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A Genome-Wide Association Study of Suicide Attempts in the Million Veterans Program Identifies Evidence of Pan-Ancestry and Ancestry-Specific Risk Loci

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Author Contributions

This study was conceived and designed by NAK, AAK, ERH, MAH, and JCB. Statistical analyses were conducted by XJQ, JHL, and MEG, and were supervised by AAK and ERH. NAK, AAK, ERH, MAH, JCB, RKM, DAJ, JAT, HC, ARD, NM, and DMM reviewed and interpreted statistical findings. NAK, AAK, MFD, LPH, JEH, HC, ARD, JK, NM, DMM, PDH, BHM, DWO, ERH, MAH, and JCB were involved in data acquisition and data preparation. NAK, AAK, XJQ, JHL, and MEG wrote the initial draft of the manuscript. All authors reviewed the results and approved the final version of the manuscript.

Conflicts of Interest

The authors have no conflicts of interest to declare at this time.

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Abstract

To identify pan-ancestry and ancestry-specific loci associated with attempting suicide among veterans, we conducted a genome-wide association study (GWAS) of suicide attempts within a large, multi-ancestry cohort of U.S. veterans enrolled in the Million Veterans Program (MVP). Cases were defined as veterans with a documented history of suicide attempts in the electronic health record (EHR; *N*=14,089) and controls were defined as veterans with no documented history of suicidal thoughts or behaviors in the EHR (*N*=395,064). GWAS was performed separately in each ancestry group, controlling for sex, age and genetic substructure. Pan-ancestry risk loci were identified through meta-analysis and included two genome-wide significant loci

on chromosomes 20 (p=3.64×10^{-9}) and 1 (p=3.69×10^{-8}). A strong pan-ancestry signal at the *Dopamine Receptor D2* locus (p=1.77×10^{-7}) was also identified and subsequently replicated in a large, independent international civilian cohort (p=7.97×10^{-4}). Additionally, ancestry-specific genome-wide significant loci were also detected in African-Americans, European-Americans, Asian-Americans, and Hispanic-Americans. Pathway analyses suggested overrepresentation of many biological pathways with high clinical significance, including oxytocin signaling, glutamatergic synapse, cortisol synthesis and secretion, dopaminergic synapse, and circadian rhythm. These findings confirm that the genetic architecture underlying suicide attempt risk is complex and includes both pan-ancestry and ancestry-specific risk loci. Moreover, pathway analyses suggested many commonly impacted biological pathways that could inform development of improved therapeutics for suicide prevention.

INTRODUCTION

Death by suicide accounts for nearly 800,000 deaths worldwide each year, making it the second leading cause of death among young adults.[1] In the U.S., the age- and sex-adjusted rate of death by suicide has increased by 33% since 1999.[2] Among U.S. military veterans, the rate has increased even faster, jumping by nearly 50% since 2005.[3] While heritability estimates range from 30–55%,[4] the genetic basis of suicide and suicide attempts remains largely unknown. There have been more than 100 candidate-gene studies of suicide and suicidal behavior to date[5]—yet few, if any, candidate single nucleotide polymorphisms (SNPs) have been reliably associated with suicidal behavior.[5] For this reason, there has been growing interest in using genome-wide association studies (GWAS) to identify novel genetic risk factors associated with suicide and suicide attempts. Multiple GWAS of suicide attempts have now been conducted,[5–8] and several have identified genome-wide significant risk loci; however, only two associations have been independently replicated.[6,8]

A GWAS of suicide attempts among active-duty military personnel identified multiple genome-wide significant loci near *Melanocortin 2 Receptor Accessory Protein 2 (MRAP2),* which was subsequently replicated in an independent sample of U.S. veterans.[6–7] More recently, Mullins and colleagues[8] reported genome-wide significant associations between suicide attempts and the major histocompatibility complex and an intergenic locus on chromosome 7 within the International Suicide Genetics Consortium (ISGC; N=549,743) cohort. Notably, the Million Veteran Program (MVP) cohort[9–10] was used to replicate the association between the chromosome 7 index SNP and suicide attempts (p=3.27×10^{-3}); however, a GWAS of suicide attempts has not yet been conducted within the MVP cohort. Accordingly, the objective of the present research was to conduct a GWAS within the MVP cohort to identify pan-ancestry and ancestry-specific loci associated with risk for attempting suicide among U.S. military veterans.

