GWAS Meta-Analysis of Suicide Attempt: Identification of 12 Genome-Wide Significant Loci and Implication of Genetic Risks for Specific Health Factors

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Genome-wide association study meta-analysis of suicide attempt identifies twelve genome-wide significant loci and implicates genetic risks for specific health factors

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NA

Comments on Human Participant Data Responses: This manuscript reports only on analyses of summary data from genetic studies of pre-existing cohorts. No individual-level data were used in these analyses.

Genome-wide association study meta-analysis of suicide attempt identifies twelve genome-wide significant loci and implicates genetic risks for specific health factors

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Abstract

Objective: Suicidal behavior is heritable and a major cause of death worldwide. Two large-scale genome-wide association studies (GWAS) recently discovered and cross-validated genome-wide significant (GWS) loci for suicide attempt (SA). The current study leveraged the genetic cohorts from both studies to conduct the largest GWAS meta-analysis of SA to date. Multi-ancestry and admixture-specific meta-analyses were conducted within groups of significant African, East Asian, and European ancestry admixtures.

Methods: This study was comprised of 22 cohorts, including 43,871 SA cases and 915,025 ancestry-matched controls. Analytical methods across multi-ancestry and individual ancestry admixtures included inverse variance-weighted fixed effects meta-analyses, followed by gene, gene-set, tissue-set, and drug-target enrichment, as well as summary-data-based Mendelian Randomization with brain eQTL data, phenome-wide genetic correlation, and genetic causal proportion analyses.

Results: Multi-ancestry and European ancestry admixture GWAS meta-analyses identified 12 risk loci at $p<5x10^{-8}$. These loci were mostly intergenic and implicated *DRD2, SLC6A9, FURIN, NLGN1, SOX5, PDE4B,* and *CACNG2*. The multi-ancestry SNP-based heritability estimate of SA was 5.7% on the liability scale (SE=0.003, $p = 5.7x10^{-80}$). Significant brain tissue gene expression and drug set enrichment was observed. There was shared genetic variation of SA with ADHD, smoking, and risk tolerance after conditioning SA on both major depressive disorder and post-traumatic stress disorder. Genetic causal proportion analyses implicated shared genetic risk for specific health factors.

Conclusions: This multi-ancestry analysis of suicide attempt identified several loci contributing to risk, and establishes significant shared genetic covariation with clinical phenotypes. These findings provide insight into genetic factors associated with suicide attempt across major ancestry admixtures, in veteran and civilian populations, and in attempt versus death.

Introduction

Suicide was the fourth leading cause of death among 15–29-year-olds in 2019, accounting for more than 700,000 deaths worldwide (1). Suicide attempts (SA; defined as self-injurious behaviors with an intent to die) are even more common (2-4). Suicide attempts are strongly associated with psychiatric conditions, poor quality of life, traumatic experiences, and social and economic burden (1), and are the single strongest predictor of future suicide death (5).

Heritability estimates for suicidal thoughts and behaviors from twin and family studies range from 30-55% (6), and recent large-scale genome-wide association studies (GWAS) have yielded promising and replicable results. The International Suicide Genetics Consortium (ISGC; total *N*=549,743; 29,782 cases) identified two loci reaching genome-wide significance for suicide attempt in individuals of primarily European ancestry admixtures, on chromosomes 6 (index SNP rs71557378, $p = 1.97 \times 10^{-8}$) and 7 (index SNP rs62474683, $p = 1.91 \times 10^{-10}$) (7). The intergenic locus on chromosome 7 remained significant after conditioning on psychiatric disorders, and was independently replicated ($p = 3.27 \times 10^{-3}$) (8) within the Million Veteran Program (MVP) cohort (9). The MVP cohort GWAS of SA (total *N*=409,153; 14,089 cases) resulted in two genome-wide significant multi-ancestry loci, on chromosomes 20 (index SNP rs56817213, $p = 3.64 \times 10^{-9}$) and 1 (index SNP rs72730526, $p = 3.69 \times 10^{-8}$) (8). A top signal identified at the *Dopamine Receptor D2* locus ($p = 1.77 \times 10^{-7}$) also showed moderate association in the ISGC GWAS ($p = 7.97 \times 10^{-4}$) (7).

These studies established the complexity of the common variant genetic architecture of suicide attempt and demonstrated the critical role of sample size for discovering novel, replicable risk loci for suicide phenotypes through GWAS (10). Together, these GWAS suggested that larger studies will identify additional genomic risk loci and refine genetic risk metrics.

The objective of the current study was to conduct a meta-analysis of the ISGC and MVP studies (total *N*=958,896; 43,871 suicide attempt and suicide death cases). Moreover, there is considerable need to increase the diversity and generalizability of GWAS data (11). Combining all ISGC and MVP cohorts allowed for the largest GWAS meta-analyses of European, African, and East Asian ancestry admixtures to date. We also tested for gene set enrichment and functional follow-up specific to these primary ancestral admixtures.

Methods

GWAS Cohorts and Phenotype Ascertainment

The International Suicide Genetics Consortium (ISGC) Cohort

The ISGC analyses included 29,782 suicide attempt (SA) and/or suicide death (SD) cases and 519,961 controls from 18 cohorts (15 SA, 2 SD, and 1 both), 12 of which were ascertained clinically for the purpose of studying psychiatric disorders. Details about the specific cohorts have been described previously (7) and cohort references and ascertainment methods are summarized in Supplementary Table S1. Twelve SA cohorts ascertained information on SA via in-person structured psychiatric interviews conducted by trained clinicians/researchers, two SA cohorts used self-report, and two SA cohorts used ICD codes or hospital records. All interviews and self-report items asked explicitly about SA rather than self-harm (which would also include non-suicidal self-injury). ICD codes were coupled with information from emergency room settings, reason for contact information, and attempt methods that were mined from physician

notes, in order to maximize evidence that suicidal intent was present. For the cohorts using interviews or self-report to ascertain SA information, the SA was non-fatal. An additional two cohorts explicitly ascertained cases of suicide death (SD). The majority of SD cases were ascertained from the Utah Office of the Medical Examiner (Utah *n* = 4,692). In these cases, suicide cause-of-death determination results from a detailed investigation of the scene of the death and circumstances of death, determination of medical conditions by full autopsy, review of medical and other public records concerning the case, interviews with survivors, and standard toxicology workups (12). Suicide determination is traditionally conservative due to its impact on surviving relatives. In the 746 suicide deaths from Kobe, Japan, autopsies on suicides were performed and cause of death was determined through discussion with the Medical Examiner's Office and the Division of Legal Medicine in the Kobe University Graduate School of Medicine. The Columbia University cohort of both SA and SD included 317 suicide deaths that were determined by psychological autopsy and the coroner or medical examiner. A psychological autopsy is a method of determining the psychological factors that may have contributed to a death, considering additional information from family members, friends, acquaintances, medical records and other relevant documents to better characterize a death of uncertain cause, including suspected suicides.

