RUNNING HEAD: Genome-wide association study of suicide death

Genome-wide association study of suicide death: Results from a first wave of Utah completed suicide data (*N* = 1,420)

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Abstract

Background: Heritability of suicide risk is estimated at 43%, thus genetic risk likely plays an important role in completion of suicide. Previous genetic research has focused primarily on suicidal behavior or ideation rather than actual completed suicide. And previous genome-wide association studies of completion of suicide have been very small due to the difficulty in obtaining suicide sample data, and have been unable to identify genome-wide significant variants, likely due to power limitations. This study presents results from the first wave of a large Utah sample of completed suicides, and represent the most statistically powerful sample of completed suicide to date.

Methods: Tissue samples from 1321 decedents were collected via partnership with the Utah Office of the Medical Examiner and genotyped using the Illumina Infinium PsychArray platform. Bioconductor package RaMWAS (A.S.) was used on post-QC hard call data (271,894 common variants) to conduct GWAS. Because the sample is from Utah, the authors were able to conduct a relatively direct comparison with 1000 Genomes controls also from Utah (CEU), as well as European controls (EUR). The first GWAS with Utah CEU controls (n of only 99) was followed by a second GWAS with EUR controls (n = 503) with and without CEU included in the control sample.

Results: Analyses identified 8 SNPs in 6 genes associated with the completion of suicide. Six SNPs met genome-wide significance. Two of these variant hits were replicated using EUR controls not including the CEU sample, though the case sample was the same in both analyses. Subsequent QC steps (linkage disequilibrium analysis and EUR GWAS replication) further substantiated significant results implicating cytochrome P450 genes.

Conclusions: This GWAS and partial replication of findings across control samples, using hard call genotype data, represents a significant step toward understanding the genetic architecture of suicide. These are late-breaking results, and in January this group will follow up with analyses using the full 2 waves (N = 4800 cases), a larger control group, and imputed data to ~11 million variants. Analyses to date implicate cytochrome P450 sites involved in metabolism of arachidonic acid and related inflammatory mediators. Results implicate inflammation in suicide risk, and add to a growing body of evidence that lung function may be tied to suicide.

Introduction

Ranked as the tenth leading cause of death across all age groups in the United States[1] and annually accounting for over 800,000 deaths worldwide,[2] suicide is a critical public health issue. Suicide constitutes a global phenomenon, with 78% of suicide deaths occurring in low-income and middle-income countries in 2015.[2] In the United States, the suicide rate has been increasing on a consistent basis.[3] This has been the case across age groups, with an alarming rate increase for adolescents. A brief survey of U.S. pediatric and young adult vital statistics since 1999 demonstrates that over fifteen years the suicide rate per 100,000 steadily increased from 6.8 to 14.7 and from 11.9 to 19.2 for the age groups of 10-14 and 15-19 year-olds, respectively.[4-8] Today, suicide is the second leading cause of death for all persons aged 15-24 years old in the United States.[8] Given the prevalence and rising trend of suicide occurrence, suicide prevention is a top research priority.[9]

Current clinical strategies for assessing and mitigating the risk for death by suicide do not include empirical models of genetic risk. However, multiple lines of research point to genetic influences. Twin and adoption studies have been consistent with a significant genetic component to suicide, with a higher risk present in monozygotic twins than in dizygotic twins,[13-16] and higher risk of suicide evident in biological relatives than a proband's adoptive family.[10-12] Analyses of family pedigree data have identified families possessing an increased risk of suicide, with visualization of effects conferred across generations.[17,18] Heritability of suicide is estimated at 43% from combined meta-analyses.[19-21] Given the relevance of genetic risk factors to suicide, mapping the genetic architecture of suicide will allow us to better inform precision medicine efforts and to prevent suicide from occurring.

Genome wide association studies (GWAS) expose regions of the genome potentially indicative of increased risk. Statistical power is paramount for these types of analyses, and at the same time, the collection of satisfactorily large samples of completed suicide genetic data have posed myriad ethical, logistical, and financial complexities. For these reasons, previous GWAS have largely focused on the

phenotypes of suicidal ideation or attempts, rather than actual completed suicide.[20,22,23] These GWAS have also generally been selected samples (major depressive disorder cases, for example) rather than population-based samples.

