)	290 536 (56.7)	0.30
Prior to February 1955	2913 (2.4)	50 965 (9.9)	0.32

Abbreviation: HARE, Harmonized Ancestry and Race/Ethnicity approach; SITB, suicidal thoughts and behaviors.

whereas the African ancestry MIRECC subset included 334 individuals with SITB and 911 control individuals. GWAS effect sizes for the MVP European ancestry and African ancestry subsets were used to generate polygenic risk scores to test for associations with SITB in the comparable MIRECC ancestral groups using default parameters for linkage disequilibrium clumping in PRSice[24] to reduce redundant SNPs in high linkage disequilibrium and testing 1001 thresholds ranging from $P = .0001$ to 1 in increments of 0.001.[25] Due to testing 1001 thresholds, the multiple testing correction for this analysis was 0.05/1001 or 5×10^{-5}.

SNV Heritability, GWAS Annotation, and GWAS Enrichment Tests

Cross-trait linkage disequilibrium score regression[26,27] was used to estimate SNV heritability for SITB and the genetic correlation between SITB in the MVP European ancestry subset and the attempts-only phenotype in ISGC.[10] We also examined genetic correlations between SITB in the MVP European ancestry subset and several other phenotypes of interest, including bipolar disorder,[28] schizophrenia,[29] major depression,[30] and posttraumatic stress disorder.[31] Functional Mapping and Annotation of Genome-Wide Association Studies (FUMA)[32] was used to perform annotation and enrichment tests of cross-ancestry and ancestry-specific GWAS results, including enrichment of previously reported GWAS catalog[33] associations. Gene-based and gene-set analyses were evaluated by Multi-marker Analysis of GenoMic Annotation (MAGMA)[34] as implemented in FUMA. Gene-based tests were performed for 19 216 genes (Bonferroni-corrected P value threshold = 2.602×10^{-6}). In addition, 10 678 gene sets (curated gene sets: 4761; GO terms: 5917) from Molecular Signatures Database (MsigDB) version 6.2 were evaluated for association with SITB (Bonferroni-corrected P value threshold = 4.7×10^{-6}). Tissue-set enrichment analyses of association signal in genes expressed in 30 general tissue types from GTEx version 7 (Bonferroni-corrected P value threshold = 1.7×10^{-3}) were evaluated with MAGMA.

Finally, we used Web-Gestalt[35] to conduct overrepresentation analysis for cross-ancestry and ancestry-specific findings with the following SNV designations: exonic, intronic, ncRNA exonic, and ncRNA intronic. A single marker with the smallest P value (<.05) was chosen to represent each gene from among the 10% most significant SNVs.[11] The Kyoto Encyclopedia of Genes and Genomes (KEGG) database was used for defining pathways. Overrepresentation analysis uses a hypergeometric or Fisher exact test to compare the gene set of interest to the reference gene set for the proportion of genes in the category and then applies the Benjamini-Hochberg correction to control the false discovery rate (FDR).

Statistical Analyses

The Harmonized Ancestry and Race/Ethnicity approach[36] was used to initially assign participants to mutually exclusive ancestral groups. Principal component analysis of nonimputed genotypes was then conducted using PLINK2[37] within each of

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the 4 largest Harmonized Ancestry and Race/Ethnicity-based ancestral groups (ie, those of African ancestry, Asian ancestry, European ancestry, and Hispanic ancestry). To further control for population substructure within each ancestral group, we included 13 PCs for those of African ancestry ($\lambda = 1.05$), 8 for those of Asian ancestry ($\lambda = 0.97$), 20 for those of European ancestry ($\lambda = 1.26$; intercept, 1.04 after PC adjustment), and 11 for Hispanic ancestry ($\lambda = 1.07$). Ancestry-specific GWAS was performed with PLINK2,[37] including covariates for age, sex, and genetic PCs. Meta-analysis was performed across ancestries with METAL.[38] To assess the consistency of effects across ancestries, the QE test of heterogeneity of effect sizes[39] was computed. Manhattan and LocusZoom plots[40] were used to visualize findings.