The Million Veteran Program (MVP) Cohort

MVP recruitment and study procedures have been described previously (8) and included veterans providing a blood sample, consenting to genetic analyses and the linking of one's genetic information to the VA's electronic health records (EHR), and completing two optional surveys (9, 13). SA was defined as an act of deliberate self-harm with the intent to cause death that occurred at any point over the lifetime. Briefly, cases were defined as veterans with a documented history of SA in the 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). VA EHR sources were utilized to create a SA phenotype using: (a) diagnostic codes for intentional self-harm; (b) suicidal behavior reports from the VA's Suicide Prevention Applications Network (SPAN) database; and (c) mental health survey responses from the VA's Mental Health Assistant database indicating a history of attempting suicide. Veterans who had a history of suicidal ideation but no SA were excluded from analysis. For all ISGC and MVP cohorts, it remains undetermined which individuals with SA may have later died by suicide. Details of sample sizes by genetic ancestry admixture for the ISGC and MVP cohorts are presented in Table 1.

Genotyping, quality control, and imputation

Details of genotyping, quality control (QC), and imputation for the ISGC and MVP data sets have been described previously (7, 8). In the ISGC analyses, genotyping was performed locally by each of the research teams using comparable procedures[8] (details per cohort are available in the Table S1). Standard parameters were used to retain individuals and SNPs after quality control for missingness, relatedness, and Hardy-Weinberg equilibrium. Genetic ancestry was defined by the contributing cohorts, and we include all ascertainment, QC, and analysis details of the ISGC and MVP cohorts in Supplemental Table 1. Imputation was performed using the largest available ancestrally matched reference panels, either from 1000 Genomes or the Haplotype Reference Consortium. We confirmed the comparability of imputation across the cohorts by comparing the final set of SNPs in the meta-analysis, including the number of cohorts in which they were present, and the INFO scores across cohorts and within ancestral admixture groups. Sample overlap and/or cryptic relatedness across cohorts was assessed and corrected for using the meta-analytic tools described below. Eight of the cohorts had high control:case ratios (using an arbitrary cut-off of >15:1). In these cases, the LD Score regression

(14) (LDSC) attenuation ratio statistics were examined for evidence of population stratification or uncontrolled type 1 error in the cohort. For any evidence of inflation, the intercept was used to adjust the SE of the summary statistics.

GWAS meta-analysis of suicide attempt

For both the ISGC and MVP cohorts, the initial GWAS analysis was conducted within genetic ancestral admixture groups. For the ISGC meta-analysis, GWAS were conducted within study and genetic ancestry admixture group, covarying for at least 10 principal components of genetic ancestry, genomic relatedness matrices or factors capturing site of recruitment or genotyping batch, as required (7). For the MVP cohort, ancestry was assigned for four mutually exclusive ancestral groups utilizing a previously defined approach harmonizing genetic ancestry admixture and self-identified ancestry grouping (HARE) (15). Subsequent MVP GWAS analyses were performed within ancestral admixture group using PLINK2 (16), covarying for genetic ancestry principal components, age, and sex.

A multi-ancestry meta-analysis of SA GWAS summary statistics was conducted using an inverse variance-weighted fixed effects model (standard error) in METAL (17), assuming shared risk effects across ancestry admixtures. SNPs with a mean weighted minor allele frequency of <1%, mean weighted imputation INFO score <0.6 or SNPs present in <80% of the total effective sample size were removed to ensure adequate statistical power at every variant included. Ancestry admixture-specific GWAS meta-analyses were conducted with cohorts of significant European (EUR), African (AFR), and East Asian (EAS) ancestry admixtures using the same procedures. Only one primary ancestral admixture, Hispanic/Latino (LAT), was limited to a single cohort and thus could not be meta-analyzed. Inflation of test statistics due to polygenicity or cryptic relatedness were assessed using the LDSC attenuation ratio ((LDSC intercept - 1)/(mean of association chi-square statistics - 1)). Resulting genome-wide significant (GWS) loci were defined as those with $p<5x10^{-8}$ with LD $r^2>0.1$, within a 3,000 kb window, based on the structure of the Haplotype Reference Consortium (HRC) EUR reference panel for the multi-ancestry meta-analysis, or the HRC ancestry-appropriate reference panel otherwise. GWS loci for SA were examined for heterogeneity across cohorts via the I^2 inconsistency metric and forest plots.

Estimation of heritability and genetic association with other disorders

LDSC (14) and cov-LDSC (18) methods were used to estimate the phenotypic variance in SA explained by common SNPs (SNP-based heritability, h^2_{SNP}) from the GWAS meta-analysis summary statistics. LD scores from 1000 Genomes (EUR and EAS) were used to derive h^2_{SNP} for the multi-ancestry GWAS meta-analysis and meta-analyses of European and East Asian ancestry admixtures. To obtain acceptable attenuation ratios for Hispanic/Latino and African ancestry admixture h^2_{SNP} estimates, we used covariate-adjusted AMR LD scores from Pan UK BioBank (Pan UKBB, https://pan.ukbb.broadinstitute.org) and AA LD scores from gnomAD v2.1.1 (19). h^2_{SNP} was calculated on the liability scale assuming a lifetime prevalence of SA in the general population of 2% (middle of the range reported worldwide) (20). The default script of LDSC was used to exclude SNPs with MAF<1% and INFO<0.9 and also to restrict variants to the list of approximately 1.2 million HAPMAP SNPs that are typically well-imputed across datasets. h^2 estimates remained stable across >2% and >5% MAF thresholds. The genetic correlation attributable to genome-wide SNPs (r_G) was estimated between the ancestral admixture groups using the Popcorn package (21), and with a range of psychiatric disorders using LDSC and the largest available discovery GWAS meta-analysis summary statistics (22-33). The latter analyses were confined to European ancestry admixture for consistency with the