SUBJECTS AND METHODS

Study Participants

The MVP study, which currently includes over 800,000 veteran participants from across the U.S., is one of the largest and most diverse biorepositories in the world.[9–10] Moreover,

electronic health records (EHR) make this cohort a powerful resource for investigating the genetic basis of a wide range of phenotypes. Recruitment and study procedures for MVP have been described in detail previously and entailed donating a blood sample, consenting to genetic analyses, linking one's genetic information with the VA's EHR, and completion of two optional surveys. [9–10] The present study, which involved secondary analysis of existing data collected through the primary MVP study, [9–10] was reviewed and approved by the Department of Veterans Affairs (VA) Central Institutional Review Board (IRB). All study participants provided informed consent as part of the larger MVP study.[9–10]

Development of the Suicide Attempt Phenotype

Three VA EHR sources were utilized to create a suicide attempt phenotype in the present study, including: (a) International Classification of Diseases (ICD9 and ICD10) codes for intentional self-harm; (b) suicide behavior reports from the VA's Suicide Prevention Applications Network (SPAN) database;[11] and (c) mental health survey responses from the VA's Mental Health Assistant database indicating a history of attempting suicide (see Supplementary Phenotyping Methods and Supplementary Tables 1a–d for details). Veteran participants were classified as suicide attempt cases if their EHR contained one or more: ICD-9/ICD-10 self-injury codes; SPAN reports of suicide attempts; or mental health survey responses in which participants endorsed a history of attempting suicide. As can be seen Supplementary Table 1d, 60.3% of suicide attempt cases were identified by more than one source, 30.9% were identified by diagnostic codes only, 5.6% were identified by SPAN records only, and 3.2% were identified by mental health surveys only. Veteran participants were classified as controls if they had no documented lifetime history of suicide attempts or suicidal ideation based on qualifying ICD codes, suicide behavior reports, or mental health survey responses. Note that veterans who had a history of suicidal ideation, but not suicide attempts (N=36,732), were excluded from the present analyses to ensure that control participants did not have a history of suicidal thoughts or behaviors.

Code Availability

Please note that the code used to phenotype suicide attempts and suicidal ideation from VA EHR data in the present study are available through the VA's Centralized Interactive Phenomics Resource (CIPHER) https://www.research.va.gov/programs/cipher.cfm(VAnetworkaccessonly)).

MVP Genotyping and Imputation

Genotyping methods and quality control (QC) for the MVP genotype data have been described previously.[10] Briefly, DNA extracted from peripheral blood was genotyped on the MVP custom Axiom 1.0 array. Samples of questionable identity or with call rates below 98.5% were excluded. After phasing the chromosomes with EAGLE v 2.4, genotype data were imputed with Minimac v4[12] using the 1000Genomes p3v5 as the global reference panel. The present analysis used Release 3 of the imputed MVP dataset, excluding markers with a minor allele frequency (MAF) < 0.01 in the entire data set.

Statistical Methods

Genetic substructure.—We performed principal component analysis (PCA) using PLINK2[13] with the non-imputed genotypes within each of the four largest, mutually-exclusive racial groups assigned through a prior MVP study[14] focused on harmonizing genetic ancestry and self-identified race/ancestry (HARE) within the MVP cohort: European-Americans, African-Americans, Hispanic-Americans, and Asian-Americans. The HARE approach to assign ancestry uses a combination of genetic markers and self-report to assign individuals to major ancestral groups.[14] To further control for population substructure within ancestral group, we used 10 principal components (PC's) for the European-Americans ($lambda_{GC}$=1.06 after PC adjustment), 6 for African-Americans ($lambda_{GC}$=1.03), 8 for Hispanic-Americans ($lambda_{GC}$=1.02), and 6 for Asian-Americans ($lambda_{GC}$=0.95).

Genetic Association and meta-analysis.—Ancestry-specific GWAS was performed using PLINK 2,[13] controlling for age, gender and genetic PC's. Meta-analysis was performed with the R package metafor,[15] and the QE-test of heterogeneity of effect sizes[16] was performed across the ancestral groups. GWAS results were summarized using Manhattan plots, along with LocusZoom plots[17] for specific associated genomic regions.

Replication.—We used the ISGC[8] and the Mid-Atlantic MIRECC cohorts[7] to replicate top associations ($p<10^{-6}$). The ISGC cohort was larger (N=549,743 total subjects, N=29,782 cases), but is primarily a civilian cohort, whereas the MIRECC cohort is smaller (N=2,423 total subjects, N=218 cases), but comprised entirely of U.S. military veterans, many of whom have seen combat and have histories of PTSD, depression, and suicide attempts. Direct replication of the top GWAS associations was performed for findings from the meta-analysis as well as for European-American and African-American ancestry-specific loci in the comparable ancestral groups in ISGC, using the original SNP, or a surrogate SNP with $r^2>0.5$ or D'=1 identified with LDproxy, part of the LDlink suite of programs.[18–19] Note that some MVP loci did not have proxy SNPs in the ISGC meeting those criteria. Due to the smaller size of the MIRECC cohort, this study was used as a target sample to test polygenic risk scores (PRS) generated from the MVP cohort. Using the program PRSice,[20] the effect sizes from the MVP GWAS for the European-American and African-American groups were used to generate PRS to test for association with suicide attempts adjusting for age, sex and genetic PCs (15 for European-Americans, 3 for African-Americans) in the comparable ancestral groups in the MIRECC data set.[7]