Results

Cross-Ancestry Results

Meta-analysis identified more than 200 GWS ($P < 5 \times 10^{-8}$) cross-ancestry risk SNVs for SITB concentrated in 7 regions on chromosomes 2, 6, 9, 11, 14, 16, and 18 (**Table 2** and **Figure 1**). Top SNVs were largely intronic in nature; 5 were independently replicated in ISGC, including rs6557168 in *ESR1,* rs12808482 in *DRD2,* rs77641763 in *EXD3*, rs10671545 in *DCC*, and rs36006172 in *TRAF3*. Associations for *FBXL19* and *AC018880.2* were not replicated. LocusZoom plots for replicated GWS associations are provided in **Figure 2** and eFigure 1 in Supplement 1. Gene-based tests identified 24 additional genes not identified in the meta-analysis, several of which have previously been found to be associated with psychiatric conditions (eg, *ANKK1, TTC12, NCAM1, FURIN, TSNARE1*),[41] and the cross-ancestry genes were significantly enriched for expression in brain and pituitary tissue (**Figure 3**). Gene-set analysis revealed significant enrichment for 8 GO terms, all of which were related to synapse and ubiquitination structure and processes (eTable 5 in Supplement 1). We also observed significant enrichment for 8 GWAS catalog terms, including schizophrenia, autism spectrum disorder or schizophrenia, and bipolar disorder (eTable 6 in Supplement 1). Overrepresentation analysis identified 13 FDR-significant cross-ancestry KEGG pathways, including amphetamine addiction, axon guidance, and dopaminergic synapse (eTable 7 in Supplement 1).

Ancestry-Specific Results

Within the European ancestry subset, we identified 12 GWS loci associated with SITB (Table 2), including 7 not identified in the meta-analysis: *RNU6-463P*, *POM121L2*, *MAD1L1*, *AMN*, *METTL15/LINC02758*, *LINC00533*, and *MKNK1*. Two of these loci were subsequently replicated in ISGC: rs13211166 in *POM121L2* and rs7127383, located near *METTL15* and *LINC02758*. Gene-based tests identified 4 additional European ancestry-specific genes not identified through meta-analysis: *PHKG2*, *MACROD1*, *FES*, and *PPP6C*, and European ancestry-specific risk genes were enriched for expression in brain tissue (Figure 3) and for many GWAS catalog terms, including autism spectrum disorder or schizophrenia, neuroticism, and feeling guilty (eTable 8 in Supplement 1). FUMA-based gene-set enrichment analyses revealed significant enrichment for 45 GO terms, many of which were related to nucleosome and chromatin organization (eTable 9 in Supplement 1), whereas overrepresentation analysis identified 20 FDR-significant pathways, including axon guidance, glutamatergic synapse, oxytocin signaling, morphine addiction, long-term potentiation, and long-term depression (eTable 7 in Supplement 1).

A GWS African ancestry–specific locus was identified on chromosome 4 in *PET112/GATB* and subsequently replicated in ISGC, as was a GWS Hispanic ancestry–specific intergenic locus identified on chromosome 4 (Figure 1; eFigure 1 in Supplement 1). No GWS loci were identified within the Asian ancestry subset, and FUMA did not detect any GWS genes within the African ancestry, Asian ancestry, and Hispanic ancestry subsets. Thus, no additional analyses were conducted in FUMA for these subsets; however, overrepresentation analysis identified multiple FDR-significant KEGG pathways within the African ancestry, Asian ancestry, and Hispanic ancestry subsets (eFigure 2 in Supplement 1). Five KEGG pathways demonstrated enrichment across all 5 analyses, including axon guidance, cyclic adenosine monophosphate signaling, focal adhesion, glutamatergic synapse, and oxytocin signaling (eTable 7 in Supplement 1); however, axon guidance was the only pathway that was FDR significant across all 5 analyses.

Genetic Heritability and Genetic Correlations

Within the European ancestry subset, we estimated SNV heritability for SITB to be 0.0158 (SE = 0.0009) and observed a genetic correlation between SITB and the attempts-only phenotypes from ISGC ($r = 0.81$; $P = 1.64 \times 10^{-74}$) and MVP release 3[11] ($r = 0.97$; $P = 2.74 \times 10^{-63}$). We also identified genetic correlations with depression ($r = 0.78$; $P = 6.69 \times 10^{-107}$) and posttraumatic stress disorder ($r = 0.76$; $P = 1.13 \times 10^{-110}$), whereas associations with schizophrenia ($r = 0.36$; $P = 3.54 \times 10^{-29}$) and bipolar disorder ($r = 0.29$; $P = 2.49 \times 10^{-13}$) were substantially smaller.