discovery summary data. Tests were Bonferroni-corrected, adjusting for up to 18 phenotypes hypothesized to be associated with SA based on previous epidemiological association and/or previous evidence of genetic association in LD Hub (34). Previous LD Hub analyses in ISGC were pre-categorized manually into risk factor groups relevant to SA (5, 35, 36): autoimmune disease, neurologic disease, heart disease, hypertension, diabetes, kidney disease, cancer, alcohol use, smoking, pain, psychiatric, sleep, life stressors, socioeconomic, and education/cognition. r_G of SA in ISGC and MVP in this study were calculated using LDSC, and references for the discovery GWAS are listed in Table S2. Differences in r_G across other phenotypes using EUR GWAS meta-analyses were tested as a deviation from 0, using the block jackknife method implemented in LDSC (37). To examine phenome-wide partial genetic causality, the Complex-Traits Genetics Virtual Lab (CTG-VL) (38) was used to conduct FDR-corrected Genetic Causal Proportion (GCP) analyses on the EUR summary data.

Conditioning suicide attempt on major depressive disorder and PTSD

The results of the EUR GWAS SA meta-analysis were conditioned on genetic risks for major depressive disorder (MDD) (27) and post-traumatic stress disorder (PTSD) (32) in secondary analyses, to examine genetic associations both shared with and unique to suicide risk. Results were conditioned because MDD and PTSD are both highly co-morbid with SA, and because PTSD is particularly prevalent within military veteran populations (i.e., MVP). Conditioning was conducted using mtCOJO (multi-trait-based COnditional & JOint analysis using GWAS summary data) (39), implemented in GCTA software (40). mtCOJO estimates the effect size of a SNP on an outcome trait (e.g., SA) conditioned on exposure trait(s) (e.g., MDD). GWS SNPs for the exposure are used as instruments to estimate the effect of the exposure on the outcome, and this effect is used to perform genome-wide conditioning, yielding conditioned effect sizes and *p*-values for the outcome trait. The EUR-only SA GWAS summary statistics were used as the outcome trait, because mtCOJO requires GWAS summary statistics for the exposure trait, which were derived from EUR ancestry discovery GWAS. To select independent SNPs as instruments, we selected those more than 1 megabase (Mb) apart or with an LD $r^2<0.05$ based on the 1000 Genomes Project Phase 3 EUR reference panel (41). mtCOJO is robust to sample overlap between the GWAS of the exposure and outcome. In this analysis, statistical power to detect genetic associations at individual SNPs was reduced relative to the unconditioned analysis by the additional model parameters, but the genetic correlations using the conditioned summary statistics provide valuable insights into the relevant risk factors for SA over and above those related to MDD and PTSD.

Gene, gene pathway, and tissue enrichment analyses

Enrichment analyses of the GWAS results were performed to probe genes, biological pathways, and tissues implicated in SA, using the multi-ancestry and ancestry admixture-specific GWAS results. *P*-values quantifying the degree of association of genes and gene sets with SA were calculated using MAGMA v1.08 (42), implemented in FUMA v1.3.7 (43). Input SNPs were mapped to 18,627 protein-coding genes. Genome-wide significance was defined at $p = 0.05/18{,}627 = 2.68\text{x}10^{-6}$. Curated gene sets that included at least 10 genes from MSigDB V7.0 were tested for association with SA. Competitive gene-set tests were conducted to correct for gene size, variant density and LD within and between genes. Tissue-set enrichment analyses were also performed using MAGMA implemented in FUMA, to test for enrichment of association signal in genes expressed in 54 tissue types from GTEx V8 (44) (Bonferroni-corrected *p*-value threshold = $9.26\text{x}10^{-4}$).

Drug target enrichment analyses

Additional gene-set enrichment analyses of both the multi-ancestry and EUR GWAS meta-analysis results were performed, restricted to genes targeted by drugs, in order to investigate putative relationships of suicide attempt with specific drug types. These analyses do not identify causal relationships, but may implicate genes relevant to pharmacotherapy. This approach has been described previously (45). Gene-level and gene-set analyses were performed in MAGMA v1.08. Gene boundaries were defined using build 37 reference data from the NCBI, available on the MAGMA website (https://ctg.cncr.nl/software/magma), extended 35kb upstream and 10kb downstream to increase the likelihood of including regulatory regions outside of the transcribed region. Gene-level association statistics were defined as the aggregate of the mean and the lowest variant-level *p*-value within the gene boundary, converted to a *Z*-value. Gene sets were defined comprising the targets of each drug in the Drug-Gene Interaction database DGIdb v.2 (46) and in the Psychoactive Drug Screening Ki Database(47), both downloaded in June 2016 (45). Analyses were performed using competitive gene-set analyses in MAGMA.

Results from the drug-set analysis were then grouped according to the Anatomical Therapeutic Chemical class of the drug (45). Only drug classes containing at least 10 valid drug gene sets within them were analyzed, and drug-class analysis was performed using enrichment curves. All drug gene sets were ranked by their association in the drug-set analysis, and then for a given drug class, an enrichment curve was drawn scoring a "hit" if the drug gene set was within the class, or a "miss" if it was outside of the class. The area under the curve was calculated, and a *p*-value for this calculated as the Wilcoxon Mann-Whitney test comparing drug gene sets within the class to drug gene sets outside of the class (45). A Bonferroni-corrected significance threshold of $p < 5.79 \times 10^{-5}$ and $p < 4.35 \times 10^{-4}$ were used for the drug-set and the drug-class analysis, respectively, accounting for 863 drug-sets and 115 drug classes.