Suicidal behavior phenotypes present in diverse ways with varying levels of severity.[24,25] In contrast, the phenotypic precision of a completed suicide sample (suicide yes/no) skirts some confounds inherent in the use of suicidal behavior phenotypes. Previous research has demonstrated that suicidal behavior of higher lethality possesses a stronger correlation to neurophysiological perturbations than do behaviors of lower lethality.[26] Consequently, completed suicide may possess a more well-defined genetic profile than the suicidal behaviors previously studied.

As the genetics of completed suicide are closely examined, it will be further informative to directly compare with the genetics of suicidal ideation and behaviors. For example, comparison with very large suicidal behavior datasets in future analyses (e.g., the great strides by the PGC) will likely be highly informative. Overall, GWAS of both behaviors and actual suicide have high utility for developing actionable results to improve clinical screening and prevent suicide deaths.

Only two previous studies have utilized GWAS to specifically investigate death by suicide. Galfalvy et al. (2013) were able to conduct a GWAS on 68 subjects who died by suicide and 31 individuals who died suddenly by other means.[27] In a follow-up study, 260 cases of suicide attempt along with 317 cases of death by suicide were analyzed relative to 1233 controls.[28] These studies did not result in any genome-wide significant findings, but do point to potential candidate variants for further examination. Limitations cited in both of these studies relate to their small sample sizes, which were unlikely to produce signal capable of surpassing the strict multiple testing corrections.[27,28] It is probable that many variants confer small effect on sucide,[17,22,29,30] and clearly much larger sample sizes are indicated. This paper is the most well-powered GWAS of completed suicide to date.

Methods

Samples

GWAS data were comprised of 1,321 case samples and 503 control samples from 1000 Genomes (99 CEU and 404 EUR). In collaboration with the Utah Office of Medical Examiner (OME) DNA samples from >5000 persons who died by suicide were obtained, 1,321 of whom have been genotyped in a first wave of data processing. Utah state code specifies consistent procedures for determining cause of death, including toxicology workups and psychological autopsies; thus, the level of certainty regarding suicide vs. accidental death for these samples is quite high.[31] These decedent data are linked with records in the Utah Population Database (UPDB), which houses data on over 8 million individuals sourced from vital statistic and demographic records, and electronic health records from the two major hospital systems in the State of Utah.[32] The Utah population is primarily Northern European in ancestry and comprises a genetically homogeneous group with very low inbreeding across generations (statistically comparable to the rest of the United States).[33-35]

Samples from the 1000 Genomes Project[36] were included as the control samples for this study. The CEU population (99 samples) in the 1000 Genomes data set best matched our case samples as it included only Utah residents with northern and western European ancestry. Thus, we use CEU population as our primary control set of samples, with European superpopulation (EUR) including CEU as the secondary. Genotype data for the control samples were downloaded from the 1000 Genomes Project public repository.

Genotyping

Suicide samples were genotyped using Illumina Infinium PsychArray platform measuring 593,260 SNPs. DNA was extracted from blood using the highly reliable Qiagen Autopure LS automated DNA extractor (www.qiagen.com). Identifying information from cases with DNA was linked to data within the UPDB's secure computer servers; identifying data was then stripped before providing data to the research team. SNPs with ambiguous strand orientation, SNPs with >5% missing calls, and SNPs failing Hardy-Weinberg equilibrium ($p < 0.001$) were excluded. In both case and control data sets, SNPs with minor allele frequency below 0.01 were also excluded. PLINK[37] was used to perform quality control of the data and to combine case and control samples. The GWAS analysis was performed on around 272,000 hardcall SNPs measured for both datasets and passing the quality control.

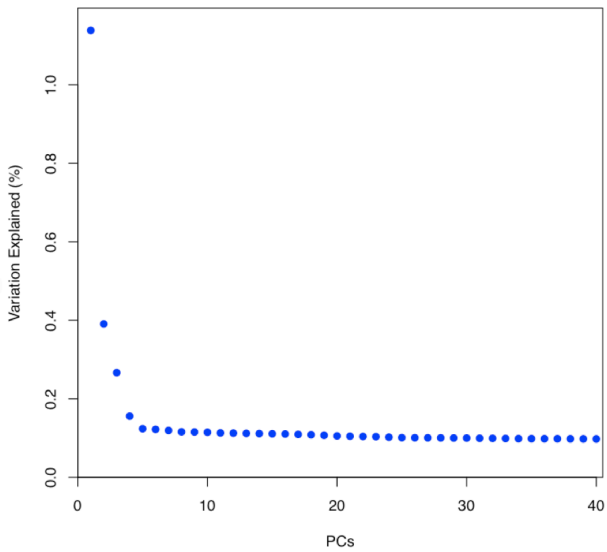

Figure 1. Principal component analysis of suicide sample and CEU controls.