Polygenic Risk Score Analyses

Ancestry-specific MVP GWAS results were used to generate polygenic risk scores to predict SITB in MIRECC. Among veterans of European ancestry, the best-performing polygenic risk score ($P < .70$) was nominally significant ($P = .01$), but not FDR significant and explained slightly less than 1% of SITB variability (eFigure 3A in Supplement 1). Among veterans of African ancestry, the best-performing polygenic risk score was $P < .07$ (nominal $P = .001$) and accounted for nearly 1.5% of SITB variability (eFigure 3B in Supplement 1).

Discussion

This analysis, which represents what is to our knowledge the largest and most diverse GWAS of SITB to date, identified 7 GWS cross-ancestry risk loci, 5 of which were independently replicated. Our top replicated cross-ancestry risk locus was rs6557168, an intronic SNV in *ESR1* that encodes an estrogen

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Table 2. Genome-Wide Significant[a] Loci for Suicidal Thoughts and Behaviors

SNV	Chromosome position	Alleles (effective/ alternate)	Effective allele frequency	*P* value	Direction of effects	Odds ratio (SE)	Annotation	*P* value for replication
Meta-analysis cross-ancestry results[b]								
rs6557168	6:152201201	T/C	0.55	3.38×10^{-12}	− − − −	NA	*ESR1*	7.74×10^{-03}
rs35675346	16:30936081	A/G	0.25	3.18×10^{-10}	− + − −	NA	*FBXL19*	2.51×10^{-01}
rs12808482	11:113294998	A/T	0.50	3.45×10^{-10}	− + − −	NA	*DRD2*	4.08×10^{-05c}
rs77641763	9:140265782	T/C	0.09	1.86×10^{-09}	+ − + +	NA	*EXD3*	2.55×10^{-03}
rs36006172	14:103371146	CAA/C	0.75	8.78×10^{-09}	− − − −	NA	*TRAF3*	8.60×10^{-03} (rs72704737)[g]
rs10671545	18:50877813	G/GTATA	0.66	1.43×10^{-08}	− − −	NA	*DCC*	3.27×10^{-06b} (rs11663824)
rs142785607	2:104267493	T/G	0.51	1.79×10^{-08}	+ + +	NA	*AC018880.2*	1.324×10^{-01} (rs67716713)[g]
European ancestry results[d]								
rs73581580	9:140251458	A/G	0.12	3.56×10^{-11}	NA	1.06 (0.0)	*EXD3*	1.23×10^{-03b}
rs3757323	6:152202007	T/C	0.44	4.51×10^{-10}	NA	1.03 (0.01)	*ESR1*	3.38×10^{-03}
rs7098086	10:107372392	A/G	0.19	8.29×10^{-10}	NA	0.95 (0.01)	*RNU6-463P*	2.223×10^{-01}
rs13211166	6:27265940	A/T	0.18	1.97×10^{-09}	NA	0.94 (0.01)	*POM121L2*	4.84×10^{-07b}
rs11763750	7:2080114	A/G	0.17	5.64×10^{-09}	NA	0.96 (0.01)	*MAD1L1*	3.434×10^{-01}
rs1190230	14:103392734	C/T	0.26	9.80×10^{-09}	NA	1.04 (0.01)	*AMN*	3.325×10^{-01}
rs7127383	11:28591587	C/T	0.48	1.21×10^{-08}	NA	0.97 (0.01)	*METTL15, LINC02758*	2.86×10^{-04b}
rs2514218	11:113392994	T/C	0.30	1.58×10^{-08}	NA	0.97 (0.01)	*DRD2*	1.04×10^{-03b}
rs9468413	6:28689672	C/A	0.21	1.60×10^{-08}	NA	0.94 (0.01)	*LINC00533*	.19 (rs15012041)[g]
rs75421528	1:47069504	A/C	0.01	1.88×10^{-08}	NA	1.17 (0.03)	*MKNK1*	4.30×10^{-01} (rs3480655)[g]
rs113696815	2:104299863	A/ATTGTT	0.45	3.34×10^{-08}	NA	1.04 (0.01)	*AC018880.2*	.12 (rs7569356)[g]
rs7200879	16:30947572	G/A	0.22	3.73×10^{-08}	NA	0.96 (0.01)	*FBXL19*	2.5×10^{-01}
African ancestry results[e]								
rs182921948	4:152619133	G/A	0.28	9.20×10^{-09}	NA	1.09 (0.02)	*PET112, GATB*	9.58×10^{-03} (rs4696289)[g]
Hispanic ancestry results[f]								
rs116015815	4:136052705	T/C	0.01	3.47×10^{-09}	NA	1.58 (0.08)	Intergenic variant	.01 (rs76431246)[g]