Summary data-based Mendelian randomization

Summary data-based Mendelian randomization (SMR) (v1.03) (48, 49) was applied to detect GWAS signals that co-localize with expression quantitative trait loci (eQTLs), in order to investigate putative causal relationships between SNPs and SA via gene expression. SMR was performed using eQTL summary statistics from the MetaBrain consortium (50), a cortex-derived eQTL dataset consisting of 2,970 EUR-cortex samples. The analysis was conducted using the EUR-only GWAS meta-analysis results, for consistency with the eQTL data. Brain eQTL data from comparable sample sizes in other ancestral groups is not currently available. SMR analysis was limited to transcripts with at least one significant *cis*-eQTL ($p < 5 \times 10^{-8}$) in the dataset (of 8,753 in MetaBrain). The Bonferroni-corrected significance threshold for the SMR analysis was $p < 5.71 \times 10^{-6}$ and the significance threshold for the HEIDI test (HEterogeneity In Dependent Instruments) (51) was $p \geq 0.01$. A non-significant HEIDI test suggests a direct causal role, rather than a pleiotropic effect, of the SA-associated SNPs on gene expression.

Polygenic risk scoring

Polygenic risk scores (PRS) for SA were tested for association with SA versus controls in six target cohorts: PGC MDD, BIP and SCZ (all European ancestry admixtures), CONVERGE (East Asian ancestry admixtures), and Yale-Penn and Grady Trauma Project cohorts (both primarily African ancestry admixtures, located in the United States). The SA GWAS meta-analysis was repeated, excluding each cohort in turn, to create independent discovery datasets. PRS were generated using PRS-CS (51), which uses a Bayesian regression framework to place continuous shrinkage priors on the effect sizes of SNPs in the PRS, adaptive to the strength of their association signal in the discovery GWAS and the LD structure from an external reference

panel. The 1000 Genomes EUR, EAS or AFR reference panels (41) were used to estimate LD between SNPs, as appropriate for each target cohort. PLINK 1.9 (16) was used to weight SNPs by their effect sizes calculated using PRS-CS and sum all SNPs into PRS for each individual in the target cohorts. PRS were tested for association with case versus control status in the target cohort using a logistic regression model including covariates as per the GWAS. The amount of phenotypic variance explained by the PRS (R^2) was calculated on the liability scale, assuming a lifetime prevalence of SA in the general population of 2% (20). The Bonferroni-corrected significance threshold adjusting for six tests was P<0.008.

Results

Significant shared genetic architecture of SA between civilian (ISGC) and military populations (MVP)

The multi-ancestry GWAS included 43,871 cases and 915,025 controls from 22 cohorts (Table 1). Cases were of predominantly European ancestry admixtures (EUR, 81%), with 11% of cases with significant African ancestry admixtures located in the U.S. (AFR), 5% with East Asian ancestry admixtures (EAS), and 3% with Hispanic/Latino ancestry admixtures located in the U.S. (LAT). Case definition was lifetime SA, with ~13% of all cases having died by suicide. Additional information on study characteristics and ascertainment methods is presented in Supplementary Table S1.

Cohorts across ISGC and MVP differed with respect to ascertainment, with ISGC being largely civilian and MVP being military (Table 1a). However, examination of the genetic correlation of EUR GWAS meta-analyses for ISGC and MVP (r_G = 0.81, SE = 0.091, $p = 2.85\text{x}10^{-19}$) indicated consistency of common-variant genetic architecture across these meta-analyses. Results from both fixed and meta-regression models were comparable in the multi-ancestry and EUR GWAS meta-analyses (all GWS effect size correlations >.99) indicating that ancestry and cohort ascertainment were unlikely to confound observed genetic effects (Table 1b).

GWAS meta-analysis of SA across and within ancestries identified 12 GWS loci

The multi-ancestry GWAS meta-analysis identified eight genome-wide significant (GWS) loci ($P<5\text{x}10^{-8}$) (Figure 1). The h^2_{SNP} of SA was significant at 5.7% (SE=0.003, $p = 5.70\text{x}10^{-80}$) on the liability scale assuming an SA population prevalence of 2%. The cov-LDSC intercept was 1.04 (SE=0.01, $p = 1.59\text{x}10^{-5}$) and the attenuation ratio was 0.13 (SE=0.03), indicating that the majority of inflation of GWAS test statistics is likely due to polygenicity (Supplementary Figure S1).

The locus most strongly associated with SA was in an intergenic region on chromosome 7 (index SNP rs62474683, odds ratio (OR) A allele = 1.05 [1.04-1.07], $p = 8.72\text{x}10^{-12}$, frequency in cases = 0.57, frequency in controls = 0.56, Forest plot Figure S2). At other GWS loci, index SNPs were intronic in the *SLC6A9, DRD2, HS6ST3* and *FURIN* genes (Table 2; additional summary data of all GWS loci are provided in Table S1b). On chromosome 3, a GWS SNP localized to the 5' untranslated region of the *NLGN1* gene, though the index SNP lacked neighboring SNPs in LD. There was no evidence of heterogeneity of effects across cohorts for any GWS locus according to I^2 heterogeneity indices (Table S1b). Forest plots for GWS loci are included in Figures S2-S9.

The EUR GWAS meta-analysis h^2_{SNP} was estimated at 7.0% (SE=0.4%) and identified four additional GWS loci (Table 2, Figure S10, Forest plots Figures S11-14), composed of mostly intergenic index SNPs. The nearest genes were *PDE4B, OTX2-AS1, CACNG2*, and one locus was in the major histocompatibility complex (MHC). GWAS meta-analyses in AFR (h^2_{SNP} = 9.8%, SE = 1.8%) and EAS (h^2_{SNP} = 9.8%, SE = 4.5%) produced no GWS loci. The LAT SA h^2_{SNP} (from the MVP GWAS) was estimated at 10.0% (SE = 6.5%). Regional plots of the 12 GWS risk loci across all meta-analyses are presented in Supplementary Figures S15-S26. Mapped genes from the top loci in multi-ancestry and ancestry admixture-specific meta-analyses are presented in Supplementary Tables S3-S6.

Genetic correlations of SA across ancestry GWAS

The genetic correlations of SA across each of the ancestral groupings were attenuated, with estimated r_Gs between 0.064 (SE = 0.574) (EAS with LAT) and 0.997 (SE = .537) (EUR with LAT) Popcorn r_G results can be found in Table S7. Individual cohort GWAS were variably powered to estimate genetic correlation estimates with the other cohorts. LDSC estimates across all individual GWAS are presented in Table S8, though cov-LDSC h^2_{SNP} and Popcorn r_Gs in Table S7 are the preferred sources for statistics involving ancestry admixtures.