Analysis

Analyses were conducted with three control populations – CEU, the EUR superpopulation which includes CEU, and EUR without CEU. The principal component analysis (PCA) of suicide decedents and CEU controls (Figure 1) indicated three significant PCs, most likely caused by variations in sample ancestry. The PCA with EUR indicated seven significant PCs.

The PCA and GWAS were performed using RaMWAS[38], a Bioconductor package which comprises a complete toolset GWAS and methylome-wide association studies. RaMWAS includes functions for principal component analysis for capturing batch effects and detection of outliers, association analysis while correcting for top PCs and covariates, creation of QQ-plots and Manhattan plots, and annotation of significant findings. The association analyses included top PCs as covariates to correct for population stratification and batch effects.

Results

GWAS of Suicide and CEU

Principal component analysis was performed to control for ancestry variation within the suicide case samples. In Figure 2, quantile-quantile plots demonstrate the reduction in inflation/deflation of SNP significance ($\lambda \rightarrow 1$) as PCs are accounted for.

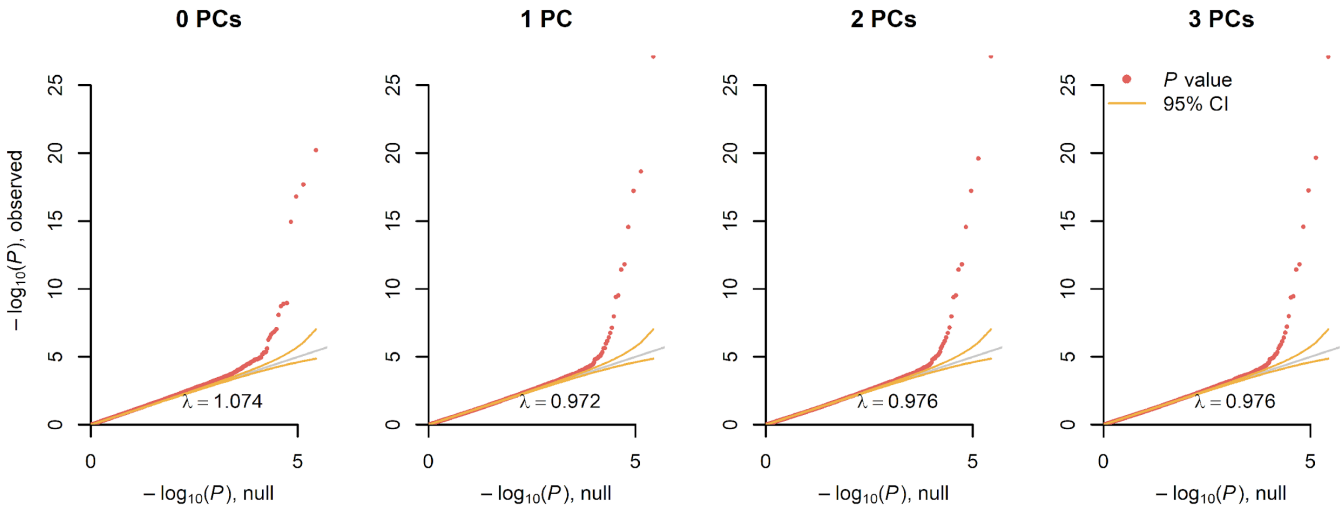

Figure 2. Quantile-quantile plots of SNP *P* values following consideration of principle components.

GWAS of Utah Completed Suicides with European 1000 Genomes Controls

Association analyses were performed on 271,894 hard called SNPs, passing QC and shared between controls and suicide cases. A GWAS with the entire European 1000 Genomes control population (EUR; n = 503) resulted in 13 variants significantly associated with completed suicide at a genome-wide significance threshold ($\alpha < .05$). A Manhattan plot of results is presented in Figure 3. Annotated variants in Figure 3 are those that remain significant when including only the CEU samples. Of the genome-wide significant SNPs, two are *CYP4F12* variants (rs609290 and rs609636). Table 1 contains a complete list of significant SNPs and their associated genes.