Genetic correlation.—Cross-trait linkage disequilibrium score regression[21] was used to estimate the genetic correlation between suicide attempts in the European-American subsets of the MVP and the ISGC. Additionally, we examined the genetic correlation between suicide attempts in the MVP European-American subset with five phenotypes relevant to suicide attempts including bipolar disorder,[22] schizophrenia,[23] major depression,[24] posttraumatic stress disorder (PTSD),[25] and sleep disorders,[26] all of which were obtained from LD Hub.[27]

Pathway analysis.—Pathway analysis was performed with Over-Representation Analysis in the Web-Gestalt package.[28] Genes were included from the following SNP designations: exonic, intronic, ncRNA exonic and ncRNA intronic. A single marker with the smallest p-value (< 0.05) was chosen to represent each gene from among the 10% most significant SNPs. The KEGG database was used for defining pathways, and the top 30 pathways for each GWAS analysis were reported.

RESULTS

Overview of Analyses

Clinical and genotype data from 409,153 individuals (including 14,089 cases) were examined in this study (Table 1). The four ancestral groups exhibited significantly different rates of suicide attempts (2.7% in Asian-Americans, 3.1% in European-Americans, 4.2% in Hispanic-Americans, 4.5% in African-Americans, p < 2.2e-16), which is consistent with national data that finds that African-Americans are more likely to attempt suicide than European Americans;[29–30] whereas European-Americans are more likely than African Americans to die by suicide.[30–31] Given these important differences in suicide attempt rates by ancestry, we elected to first conduct GWAS within each group and then to conduct a pan-ancestry meta-analysis. These analyses identified nine loci associated with suicide attempts with genome-wide significance ($p<5\times10^{-8}$; Figure 1; Table 2).

Pan-Ancestry GWAS Results

Meta-analysis across the four ancestral groups identified two genome-wide significant pan-ancestry loci on chromosomes 20 and 1 (Figure 1, Table 2). Locus zoom plots for genome-wide significant genomic regions are presented in Supplemental Figure 1. The top SNPs were close to *Teashirt Zinc Finger Homeobox 2* (*TSHZ2*), a transcription factor linked to smooth muscle development[32] and *Spermatogenesis Associated Protein 7* (*SPATA17*). The direction (same risk allele) and magnitude of the effect sizes of these associations were similar across ancestry groups. Supporting this observation, the test for heterogeneity was not statistically significant for either locus. Five other loci were associated with suicide attempts at $p<10^{-6}$ in the meta-analysis, including two SNPs near *Dopamine Receptor D2* (*DRD2*), a G protein-coupled receptor located on postsynaptic dopaminergic neurons involved in reward-mediating pathways and addictive behavior.[33] We also performed a gene-based analysis using FUMA[34] on the meta-analysis results. Two genes were genome-wide significant for the gene-based tests, including *SPATA17* on chromosome 1 and *DRD2* on chromosome 11, providing further support for these meta-analytic signals.

Ancestry-Specific GWAS Results

We also analyzed association with suicide attempt risk within each ancestral group (Figure 1, Table 2). Among European-Americans, a genome-wide significant association was identified near *ATR-Interacting Protein* (*ATRIP*), which has been associated with Seckel syndrome, a rare Mendelian disorder characterized by microcephaly and mental retardation.[35] Among African-Americans, one of the genome-wide significant SNPs from the meta-analysis (rs56817213) was also found to be genome-wide significant within this cohort. Among Hispanic-Americans, three genome-wide significant loci were

identified, including one in *Calcium Channel, Voltage-Dependent, Alpha-2/Delta Subunit 3* (*CACNA2D3*), which modulates presynaptic nerve function[36] and is associated with pain sensitivity.[37] Genome-wide significant associations were also identified near *TBC1 Domain Family Member 32* (*TBC1D32)* and near *Guanylate Cyclase 1 Soluble Subunit Beta 2 (GUCY1B2),* a pseudogene, among Hispanic-Americans. Finally, among Asian-Americans, three genome-wide significant SNPs were identified near *Fibrillin 1* (*FBN1*). Locus Zoom plots of these regions are provided in Supplemental Figure 1.