SA GWS loci are enriched for brain-expressed genes and overlap with previous genetic associations to known risk factors

Significant signal enrichment was observed in genes expressed in pituitary gland and brain tissues, based on the multi-ancestry GWAS (Table S9). Significant gene expression in brain was also observed in the EUR analysis (Table S10). Tissue-set enrichment analyses and corresponding GTEx gene expression heatmaps for all of the multi- and ancestry admixture-specific GWAS are provided in Tables S9-S12 and Figures S31-S34.

Several GWS genes were identified in MAGMA analyses of the multi-ancestry and EUR meta-analyses (Table S13; enrichment of SA signal with genes and gene sets across all meta-analyses are presented in Supplementary Tables S13-S14). MAGMA gene-based tests of the GWAS meta-analyses, with GWS results, are presented in Manhattan plots and QQ-plots in Figures S27-S30. EAS and AA *p*-value thresholds for inclusion of GWAS variants in follow-up analysis were relaxed to $p < 1x10^{-5}$ and $1x10^{-6}$, respectively, in order to explore gene-based tests of top ancestry-specific GWAS variants. Top genes implicated in the EAS analysis included *C11orf87*, *MYO1C*, and *FAXC*, and top genes implicated in the AFR analysis included *CNTNAP2*, *IGF2R*, *MAN1B1*, and *SLC22A1*. Neither set of genes was significantly associated with any pathway or tissue enrichment.

Gene-set analyses from the multi-ancestry and EUR GWAS identified 519 significant gene sets (31 and 488, respectively), spanning multiple domains, including epigenetics, gene regulation and transcription, cellular response to stress, DNA repair, and immunologic signatures (Table S14). The 31 multi-ancestry gene sets included schizophrenia and autism, containing protein-coding genes such as *FURIN, FES,* and *DRD2,* mapped from GWS loci. Most of the 488 EUR gene sets were due to overlap with a small group of 35 histone-coding genes.

Significant proportions of overlapping genes in GWAS Catalog (52) gene sets were observed for both multi-ancestry and EUR meta-analyses (Figures S35-S36). The 12 GWS loci from the multi-ancestry and EUR GWAS meta-analyses were tagged in several GWAS including cognition, smoking, insomnia, and risky behavior. Six of the 12 risk loci had *p*-values < 0.005 for the "*Suicide or Other Intentional Self-Harm*" analysis in FinnGen. A comprehensive list of results

of SNP associations from the GWAS Catalog is presented in Table S15. Examination of the pheWAS results ($p < 0.005$) across UK Biobank, FinnGen and the GWAS Catalog resulted in the identification of several psychiatric, weight/BMI- and immune-related traits (Table S16).

Two loci implicated specific genes, *FES* and *TIAF1*, that were significantly associated with SA in SMR analyses and passed the HEIDI test. SMR results suggested that SA risk may be mediated by an increased expression of *FES* (previously implicated in cross-ancestry schizophrenia(53)) and decreased expression of *TIAF1* in cortex (Table S17).

Significant overlap of SA GWS loci and targets of antipsychotics and antidepressants

Drug target enrichment results suggested that SA risk is most associated with the targets of antipsychotic and antidepressant drug classes. In the multi-ancestry gene-set analysis of the targets of drug classes defined by their Anatomical Therapeutic Chemical (ATC) classes (45), there was significant enrichment in the targets of four drug classes: *Antipsychotics, Psychoanaleptics*, which includes individually significant *Antidepressants* and its subclass *Other Antidepressants* (Table S18). The class of *Other Antidepressants* includes those not classified as selective serotonin reuptake inhibitors, monoamine oxidase inhibitors or monoamine reuptake inhibitors.

In the EUR ancestry admixture GWAS analysis, there was significant enrichment in the targets of just three drug classes, including *Antipsychotics*, the broad class of *Psycholeptics* (drugs with a calming effect on behavior), and the class *Cytotoxic Antibiotics and Related Substances* (Table S19). Only one drug, the insecticide cyfluthrin, was significantly enriched when grouping genes targeted by individual drugs (from the Drug-Gene Interaction Database DGIdb v.2 and the Psychoactive Drug Screening Ki Database) and this was only observed in the EUR GWAS results (see Tables S20 and S21 for multi-ancestry and EUR results).

Significant genetic correlation of SA with known non-psychiatric risk factors minimally affected after conditioning on MDD and PTSD

The out-of-sample polygenic risk analyses based on the new ISGC+MVP discovery GWAS meta-analysis statistics resulted in higher R^2 estimates than were observed in ISGC1, particularly for AA (maximum variance explained $R^2 = 0.66\%$, $p = 0.01$, and a maximum increase of 146%) and EAS ($R^2 = 0.34\%$, $p = 8.1 \times 10^{-6}$, a 36% increase. EUR maximum variance explained = 1.11%, $p = 6.2 \times 10^{-22}$, a 24% increase from ISGC1 (Table S22). Figure 2 presents a forest plot of the genetic correlations of the EUR GWAS meta-analyses of suicide attempt with several physical and mental health phenotypes, as well as one control phenotype (body mass index, BMI). Significant shared genetic covariation of EUR SA with smoking ($r_G = 0.46$, SE = 0.03, $p = 8.06 \times 10^{-63}$), ADHD ($r_G = 0.55$, SE = 0.04, $p = 2.98 \times 10^{-41}$), risk tolerance ($r_G = 0.32$, SE = 0.02, $p = 1.34 \times 10^{-59}$), and chronic pain ($r_G = .45$, SE = 0.03, $p = 9.50 \times 10^{-50}$) were observed both before and after conditioning on MDD and PTSD. Significant positive genetic correlations of neuroticism, schizophrenia, bipolar disorder, and self-harm ideation with SA ($r_G = 0.45$ SE = 0.03, $p = 1.0 \times 10^{-52}$; $r_G = 0.43$, SE = 0.03, $p = 1.32 \times 10^{-55}$; $r_G = 0.48$, SE = 0.04, $p = 1.81 \times 10^{-37}$; $r_G = 0.83$, SE = 0.06, $p = 1.94 \times 10^{-51}$) did not remain significant after conditioning on both MDD & PTSD.