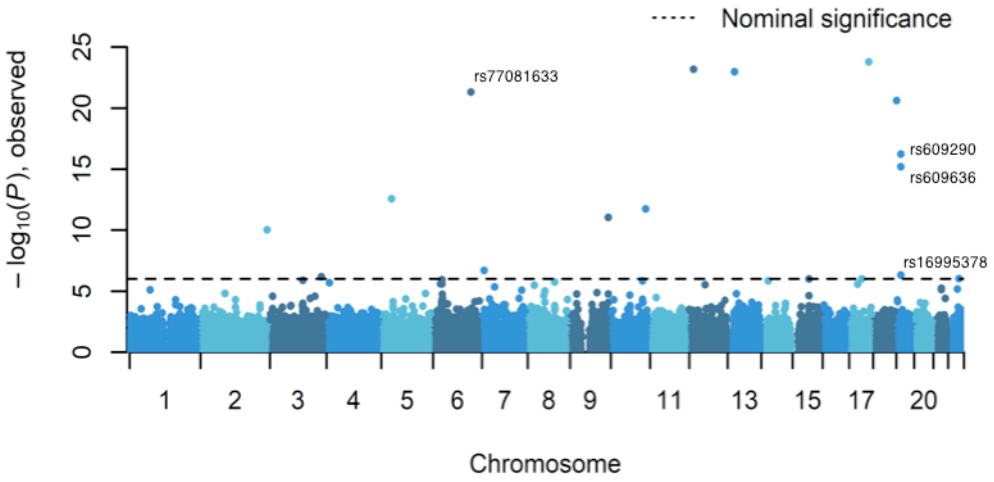

Figure 3. Manhattan plot of GWAS *P* values in suicides vs. EUR super population controls.

Table 1. *P* values, associated genes, and literature review of top SNPs.

SNP	Chr.	Gene	P Value	Gene Description	Clinical Implications
rs7570971	2	*RAB3GAP1*	8.10×10^{-28}	RAB3 GTPase activating protein catalytic subunit 1	Neurodevelopment, Warburg micro syndrome
rs609290**	19	*CYP4F12*	5.63×10^{-18}	Cytochrome P450 Family 4 Subfamily F Member 12	Pro-inflammatory lipid metabolism
rs609636**	19	*CYP4F12*	2.60×10^{-15}	Cytochrome P450 Family 4 Subfamily F Member 12	Pro-inflammatory lipid metabolism
rs6705916	2	*TMEM163*	3.50×10^{-10}	Transmembrane protein 163	Cation binding and Transport
rs10496731	2	*ACMSD*	4.16×10^{-10}	Aminocarboxymuconate semialdehyde decarboxylase	NAD synthesis, Neurodegenerative Disorders, Excitotoxicity
rs77081633*	6	*BCLAF1*	1.01×10^{-08}	BCL2 associated transcription factor 1	Apoptosis regulator, Giant axonal neuropathy, Emery-Dreifuss muscular dystrophy
rs3844435	17	*LOC105371553*	6.15×10^{-08}	Uncharacterized ncRNA	Unknown
rs16995378*	19	*CYP4F12*	1.65×10^{-07}	Cytochrome P450 Family 4 Subfamily F Member 12	Pro-inflammatory lipid metabolism

Note: SNP = single nucleotide polymorphism, Chr. = chromosome
*SNP identified in both CEU and complete EUR GWAS
**SNP identified across all analyses: CEU, EUR GWAS with and without exclusion of CEU

CYP4F12 associations were observed across two follow-up GWAS dividing EUR into CEU (Utah-specific controls; n = 99) and non-CEU EUR controls (n = 404 controls). In the CEU analysis, 11 SNPs attained genome-wide significant association with completed suicide (8 in known regions, annotated in Figure 4) after Bonferroni correction ($\alpha < 0.05$), with no inflation of test statistics ($\lambda = 0.976$). Several variants are located on chromosomes 2 and 19 (Figure 4). LocusZoom[39] was used to plot LD in surrounding regions and evidence of linkage disequilibrium in variants immediately flanking top SNPs was identified (Figures S1 and S2). GWAS excluding the CEU control subsample (Figure 5) produced 9 significant associations, two of which were the *CYP4F12* variants identified in the previous GWAS. Variants that were significant across all control sample GWAS are denoted with ** in Table 1 and annotated in Figure 5.