[a] Defined as $P < 5 \times 10^{-8}$.

[b] N = 633 778, including 121 211 individuals with suicidal thoughts and behaviors and 512 567 control individuals. Nonsignificant directions of effects in the meta-analysis were (African ancestry, Asian ancestry, European ancestry, Hispanic ancestry): rs6557168 (− − − −), rs35675346 (− + − −), rs12808482 (− + − −), rs77641763 (+ − + +), rs559 rs36006172 (− − − −), rs10671545(− − − −), rs142785607(+ + + +).

[c] Result met Bonferroni multiple testing correction of .002.

[d] N = 452 767, including 75 941 individuals with suicidal thoughts and behaviors and 376 826 control individuals.

[e] N = 121 118, including 30 283 individuals with suicidal thoughts and behaviors and 90 835 control individuals.

[f] N = 51 608, including 13 230 individuals with suicidal thoughts and behaviors and 38 378 control individuals.

[g] Original marker was not available in the replication data set and was replaced as indicated.

receptor. An integrated multiomics analysis[42] recently identified *ESR1* as a causal genetic driver gene for the development of posttraumatic stress disorder and depression, both of which are risk factors for SITB among veterans.[19,20,43] Estrogen has also been hypothesized to potentially help to explain sex differences in depression rates,[44] and loss of ESR1 has been found to produce effects on brain tissue in men.[45] Notably, rs6557168 was also recently identified as a likely causal variant for the *ESR1* locus in relation to anxiety.[46]

Our second strongest replicated cross-ancestry locus was rs12808482, an intronic variant in *DRD2*, which encodes the D2 dopamine receptor subtype. DRD2 is highly expressed in brain tissue[47] and has been associated with numerous psychiatric phenotypes,[33] including suicide attempts.[11,48] Notably, our prior study of suicide attempts only also identified a strong cross-ancestry signal at *DRD2* (odds ratio = 0.93; SE = 0.01; $P = 1.77 \times 10^{-7}$).[11] While *DRD2* has been associated with many other risk factors for SITB, such as schizophrenia, mood