For completeness of comparison across cohorts and phenotypic subgroups (SA versus SD), genetic correlation estimates for phenotypes are presented in Table S23 using the European ancestry admixture GWAS summary statistics from 1) ISGC + MVP, 2) ISGC only, 3) MVP only, 4) ISGC without suicide death, 5) ISGC suicide death only (the Utah Suicide Study, current N =

4,692 EUR suicide deaths and 20,702 controls), and 6) conditioning on MDD and PTSD for MVP, ISGC, and MVP + ISGC. LDSC jackknife tests of differences between these genetic correlation estimates are presented in Table S24, and more exhaustive comparison of phenome-wide r_G and genetic causal proportion analyses, with the European admixture GWAS meta-analysis, are provided in Table S25. Genetic causal proportion analyses implicated several non-psychiatric genetic risks in EUR SA, including particulate air matter pollution exposure (pm 2.5), smoking exposures, and pulmonary health factors. Risk factors with significant partial genetic causality estimates are presented in Table S25.

Discussion

This study presents the largest GWAS meta-analysis of SA to date, incorporating multiple ancestries and expanding the set of GWS loci from four to 12. Discovery of three of the novel GWS loci, and improved out-of-sample PRS prediction across ancestry, was only possible with the aggregation of all ancestral cohorts. For the first time, we show that implicated genes are highly expressed in brain tissue, enriched in pathways related to gene regulation and transcription, cellular response to stress, DNA repair, and immunologic signatures, and are shared with epidemiological risk factors. Genetic correlation and causal proportion analyses implicate a number of non-psychiatric genetic risks in SA, including pulmonary health factors. We also provide important evidence that a significant proportion of the common variant genetic architecture of SA is shared across large civilian and veteran populations with disparate demographics.

One advantage of combining the ISGC with MVP was the opportunity to examine genetic effects across heterogeneous cohorts. For example, the sample composition and ascertainment across the ISGC is predominantly civilian and international, with a large proportion of females (7). A number of the ISGC samples from the Psychiatric Genomics Consortium cohorts (Table 1) are collected from individuals with major psychiatric disorders, representing a more clinical population. In contrast, the MVP cohorts are predominantly male (8), and all are military veterans ascertained through the U.S. Department of Veterans Affairs (VA) healthcare system. The consistency of SA common variant genetic architecture across EUR MVP and ISGC cohorts indicates that power may be further enhanced by combining future cohorts with differing ascertainments.

As expected, the increase in sample size, and resulting increase in power, led to the identification of several new GWS loci and improved out-of-sample PRS prediction, across ancestries, relative to the previous ISGC-only analyses. The loci identified in this study implicate genes expressed in brain. Genes associated with SA in this study are highly enriched among psychiatric phenotypes and overall health and wellness risk factors for SA. Brain is the predominant tissue enriched for associated genes, and there is also significant enrichment in pituitary gland, consistent with previous association of SA with hypothalamic-pituitary-adrenal system dysregulation (54). In addition, the enrichment of pathways related to epigenetics and gene regulation and transcription suggest that epigenetic modifications, such as DNA methylation, may play a role in modulating the effect of SA-associated genetic variants. However, epigenetic pathways were only enriched in GWAS of European ancestry admixture, pointing to the potential importance and varied impact of epigenetic mechanisms in diverse biological systems that may contribute to SA risk. Pathways enriched in the multi-ancestry GWAS were absent of histone-coding genes, and contained protein-coding genes mapped from GWS loci such as *FURIN, FES,* and *DRD2*. These multi-ancestry pathway results, while harder to interpret, may be more generalizable to the global population.

Drug target enrichment results suggest that SA risk is associated with the targets of antipsychotic and antidepressant drug classes. One explanation may be that psychiatric symptoms associated with SA risk are also associated with these drug targets, though the direction of any association of drugs with risk cannot be assumed and is not directly tested here. The SMR analysis of EUR results implicated *FES* and *TIAF1* in SA. *FES* has been previously implicated in cross-ancestry schizophrenia (53).

Genetic correlations of SA with ADHD, smoking, pain, and risk tolerance remained significant after conditioning SA on both MDD and PTSD, while schizophrenia, bipolar disorder, and neuroticism did not. This suggests a potential role for health factors in SA risk that are both shared with and distinct from psychiatric disorders, as proposed in Mann & Rizk's stress diathesis model (55) of suicidal behavior based on clinical and biological studies. The suicide diathesis includes altered decision-making that may be more pronounced in the context of ADHD and smoking, and may be aggravated by sleep problems. Pain is associated with the stress domain of suicidal behavior, and is also associated with increased access to prescription opioids. Overall, this study leverages genetic data to examine important risk phenotypes that may or may not be present in medical records.

Some limitations of this study should be considered. First, a meta-analysis of such a large number of diverse cohorts, with different assessments of SA, could reduce statistical power by increasing heterogeneity. Our analyses remain still more conservative with the inclusion of age and sex covariates in three of the ISGC cohorts and MVP. However, GWAS of the primary datasets typically produced significant—and high—genetic correlation estimates. GWS loci produced similar effect sizes across cohorts and across fixed and meta-regression models (correlations of EUR and multi-ancestry GWS effect sizes across models exceeded 0.99). Indeed, the apparent consistency of genetic architecture across EUR ISGC and MVP cohorts is important given marked demographic and ascertainment differences.

This study also provides GWAS meta-analyses specific to African and East Asian ancestry admixtures. The lack of GWS loci specific to these SA meta-analyses underscores a strong need for greater ancestral diversity and representation in suicide genetics research. With high variability of sample sizes of individual ISGC and MVP ancestral cohorts (case *n*s ranging from 115 to 9,196) some GWAS yielded h^2 and r_G estimates, while others did not. Variability in r_G indicates that increasing the examination of non-European ancestries in the future will significantly increase the generalizability of the genetic risk signals identified from studies of suicide phenotypes and the portability of polygenic scores. Importantly, broader ancestral representation, particularly from population-dense areas such as India, Western Asia, and the Global South, will be critical for improving the rigor and generalizability of GWAS results in future research.