Replication

We attempted to replicate findings in the ISGC cohort[8] (29,782 cases; 519,961 controls) for SNPs in Table 2, or high LD surrogates, when available. We observed strong replication of three SNPs identified in *DRD2* in the overall meta-analysis and in European Americans. Two African-American loci were also replicated, including *WDR1* (*WD-repeat containing protein 1*) and *EDIL3* (*EGF-like Repeats and Discoidin I-like Domains Containing Protein 3*).

Polygenic Risk and Top Loci Follow-Up in an Independent Veteran Cohort

Results from the MVP GWAS were used to construct polygenic risk scores (PRSs). We then evaluated the association between these PRSs and suicide attempts in the MIRECC cohort.[7] For African-Americans (*N*=1,245), the MVP PRS was significantly associated with suicide attempts (p=0.001), with the most significant association achieved using MVP p-values below 0.3 (P_T=0.3; Supplemental Figure 3). This PRS explained slightly less than 2% of the phenotypic variability of suicide attempts within the MIRECC cohort. Among European-Americans (*N*=1,178), none of the MVP PRSs were significantly associated with suicide attempts.

Genetic Correlations

The SNP heritability of suicide attempts in the MVP was estimated to be 0.0125 (se 0.0022). Using the EA subset of the MVP as the reference, we found a large genetic correlation (r_{GC}=0.86; p=1.30e-21) for suicide attempts between the MVP and ISGC data sets, despite ISGC being a largely civilian cohort. The LDSC intercept for this analysis was 0.0062 (se 0.0059), providing support that the two data sets were independent. We also estimated r_{GC} between suicide attempts in the MVP European-American subset with several other psychiatric disorders, including bipolar disorder (r_{GC} = 0.38; se=0.0641; p=4.5E-09), schizophrenia (r_{GC} =0.46; se=0.0571; p=9.23E-16) major depression (r_{GC} =0.63; se=0.0685; p=1.9E-20), and PTSD (r_{GC} =0.57; se=0.073; p=5.59E-15). We observed a small correlation with sleep disorders (r_{GC} = 0.096; se=0.0347 p=0.0057). All of the r_{GC} estimates with suicide attempts remained significant after a Bonferroni correction for the number of phenotypes examined (corrected p = 0.05/5 = 0.01).

Pathway Analysis

Thirty pathways were significantly over-represented in the multi-ancestry meta-analysis (Table 3), including oxytocin signaling, glutamatergic synapse, axon guidance, calcium signaling, circadian entrainment, cortisol synthesis and secretion, dopaminergic synapse, and

circadian rhythm (all FDR <0.05). There was striking consistency for the pathway analyses across the ancestral groups, including two that were significant across all five analyses: arrhythmogenic right ventricular cardiomyopathy (ARVC), and phospholipase D signaling, the latter of which mediates alcohol's effect on ion channels[38] and has been linked to Alzheimer's disease.[39]

Association between Sleep Problems and Suicide Attempts within MVP

Given the overrepresentation of both the circadian entrainment and circadian rhythm pathways, we examined the association between suicide attempts and sleep problems (see Supplementary Phenotyping Methods for details) in the MVP cohort, using the MVP Lifestyle Survey,[9] which was available for 53.7% (N=220,001) of the participants from the current cohort. We observed significant, clinically-meaningful differences between suicide attempt cases and controls on total number of sleep problems endorsed (overall sample: 3.4 vs 2.1, $p < 0.001$; standardized mean difference = 0.65; Supplementary Table 3). Notably, these differences were highly consistent with respect to both direction and magnitude of effect across all four ancestries (Supplemental Figure 4), providing strong support for the potential role of sleep disturbance in suicide attempt risk among veterans.

DISCUSSION

We report here findings from the largest GWAS of suicide attempts among U.S. veterans to date. Meta-analysis across four ancestral groups identified two genome-wide significant pan-ancestry loci on chromosomes 20 and 1. Both loci demonstrated homogeneity of effects across ancestral groups, suggesting that common genetic factors underlie risk for attempting suicide among veterans. A strong pan-ancestry signal at the *Dopamine Receptor D2* locus was also identified ($p<10^{-7}$) and subsequently replicated in a large, independent international cohort. Ancestry-specific genome-wide significant risk loci were detected for each ancestral group examined, and an MVP-based PRS significantly predicted suicide attempts in an independent cohort of African-American veterans. As expected, we also observed significant genetic correlations between suicide attempts and other psychiatric disorders, including bipolar disorder, schizophrenia, PTSD, and depression. Perhaps most notable was the magnitude of the genetic correlation for suicide attempts across the MVP and ISGC cohorts (GC=0.86, $p=1.30^{-21}$), which suggests that similar genetic factors influence risk for suicide attempts across diverse environmental exposures (e.g., combat), providing strong support for consortium-based studies of genetic risk for suicide.