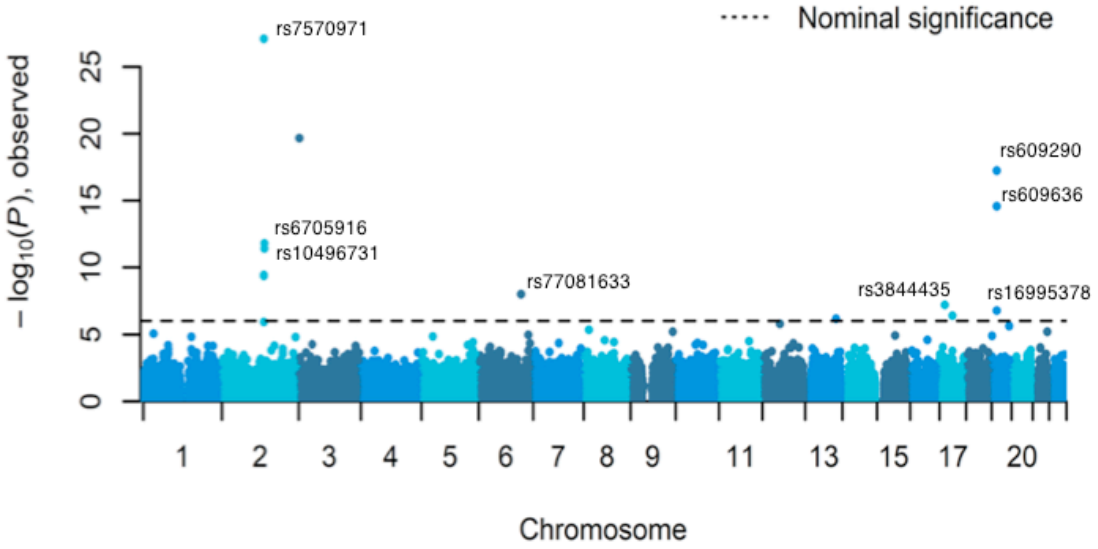

Figure 4. Manhattan plot of GWAS *P* values in suicides vs. CEU controls.

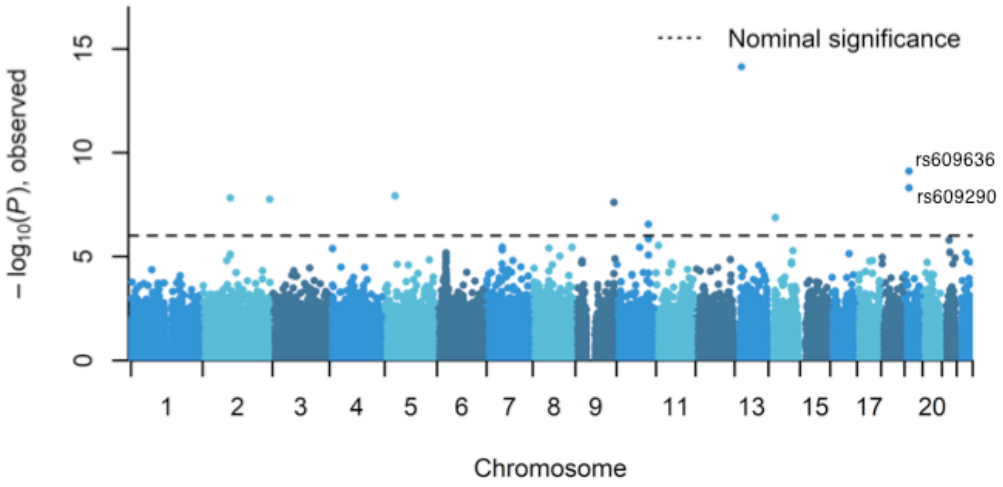

Figure 5. Manhattan plot of GWAS *P* values in suicides vs. EUR controls without CEU (Utah) included. Annotated variants were genome-wide significant across CEU and EUR control groups.