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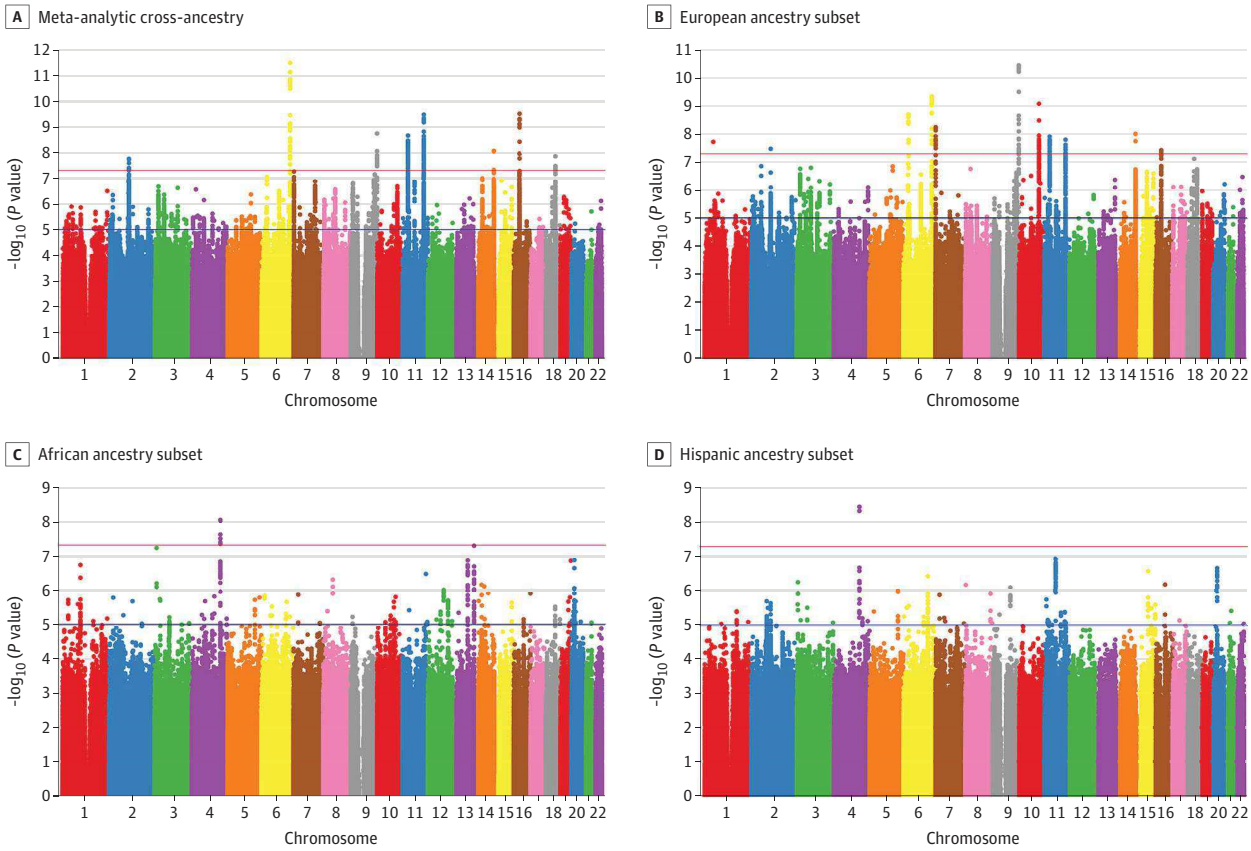
Figure 1. Manhattan Plots Summarizing Results From the Cross-Ancestry and Ancestry-Specific Genome-Wide Association Studies



disorders, attention-deficit/hyperactivity disorder, risky behaviors, alcohol use, and alcohol use disorder,[33] it is plausible that DRD2 contributes to suicide risk directly, as it is highly expressed in the prefrontal cortex, nucleus accumbens, substantia nigra, and hippocampus. Moreover, recent work has demonstrated that DRD2-expressing neurons that project from the central amygdala to the bed nucleus of the stria terminalis regulate impulsive behavior,[49] another established risk factor for SITB.[50]

A cross-ancestry GWS association was also observed for rs10671545, an intronic insertion/deletion variant in *DCC*, which encodes a netrin 1 receptor. *DCC* is also an outstanding candidate gene, as it is expressed in brain tissue across the lifespan; is involved in synaptic plasticity, axon guidance, circadian entrainment, and long-term potentiation; and has been associated with multiple psychiatric phenotypes.[33,51] Additionally, Strawbridge et al[12] found an association between *DCC* and SITB using a gene-based approach. *DCC* is also crucial for the development of appropriate medial prefrontal cortex functioning and is elevated in the prefrontal cortex of individuals who die by suicide.[52]

Cross-ancestry GWS associations were also found for *EXD3,* a 3′ to 5′ exonuclease involved in nucleic acid binding, and *TRAF3,* which regulates type-1 interferon production. While the functional significance of *EXD3* for SITB is unclear presently, it has been associated with several other relevant phenotypes, including insomnia and depression.[33] The association between *TRAF3* and SITB is more intriguing, as large portions of patients receiving interferon therapy develop major depressive disorder and experience suicidal ideation.[53] *TRAF3* is also associated with major depressive disorder, antisocial behavior, substance use, and attention-deficit/hyperactivity disorder.[33] In addition, lithium—a gold standard treatment for bipolar disorder shown to reduce suicide risk[54]—modulates the expression of *TRAF3* and several other inflammatory genes.[9]