The strongest meta-analytic association identified in the present study was near *TSHZ2*, which is highly expressed in human cerebral cortex[40] and has been previously associated with sleep duration[41] and comorbid depression, alcohol dependence.[42] Notably, the *TSHZ2* locus was also genome-wide significant within African-Americans.

Strong associations were also observed between *DRD2* and suicide attempts in both the pan-ancestry meta-analysis and the European-American cohort. Moreover, this association was also replicated within the ISGC cohort and was genome-wide significant in the meta-analytic gene-based analysis. DRD2 is a G protein-coupled receptor located on postsynaptic dopaminergic neurons that is highly expressed in human and murine basal ganglia. It is

centrally involved in reward-mediating pathways and is consistently associated with risk for substance use disorders.[43] *DRD2* is also associated with risk for schizophrenia,[44] attention-deficit/hyperactivity disorder (ADHD),[45] and sleep duration,[46] all of which are, in turn, risk factors for suicide and suicidal behavior.[47–49] *DRD2* has also been associated with suicidal behavior previously;[50–52] however, the present findings provide the strongest support to date.

The genome-wide significant association between *CACNA2D3* and suicide attempts in the Hispanic-American cohort also represents a promising avenue for future investigation. *CACNA2D3* has been associated with bipolar disorder,[53] depression,[54] schizophrenia,[55] autism spectrum disorder,[56] nicotine dependence,[57] and pain sensitivity.[37]

Within the European-American cohort, the only SNP that reached genome-wide significance was located on chromosome 3 near *ATRIP*, which encodes a key component of the DNA damage checkpoint. A recent GWAS of shared risk across psychiatric disorders identified a genome-wide significant locus near *ATRIP*;[58] however, we note that this region on chromosome 3 exhibits considerable LD in European-Americans, making it challenging to discern whether *ATRIP* or another gene is driving this association.

Among Asian-Americans, three genome-wide SNPs were identified, all within the *Fibrillin 1* gene (*FBN1*), in which mutations give rise to Marfan syndrome,[59] a heritable connective tissue disorder. While the functional significance of *FBN1* to suicide is presently unclear, a prior GWAS found a suggestive association between *FBNI* and bipolar disorder among Norwegian individuals, which was subsequently replicated in an Icelandic sample.[60]

Finally, we identified a number of pathways of high relevance to suicide risk. Oxytocin signaling plays a key role in social bonding and feelings of well-being, and lower serum oxytocin concentrations have been associated with suicidal intent and suicide attempts.[61–62] Over-representation of the glutamatergic synapse pathway is also of great interest, as neuroimaging studies have identified glutamatergic dysfunction among patients with schizophrenia and other psychiatric disorders,[63] and at least two postmortem studies have found that suicide decedents are more likely than controls to have increased glutamatergic gene expression in the prefrontal cortex.[64–65] Moreover, the glutamatergic modulator ketamine has been found to produce rapid decreases in suicidal ideation.[66]

Multiple stress pathways were also overrepresented, including cortisol synthesis and secretion, as well as blood pressure regulating pathways (e.g., renin secretion, aldosterone synthesis and secretion). Also featured were the circadian entrainment and circadian rhythm pathways, which have been shown to be stimulated by DRD2. Disruptions of circadian rhythm profoundly affect mood, as CLOCK protein regulates dopaminergic transmission in the ventral tegmental area—the critical neurological reward circuits.[67] Furthermore, many psychiatric disorders (e.g., schizophrenia, mood disorders) are characterized by impaired circadian-clock controlled functions, such as sleep and cortisol secretion.[68] A genome-wide significant association with a functional variant in the CLOCK gene *PER1* has recently been reported for suicide death.[69] We also found clear evidence for increased sleep problems among veterans with a history of suicide attempts within the MVP cohort, providing direct

support for sleep disturbance in suicide risk among veterans. Notably, another recent study identified both circadian rhythms and glutamatergic signaling as top biomarker candidates for mood disorders.[70]

Study Limitations

Out of necessity, suicide attempts were defined from VA EHR sources, including ICD codes, SPAN reports, and survey responses, rather than by rigorous diagnostic interviews. It is possible that some control participants had a history of attempts that were not recorded in the VA's EHR (particularly those that occurred prior to military service); however, while this might decrease statistical power, it is unlikely to introduce false positive SNP associations. A second limitation concerns the lack of replication for many of our top findings. In several cases, genotyped markers within loci of interest (i.e., *TSHZ2, CACNA2D3, FBNT1*) were simply not available within the ISCG cohort; in other instances (e.g., *SPATA17, ATRIP)*, appropriate markers were available, but no replication was observed. This could be due to false positive associations in the MVP study, or alternatively, could represent population differences between the two data sets, such as the veteran vs. civilian nature of the ascertainments or the increased diversity present in the MVP study. A notable exception to this pattern was for *DRD2*, where we were able to replicate all three of our top SNPs in the ISGC cohort.