Discussion

This first wave of Utah data analysis identified eight SNPs in six genes reaching nominal significance for association with completed suicide. Six SNPs met genome-wide significance, and two of these variant associations replicated using separate control samples (rs609290 and rs609636). This GWAS of completed suicide resulted in statistically significant biomarkers for risk including variants on cytochrome P450 sites. These variants, along with the other nominally significant hits, are overwhelmingly expressed in frontal cortex, implicate fatty acid metabolism, are targets for psychotropic drugs including carbamazepine, and have been implicated in previous molecular studies of severe depression.[40,41]

The binary and definitive nature of our phenotype, in contrast with previous studies of suicidal behavior phenotypes, adds a level of potency to these findings. Although sample sizes are modest, genome-wide significant findings with the entire EUR super population of the 1000 Genomes Project, both excluding and including CEU data, bolsters these results. While larger than the CEU population, the EUR is considerably more genetically heterogeneous, thus making the partial replication more notable. Identification of linkage disequilibrium in the polymorphisms surrounding significant SNPs supports a biological link to suicide completion.

Of special interest are 3 SNPs identified in both CEU and EUR GWAS and found within a single gene, *CYP4F12*, which is part of the cytochrome P450 superfamily. A majority of drug metabolism occurs through the cytochrome P450 pathway, including metabolism of SSRIs and antipsychotics.[42-44] Previous literature has found that polymorphisms in cytochrome P450 genes result in isoenzymes with modulating effects on metabolism of these pharmaceutics. This finding generated considerable excitement in psychiatry, and it was proposed that these metabolic disparities could in turn modulate response to psychopharmacological treatment outcomes,[45,46] and consequently impact proclivity toward suicidal behavior. However, when investigators failed to predict treatment response via cytochrome P450 genotyping,[47,48] much of the attention on this pathway as a mediator of psychiatric treatment response waned. And yet, previous research of this paradigm has so far only investigated a small fraction of the genes which comprise the cytochrome P450 superfamily.

CYP4F12 is known to metabolize endogenous pro-inflammatory lipids, particularly arachidonic acid, prostaglandins, and leukotriene B4.[49,50] Exogenous antihistamines such as ebastine and terfenadine have also been identified as substrates for *CYP4F12* activity, thus solidifying the gene's role as an inflammatory mediator.[51,52] In the mise en scène of literature linking inflammation and depressive disorders,[53,54] the association of an inflammatory mediator such as *CYP4F12* with suicide may be a compelling reason to reinvigorate cytochrome P450 research as it relates to psychiatric illness and treatment outcomes.

Finally, one SNP whose association with suicide was observed in both CEU and EUR GWAS is located on *BCLAF1*, an important regulator of apoptosis,[55] a well-known pathological feature of many neurodegenerative disorders.[56] Mice with reduced *BCLAF1* expression have been observed to exhibit deficiencies in lung development and function.[57] Given that asthma,[58] altitude,[59] and chronic obstructive pulmonary disease[60] have all be associated with increased suicide risk, it has been proposed that hypoxia may increase risk for suicide by way of chronic metabolic stress.[61]

99 of the participants in the Thousand Genomes Project were from Utah and thus represented a compelling, albeit small control group. While our first wave of case data exceeds the power of previous studies, these previous studies have been very small, and our analysis only included a small number of controls. Our choice to report data from the 1000 Genomes Project, until an appropriate larger control sample is identified, avoids spurious conclusions due to ancestry but also limits our power.[36]

Replication across control samples in this early-stage study is promising, but it must be emphasized that this replication is partial and that replication across case samples has not yet been attempted. The prolepsis of these results also bears repeating; this preprint is most valuable as a predecessor and justifier of what is to come, as our sample size grows in the coming months.

Future Directions

This group is currently conducting follow-up GWAS with imputed data and larger numbers of newly available decedent samples. The sample size of genotyped cases will reach 4800 by January of 2018.

PCAs have demonstrated that samples collected in UK are ancestrally comparable to the Utah data and future analyses will leverage these much larger control groups.

Imputation to ~11 million variants will allow for examination of novel segments of the genome, and we will additionally work with the PGC to integrate datasets to further inform the genomic architecture of suicide. As independent replication is of great interest, we appeal to readers for secondary analyses, replication, meta-analysis, and pathway research from interested collaborators. Summary statistics for our GWAS are available from the corresponding author and will also be housed at the Psychiatric Genomics Lab website, pglab.org.

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Contribution
AD planned the analyses and oversaw the project. AS, AD, and JA conducted the analyses. JA, JS, AD, and AS drafted the first cut. All authors contributed edits and feedback to this final drafted pre-print.