Taken together, the present findings, in conjunction with prior work in this area,[10-12,33,41,42,44-54] provide compelling evidence that *ESR1, DRD2, TRAF3,* and *DCC* are highly plausible cross-ancestry candidate risk genes for SITB that should be targeted in future investigations of the biology of suicide. Gene-based tests identified 24 more unique cross-ancestry risk genes, including *FURIN*, *TSNARE1*, and the *NCAM1-TTC12-ANKK1-DRD2* gene cluster, which also represent promising avenues for future inquiry,[11,33,41] as do the numerous FDR-significant cross-ancestry pathways identified through enrichment analyses, including dopaminergic, cyclic adenosine monophosphate, and mitogen-activated protein kinase signaling, axon guidance, and parathyroid hormone synthesis and action.

We also identified 9 ancestry-specific GWS risk loci that were not observed in the meta-analysis, 4 of which were

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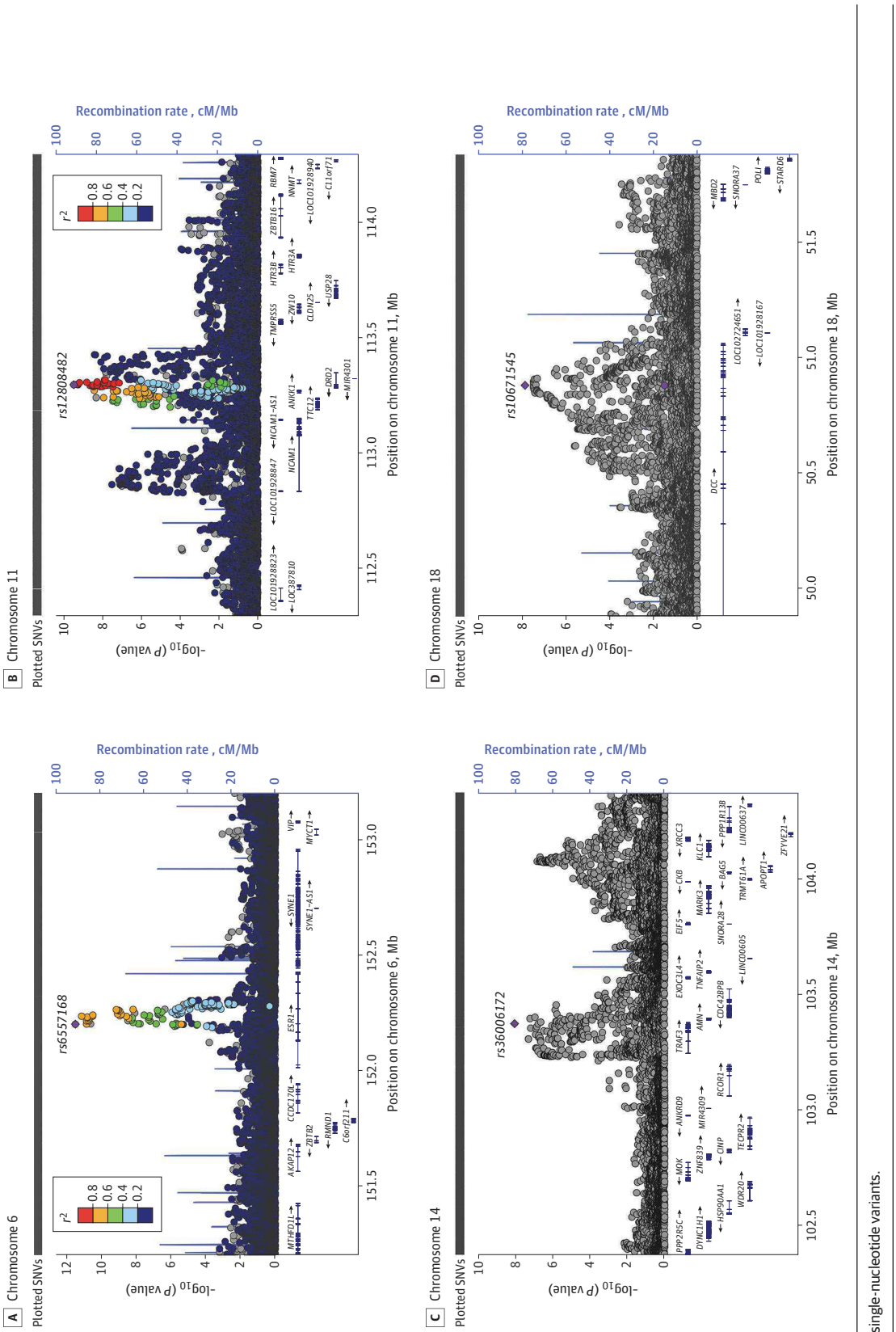