Conclusions

We report here findings from the largest GWAS of suicide attempts among U.S. veterans to date. Meta-analysis across ancestral groups identified genome-wide significant loci near *TSHZ2* and *SPATA17*. Ancestry-specific genome-wide significant loci were also detected for each ancestral group examined and included *TSHZ2, ATRIP, CACNA2D3,* and *FBN1*. A strong pan-ancestry signal at the *DRD2* locus was also identified and subsequently replicated in the ISGC cohort. Taken together, our findings confirm that the genetic architecture underlying suicide attempt risk is complex and includes both pan-ancestry and ancestry-specific risk loci. Moreover, findings from the pathway analyses suggest a number of promising biological pathways that could inform development of improved therapeutics for suicide prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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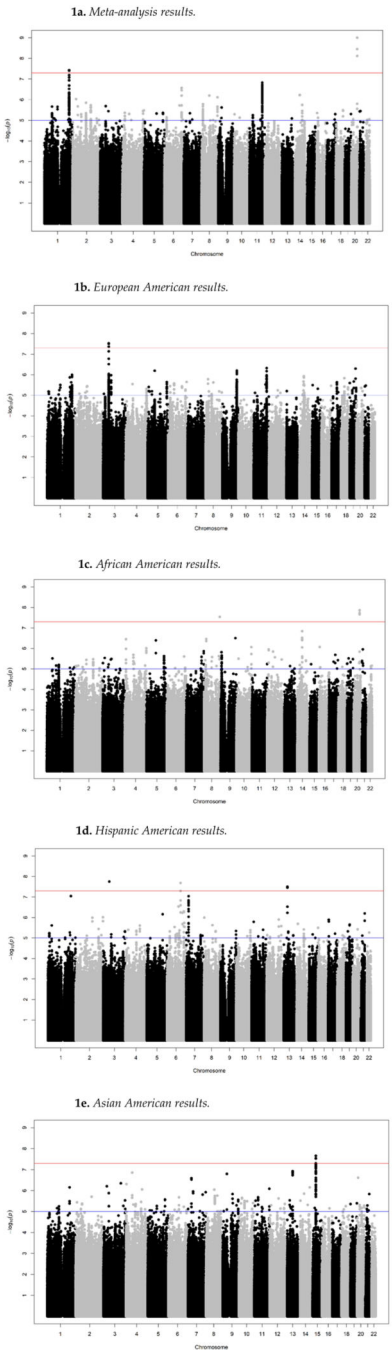

Figure 1. Manhattan plots summarizing the GWAS results for the pan-ancestry meta-analysis and ancestry-specific GWAS.

Notes: Red line indicates genome-wide ($p<5X10^{-8}$) significant threshold. Figure la) Metaanalysis; Figure lb) European Americans; Figure lc) African Americans; Figure Id) Hispanic Americans; Figure le) Asian Americans.

Table 1

Sample characteristics.

	Controls	Cases	Standardized Mean Difference[1]
Total (%)	395,064 (96.6)	14,089 (3.4)	
Age (mean (SD))	62.84 (13.63)	52.01 (12.77)	0.820
Age Group (%)			0.814
18–29	9,192 (2.3)	898 (6.4)	
30–39	20,058 (5.1)	1,811 (12.9)	
40–49	31,109 (7.9)	2,292 (16.3)	
50–59	67,781 (17.2)	4,855 (34.5)	
60 and over	266,710 (67.5)	4,228 (30.0)	
Missing	214 (0.1)	5 (0.0)	
Male (%)	363,773 (92.1)	12,005 (85.2)	0.218
HARE Ancestry Group (%)			0.170
European-American	287,370 (72.7)	9,196 (65.3)	
African-American	74,306 (18.8)	3,507 (24.9)	
Asian-American	4,082 (1.0)	115 (0.8)	
Hispanic-American	29,306 (7.4)	1,271 (9.0)	
Self-Reported Race[2](%)			
White (only)	293,512 (74.3)	9,544 (67.7)	0.145
Black (only)	69,986 (17.7)	3,339 (23.7)	0.148
Asian (Only)	3,434 (0.9)	93 (0.7)	0.024
Self-Reported Ethnicity (%)			0.053
Hispanic or Latino/a	23,917 (6.1)	1,031 (7.3)	
Not Hispanic or Latino/a	362,546 (91.8)	12,784 (90.7)	
Military Service[3](%)			
September 2001 or later (%)	42,128 (10.7)	2,396 (17.0)	0.184
August 1990 to August 2001 (includes Persian Gulf War) (%)	83,531 (21.1)	4,788 (34.0)	0.290
May 1975 to July 1990 (%)	90,036 (22.8)	4,568 (32.4)	0.217
Prior Feb1975 (includes Vietnam, Korea, World War II) (%)	267,917 (67.8)	5,077 (36.0)	0.671