Implicated genes and established genetic relationships with ADHD, smoking, and risk tolerance help to inform our understanding of biological contributions to risk of SA. From a clinical standpoint, impulsivity, smoking status, and risk-taking behaviors are intuitive co-morbid indicators of suicide risk. Genetic causal proportion analyses implicate these and other health factors—pulmonary and cardiovascular—in risk for SA. And our preliminary comparison of genetic correlations across SA vs. SD GWAS cohorts appears to implicate risk tolerance in the severity of the suicide phenotype. Further study, comparing SD and SA with subjects with suicidal ideation, will allow for a comparison of those who think about suicide and those who act. Importantly, genetic risk for SA, calculated in new independent cohorts using these GWAS summary data, will contribute to a deeper understanding of the clinical implications of genetic

risk for suicide. The future addition of multiple ancestral cohorts is likely to yield continued discovery and increased opportunity for clinical translation.

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Figure Titles and Legends

Figure 1: Manhattan plot of multi-ancestry GWAS meta-analysis of suicide attempt. The *x*-axis shows genomic position and the *y*-axis shows statistical significance as $-\log_{10}$(P value). The horizontal line shows the genome-wide significance threshold ($P<5.0\times10^{-8}$). Labels represent the nearest gene to the index SNP. Regional plots of the eight genome-wide significant loci across ancestries and the four genome-wide significant loci in EUR are presented in Supplementary Figures S3-S14.

Figure 2: Forest plot of genetic correlations of the multi-ancestry GWAS meta-analyses of suicide attempt with physical and mental health phenotypes. The *x*-axis presents genetic correlation values with 95% confidence intervals (CI), and the *y*-axis presents the discovery GWAS for multiple phenotypes. ISGC = International Suicide Genetics Consortium meta-analysis; ISGC + MVP = the primary meta-analysis including GWAS from both ISGC and Million Veterans Program sets of cohorts; ISGC + MVP | MDD & PTSD = the combined GWAS meta-analysis of both cohorts conditioning on major depressive disorder and post-traumatic stress disorder.

Table 1. Summary of GWAS cohorts and primary ancestry admixtures

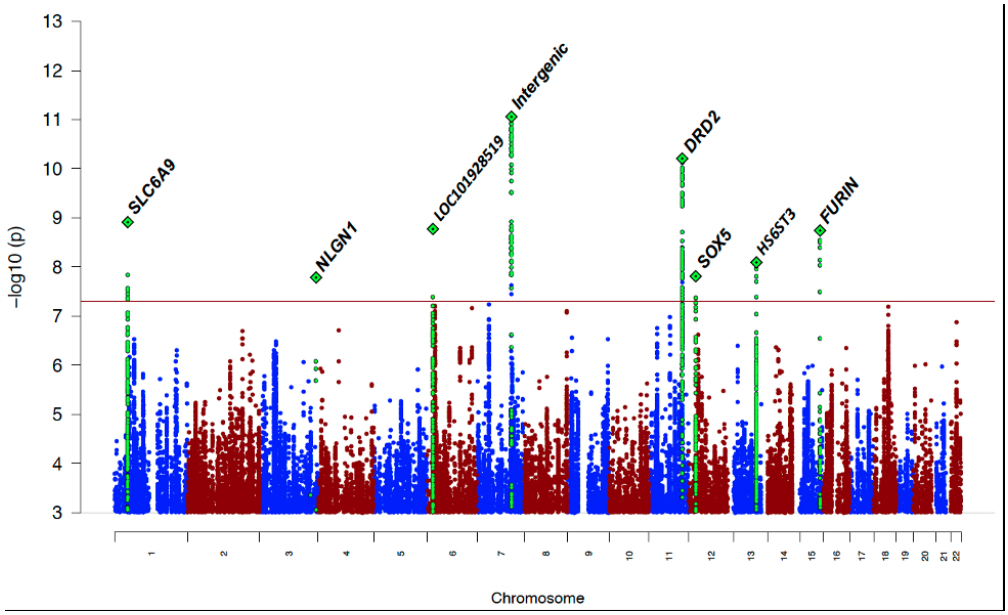
Cohort	Attempt/Death	Ascertainment	Cases	Controls
EUR				
Army STARRS	Attempt	Military	670	10,637
Australian Genetics of Depression Study	Attempt	Psychiatric	2,792	20,193
Columbia University	Attempt & Death	Psychiatric	577	1,233
Genetic Investigation of Suicide and SA (GISS)	Attempt	Psychiatric	660	660
German Borderline Genomics Consortium	Attempt	Psychiatric	481	1,653
iPSYCH	Attempt	Population	7,003	52,227
Janssen	Attempt	Psychiatric	255	1,684
Million Veteran Program	Attempt	Military	9,196	287,370
Psychiatric Genomics Consortium BIP	Attempt	Psychiatric	3,214	17,642
Psychiatric Genomics Consortium ED	Attempt	Psychiatric	170	5,070
Psychiatric Genomics Consortium MDD	Attempt	Psychiatric	1,528	16,626
Psychiatric Genomics Consortium SCZ	Attempt	Psychiatric	1,640	7,112
UK Biobank	Attempt	Population	2,433	334,766
University of Utah	Death	Population	4,692	20,702
Yale-Penn	Attempt	Psychiatric	475	1,817
Total			**35,786**	**779,392**
EAS				
CONVERGE Consortium	Attempt	Psychiatric	1,148	6,515
Kobe University	Death	Population	746	14,049
Million Veteran Program	Attempt	Military	115	4,082
Total			**2,009**	**24,646**
AA				
Grady Trauma Project	Attempt	General medical	669	4,473
Million Veteran Program	Attempt	Military	3,507	74,306
Yale-Penn	Attempt	Psychiatric	629	2,902
Total			**4,805**	**81,681**
LAT				
Million Veteran Program	Attempt	Military	**1,271**	**29,306**
Multi-ancestry Total			**43,871**	**915,025**

Note: EUR = European, EAS = East Asian, AFR = African, LAT = Hispanic/Latino, BIP = bipolar disorder, ED = eating disorders, MDD = major depressive disorder, SCZ = schizophrenia