Figure 2. Cross-Ancestry Locus Zoom Plots for Top Replicated Genome-Wide Significant Loci on Chromosomes 6, 11, 14, and 18

SNVs indicates single-nucleotide variants.

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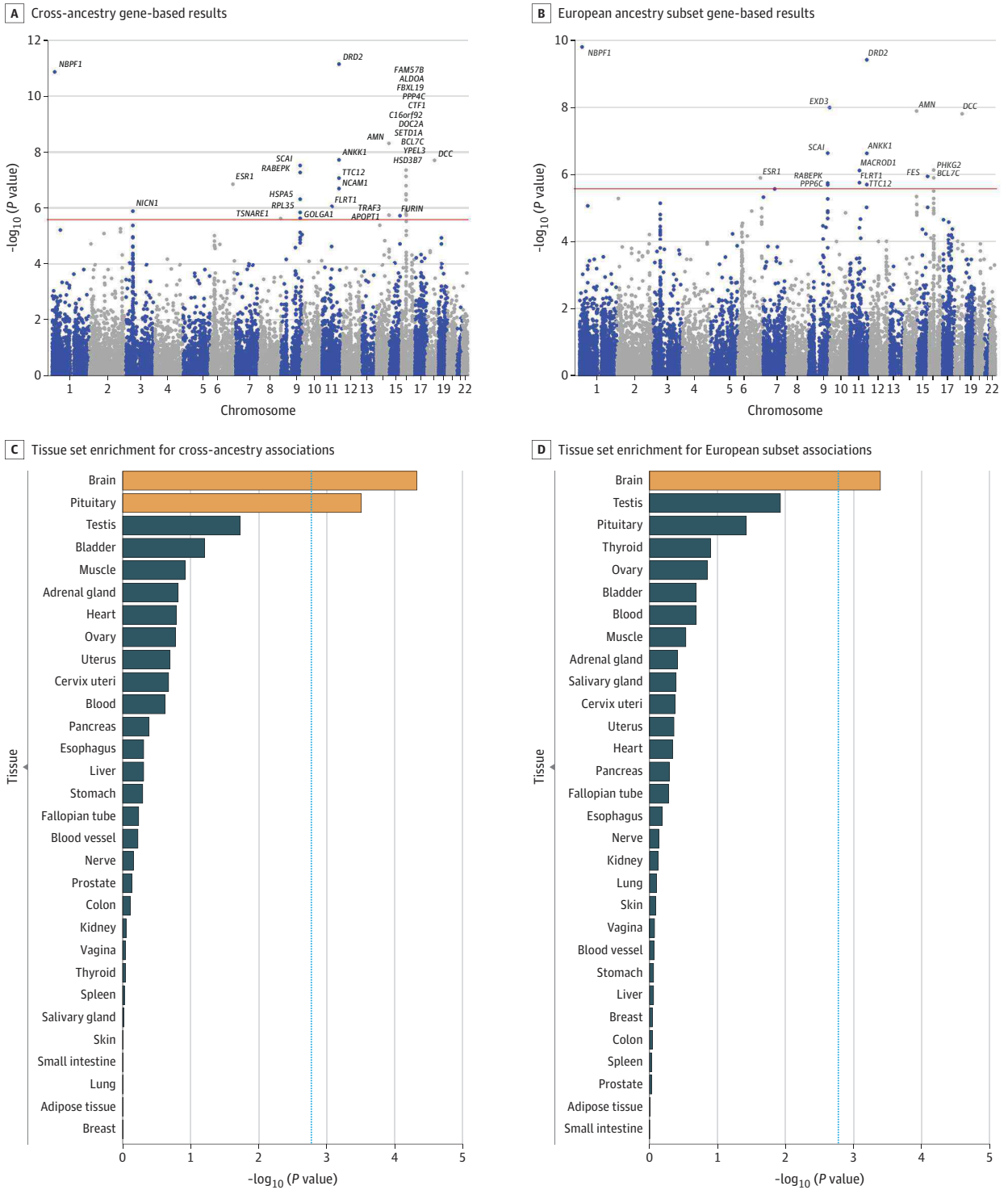
Figure 3. Functional Mapping and Annotation Results for Cross-Ancestry and European Subset Genome-Wide Association Study Results