Notes:

[1] Standardized mean differences of 0.2, 0.5, and 0.8 can be interpreted as small, medium, and large effects sizes, respectively.

[2] Self-reported race utilized a “mark all that apply format,” we report here results for participants who endorsed only one race category to facilitate comparison with the ancestral groups that were utilized, which were mutually exclusive.

[3] Military service utilized a “mark all that apply format.” Thus, these categories are not mutually exclusive.

Table 2

SNP Associations with $p<10^{-6}$ from Meta-Analysis and Ancestry-Specific Genome-Wide Association Studies.

SNP	Chromosome: position	Alleles eff/alt	p-value	Odds Ratio (SE)	Annotation	Replication
***Meta-Analysis Results (14089 (3.4%) cases, 395064 (96.6%) controls)**						
rs56817213	20: 51818256	A/G	3.64×10^{-9}	1.22 (0.03)	*TSHZ2*	
rs72730526	1: 218026968	A/T	3.69×10^{-8}	1.21 (0.03)	*SPATA17*	6.75×10^{-1}
rs10407501	19: 30569741	A/G	5.41×10^{-8}	1.23 (0.04)	*URI1, ZNF536*	
rs116165183	8: 138806806	A/G	7.25×10^{-8}	1.35 (0.06)	*LOC101927915, LOC401478*	
rs12883260	14: 56398379	A/G	1.62×10^{-7}	1.11 (0.02)	*LINC00520, PELI2*	9.44×10^{-1}
rs6589377	11: 113355736	A/G	1.77×10^{-7}	0.93 (0.01)	*DRD2, TMPRSS5*	7.97×10^{-4}
rs1107162	11: 113289037	A/G	2.16×10^{-7}	0.93 (0.01)	*DRD2*	2.52×10^{-5}
rs28731324	14: 61747119	C/G	2.28×10^{-7}	1.20 (0.04)	*TMEM30B*	
European American Results (9196 (3.1%) cases, 287370 (96.9%) controls)						
rs4858820	3: 48484016	T/A	3.20×10^{-8}	1.10 (0.02)	*ATRIP*	1.73×10^{-1}
rs202061221	3: 48412264	CG/C	3.10×10^{-7}	1.10 (0.02)	*SPINK8, FBXW12*	1.23×10^{-1} (rs56023037)
rs555562525	11: 113318196	GA/G	4.80×10^{-7}	0.91 (0.02)	*DRD2*	1.89×10^{-4} (rs17601612)
rs376014007	19: 51031620	C/T	5.10×10^{-7}	1.09 (0.02)	*LRRC4B*	5.66×10^{-2}
rs360210	9: 127797945	C/T	6.39×10^{-7}	0.92 (0.02)	*SCA1*	3.94×10^{-2}
rs2174168	5: 62971367	A/T	6.44×10^{-7}	1.08 (0.02)	*IPO11, HTR1A*	3.50×10^{-1} (rs2365873)
African American Results (3507 (4.5%) cases, 74306 (95.5%) controls)						
rs56817213	20: 51818256	G/A	1.38×10^{-8}	1.22 (0.04)	*TSHZ2*	
rs116165183	8: 138806806	G/A	2.90×10^{-8}	1.37 (0.06)	*LOC101927915, LOC401478*	
rs28731324	14: 61747119	C/G	1.46×10^{-7}	1.21 (0.04)	*TMEM30B*	
rs536061513	9: 131007176	C/A	3.16×10^{-7}	1.82 (0.12)	*DNM1*	
rs34326041	8: 19193436	T/G	3.50×10^{-7}	1.18 (0.03)	*SH2D4A*	6.70×10^{-1}
rs3796820	4: 10097446	A/G	3.59×10^{-7}	1.58 (0.09)	*WDR1*	4.72×10^{-2}
rs75861007	14: 61730115	G/T	3.60×10^{-7}	1.32 (0.05)	*SNORD112*	
rs114579897	5: 83946735	T/G	4.10×10^{-7}	2.26 (0.16)	*EDIL3, NBPF22P*	2.42×10^{-2} (rs78097367)
rs369284963	16: 7462413	C/CA	8.58×10^{-7}	1.15 (0.03)	*RBFOX1*	9.98×10^{-2} (rs8050278)
rs61859846	10: 131294704	C/A	8.67×10^{-7}	1.21 (0.04)	*MGMT*	3.09×10^{-1}
rs56291711	4: 190043389	T/C	9.89×10^{-7}	0.87 (0.03)	*LINC02508, LINC01262*	$9.85.x10^{-2}$ (rs57050950)
Hispanic American Results (1271 (4.2%) cases, 29306(95.8%) controls)						
rs34173987	3: 54892449	G/A	1.76×10^{-8}	2.34 (0.15)	*CACNA2D3*	