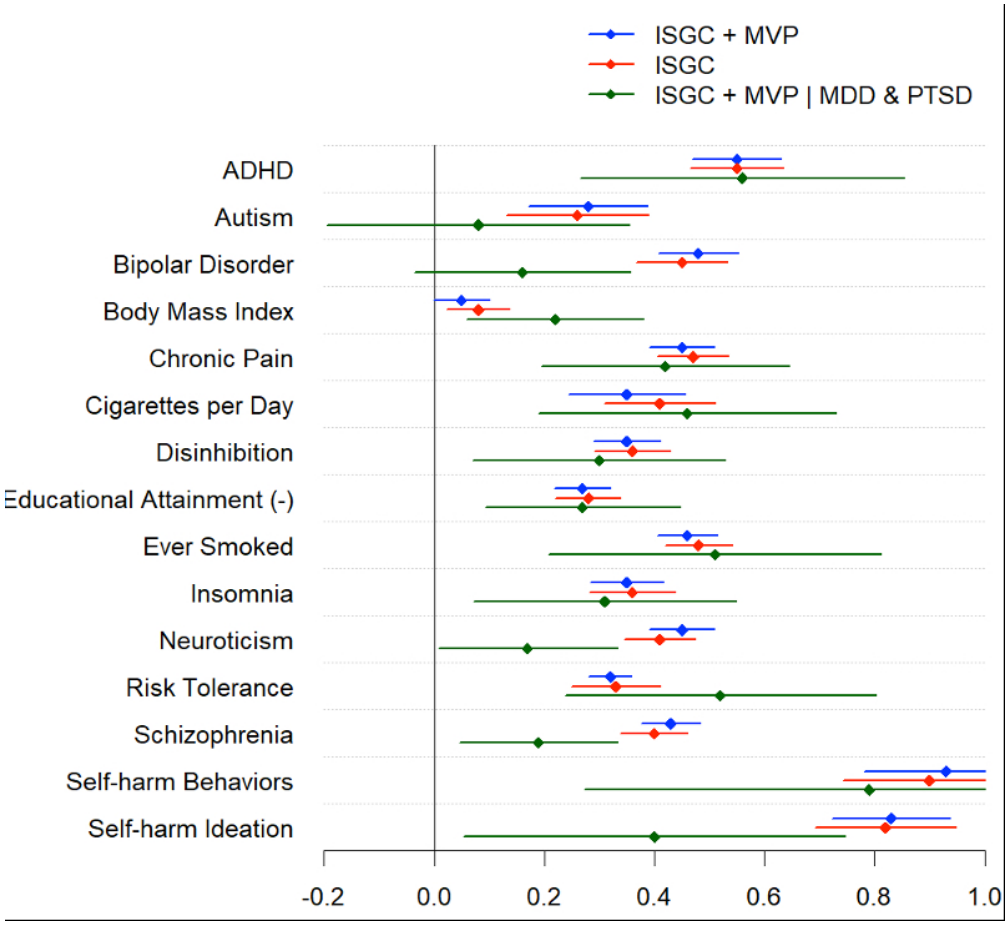
Table 2: Results from meta-analyses of suicide attempt showing the index SNP from each genome-wide significant locus

CHR	Index SNP	BP	Locus Start..Stop	Nearest gene (distance to index SNP in kb)	P	OR	SE	A1	A2	Direction	$N_{Cohorts}$	N_{Total}	N_{Eff}
Multi-Ancestry													
1	rs3791129	44480093	44,462,155..44,497,134	*SLC6A9* (0.0)	1.22E-09	1.055	0.009	G	A	+-+++++--+-+?+++?+??++	18	933,136	158,078
3	rs7649709	173129819	173,113,742..174,012,162	*NLGN1* (0.0)	2.32E-08	1.054	0.010	A	C	++++++-+++-+?++-++++++	21	954,890	164,921
6	rs62404522	19307114	19,068,774..19,180,711	*LOC101928519* (-76.4)	1.68E-09	1.067	0.011	C	T	+--+++--++++-++-+-++++	22	956,659	166,924
7	rs62474683	115020725	114,763,653..114,871,409	*LINC01392* (-149.3)	8.72E-12	1.054	0.008	A	G	+-++++-++++++++-++-+++	22	958,896	167,455
11	rs7131627	113299829	113,280,327..113,346,120	*DRD2* (0.0)	6.2E-11	1.053	0.008	G	A	+++++--+++++++++?-++++	21	944,101	164,620
12	rs17485141	24213634	23,682,438..24,715,425	*SOX5* (0.0)	1.54E-08	1.049	0.009	C	T	+++-++++++++-+++++++++	22	958,896	167,455
13	rs9525171	96908223	96,742,361..97,491,816	*HS6ST3* (0.0)	8.07E-09	1.044	0.008	C	G	+-+++++--+-+-+++++-+++	22	958,896	167,455
15	rs17514846	91416550	91,411,818..91,426,687	*FURIN* (0.0)	1.81E-09	1.048	0.008	C	A	++++++++++-+-+++?+?+++	20	938,959	162,145
EUR													
1	rs2503185	66461401	66,258,193..66,840,262	*PDE4B* (0.0)	3.42E-08	1.047	0.008	A	G	++++++---+++-++	15	815,178	136,860
6	rs35869525	26946687	29,640,168..30,152,231	--MHC--	2.18E-08	1.089	0.015	C	T	+?-+-+++-++++++	14	803,626	134,461
14	rs850261	57346423	57,278,724..57,398,026	*OTX2-AS1* (0.0)	1.37E-08	1.049	0.008	A	G	++-+-++++++++++	15	815,178	136,860
22	rs2284000	37053338	36,956,904..37,099,797	*CACNG2* (0.0)	1.98E-08	1.055	0.010	C	G	++++++-+-+-+?++	14	812,886	135,108

Note: CHR = chromosome, SNP = single nucleotide polymorphism, BP = GRCh37 base pair position, kb = kilobases, OR = odds ratio, SE = standard error, A1 = tested allele, A2 = other allele, EUR = European, $N_{Cohorts}$ = number of cohorts included, N_{Total} = Total cases and controls, N_{Eff} = total effective sample size, MHC = major histocompatibility complex.



165x100mm (150 x 150 DPI)



135x124mm (150 x 150 DPI)