independently replicated. The first of these loci was European ancestry specific and located near *POM121L2* on chromosome 6. Relatively little is known about the function of *POM121L2* other than it encodes a structural constituent of the nuclear pore; however, *POM121L2* has been previously associated with neuroticism, depressive symptoms, risk taking, and schizophrenia.[33] It is also located within the major histocompatibility complex, a highly complex region recently identified by Mullins et al[10] in relation to suicide attempts only within the ISGC. A second European ancestry-specific association was identified near *METTL15* and *LINC02758*, both of which have been previously associated with attention-deficit/

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hyperactivity disorder, substance misuse, antisocial behavior, risk taking, and depression.[33] Genes from the European ancestry subset were also enriched for expression in brain tissue and for many pathways of interest, such as glutamatergic and oxytocin signaling, axon guidance, thyroid and parathyroid hormone synthesis, long-term potentiation, and long-term depression.

We identified 2 additional GWS ancestry-specific loci within the African ancestry and Hispanic ancestry subsets, both of which were replicated. While identification of these novel, replicable ancestry-specific loci for participants of African and Hispanic ancestry is highly encouraging, the fact that we identified far fewer GWS loci among participants of African, Asian, and Hispanic ancestry relative to participants of European ancestry is perhaps the most important point. As expected, we observed a robust positive association between number of cases and number of ancestry-specific GWS loci identified (r^2 = 0.99) (eFigure 4 in Supplement 1), highlighting the critical importance of enrolling more non-European participants in future GWAS of SITB.

Furthermore, it is noteworthy that none of the GWS loci identified in the present analysis were identified in our prior study of suicide attempts only,[11] which only identified 2 cross-ancestry GWS loci, neither of which was replicated. While it is encouraging that our prior study did observe a strong cross-ancestry signal for *DRD2* that was nearly GWS ($P < 10^{-7}$),[11] the substantial increase in replicable, GWS loci identified in the present work highlights the potential utility of broader phenotypes, like SITB, which can substantially increase the number of cases available for analysis and subsequently enhance studies statistical power to discover novel risk loci.

Limitations

The present findings should be interpreted within the context of several limitations. First, our exclusive reliance on electronic health record sources to phenotype SITB likely increased our risk for type II errors. A second limitation concerns the nature of the replication samples used. While it is encouraging that we were able to replicate more than half (ie, 9 of 16) of the unique GWS associations observed in the present study, additional replication work is still needed that uses the broader SITB phenotype (as opposed to the suicide attempts-only phenotype). Third, given that our sample was composed entirely of military veterans and was only 9% female, it remains unclear the degree to which our findings might generalize to the general population. Fourth, while the present work represents what is to our knowledge the most diverse GWAS of SITB to date, individuals of non-European ancestry were still greatly underrepresented, limiting our ability to identify ancestry-specific GWS loci among the African ancestry, Asian ancestry, and Hispanic ancestry subsets (eFigure 4 in Supplement 1).

Conclusions

We report here findings from what is to our knowledge the largest and most diverse GWAS of SITB to date, which identified 16 GWS risk loci, 9 of which were independently replicated. Among the top replicated loci, *ESR1, DRD2, TRAF3,* and *DCC* appear to be particularly promising cross-ancestry candidate risk genes for SITB that should be targeted in future investigations of the biology of suicide; however, additional work is still needed to determine if and how these genes might impact clinical care.

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