SNP	Chromosome: position	Alleles eff/alt	p-value	Odds Ratio (SE)	Annotation	Replication
rs6907713	6: 120589671	C/A	2.08×10^{-8}	15.67 (0.49)	*MIR3144, TBC1D32*	
rs9596440	13: 51646178	G/C	3.17×10^{-8}	2.73 (0.18)	*GUCY1B2*	
Asian American Results (115 (2.7%) cases, 4082 (97.3%) controls)						
rs199633759	15: 48822272	A/G	2.20×10^{-8}	2.77 (0.18)	*FBN1*	
rs77378519	15: 48831864	C/T	2.89×10^{-8}	2.69 (0.18)	*FBN1*	
rs57790277	15: 48855753	T/C	2.98×10^{-8}	3.07 (0.20)	*FBN1*	

* For the meta-analysis, the direction of effects were (EA AA HA AS): rs56817213 (- - - -), rs72730526 (+ + + +), rs10407501 (+ + + +), rs116165183 (- - + -), rs12883260 (+ - + +), rs6589377 (+ - + +), rs1107162 (- + - -), rs28731324 (+ - + -).

Table 3

Top 30 False-Discovery Rate (FDR)-Significant Findings from the Pathway Analyses.

Gene Set	Description	Meta-Analysis Ratio	European-Americans Ratio	African-Americans Ratio	Hispanic-Americans Ratio	Asian-Americans Ratio
hsa00604	Glycosphingolipid biosynthesis	4.98				
hsa04710	Circadian rhythm	3.37				
hsa04520	Adherens junction	3.32				
hsa04924	Renin secretion	3.22	2.88		2.75	
hsa04540	Gap junction	3.06	2.66			
hsa04724	Glutamatergic synapse	3.01	2.33	2.67	2.99	
hsa04921	Oxytocin signaling	2.95		2.31	2.56	2.25
hsa05412	Arrhthmogenic righ ventricular cardiomyopathy	2.90	2.82	2.75	3.16	3.09
hsa04927	Cortisol synthesis and secretion	2.80	3.42	2.86		
hsa04713	Circadian entrainment	2.80	2.60	2.22	2.71	
hsa04925	Aldosterone synthesis and secretion	2.65	2.44	2.70	2.37	
hsa04360	Axon guidance	2.56	1.96	2.00		
hsa05414	Dilated cardiomyopathy	2.49		2.37	2.53	2.66
hsa04270	Vascular smooth muscle contraction	2.47	2.32	2.65		
hsa04020	Calcium signaling	2.45	2.22	2.08	2.13	
hsa04070	Phosphatidylinositol signaling	2.41	2.37	2.46		
hsa04912	GnRH signaling	2.41				
hsa04725	Cholinergic synapse	2.40	2.23	2.99		
hsa04072	Phospholipase D signaling	2.35	2.46	2.40	2.22	2.34
hsa05410	Hypertrophic cardiomyopathy	2.34			2.74	2.68
hsa04911	Insulin secretion	2.28				
hsa04750	Inflammation/transient receptor potential channels	2.26		2.31		
hsa04022	Cyclic guanosine monophosphate-protein kinase G signaling	2.11		2.62		
hsa04024	Cyclic adenosine monophosphate signaling	2.10	2.36	1.91		
hsa04371	Apelin signaling pathway	2.07				
hsa04728	Dopaminergic synapse	2.05				
hsa04015	Ras-associated protein-1 signaling	2.03	1.82	2.15	1.89	

Gene Set	Description	Meta-Analysis Ratio	European-Americans Ratio	African-Americans Ratio	Hispanic-Americans Ratio	Asian-Americans Ratio
hsa04261	Adrenergic signaling cardiomyocytes	1.97	2.17			2.49
hsa04514	Cell adhesion molecules	1.97		2.01	2.14	2.26
hsa04934	Cushing syndrome	1.94	2.03			

Notes: All values shown are significant at FDR < 0.05.