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Suicidality GWAS in mood disorders

Genome-wide association study of suicidal behaviour severity in mood disorders

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ABSTRACT

Objective: Suicide is a major public health problem and it has a prominent genetic component. We performed a genome-wide association study (GWAS) of suicidal behaviour severity.

Methods: Suicide behaviour severity was assessed within the Schedules for Clinical Assessment in Neuropsychiatry in our mood disorder sample (N=3506) for the GWAS. We also performed polygenic risk score analyses to explore genetic sharing between suicidal behaviour severity and a number of phenotypes, including bipolar disorder, major depressive disorder, alcoholism, post-traumatic stress disorder, impulsivity, insomnia, educational attainment, loneliness, maltreatment, and amygdala volume.

Results: We did not detect genome-wide significant findings at the single-marker or gene level. We report a number of suggestive single-marker and gene-based findings. Our polygenic risk score analyses did not yield significant findings with these phenotypes.

Conclusions: Larger sample sizes are required to detect moderate effects.

INTRODUCTION

Suicide claims over 800,000 lives worldwide each year, and 3%–5% of adults attempt suicide at least once in their lifetime, making it a serious public health issue (Kessler et al. 1999; Weissman et al. 1999; Szadoczky et al. 2000; WHO 2014). Whilst the mortality rates of cancers, HIV, diabetes, and cardiovascular diseases have been declining steadily, rates of suicide have declined much more slowly over the years (Statcan 2017). Lifetime prevalence of suicide attempt is over 30% in both bipolar disorder and major depressive disorder; thus it is important to study risk factors of suicide in mood disorders (Dong et al. 2019a; Dong et al. 2019b). Suicidal thinking (ideation) and behaviour/attempt (SIB) are very complex and are likely affected by many variables. Family history appears to be an important risk factor for suicide (Turecki and Brent 2016).

Family, twin, and adoption studies support a prominent genetic component for SIB (Tidemalm et al. 2011; Zai et al. 2012a). Heritability of suicide attempt/completion is estimated to be at 43% (95% confidence interval: 27-60%)(McGuffin et al. 2010), with genetic component for suicidality at least partly independent of that for the underlying psychiatric disorders (Zai et al. 2012a). A number of promising genetic markers have arisen from genetic association studies of SIB (Zai et al. 2012a; Sokolowski et al. 2014). Our group reported in a meta-analysis that the Brain-derived Neurotrophic Factor (*BDNF*) rs6265 Met66 allele was associated with suicide attempt (Zai et al. 2012b). Evidence for its receptor Neurotrophic Receptor Tyrosine Kinase 2 (*NTRK2*) has also been growing (Pulay and Rethelyi 2016). Meta-analyses have supported the roles of the serotonin transporter gene (*SLC6A4*) promoter polymorphism (HTTLPR) (Li and He 2007), FK506 binding protein 5 (*FKBP5*) rs3800373 and rs1360780, Corticotropin-releasing Hormone Receptor 1 (*CRHR1*) rs2664008, rs1724425, and rs878886 (De la Cruz-Cano 2017), Catechol-O-methyltransferase (*COMT*) rs4680 (Sadeghiyeh et al. 2017), tryptophan hydroxylase 1 (*TPH1*) rs1800532 and rs1799913. In addition, the Acid Phosphatase (*ACP1*) rs300774 identified in a suicide attempt genome-wide association studies (GWAS) (Willour et al. 2012) was replicated recently in two samples (Pawlak et al. 2016; Li et al. 2017). Among GWAS of SIB conducted (Bani-Fatemi et al. 2016; Coon et al. 2018; Kimbrel et al. 2018; Brick et al. 2019), more recent GWASs of suicide attempt have identified additional significant markers. These include rs4809706 in the iPSYCH Danish population birth cohort study (Erlangsen et al. 2018), centrosomal protein 162 rs12524136 from US military cohorts (Stein et al. 2017), olfactory receptor family 7 subfamily G member 2 rs12972618 for high suicide attempt risk in a patient sample from the Vanderbilt University Medical Center (Ruderfer et al. 2018), zinc finger CCHC-type containing 7 rs62535711 from the UK Biobank (UKB) (Strawbridge et al.

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2019), Cortixin Domain Containing 1 rs72740082 from the Yale-Penn study on genetics of drug and alcohol dependence (Levey et al. 2019), and interacts with SUPT6H, CTD assembly factor 1 rs138689899 from the Psychiatric Genomics Consortium (Mullins et al. 2019). Aside from the replication of *ACP1* rs300774, other GWAS findings have not been successfully replicated. Though earlier candidate genes findings in *BDNF* and *NTRK2* have not been implicated in suicidality GWAS, neurodevelopment in the form of gene-based analysis or polygenic risk scores calculated from neurodevelopmental genes has been implicated in SIB (Pulay and Rethelyi 2016; Sokolowski et al. 2016).

While most GWASs focused on the binary phenotype of suicide attempt, few have looked into quantitative measures of suicidality in GWASs. Examining the continuous variable of severity of SIB may offer more statistical power to detect an effect size than suicide attempt (Bhandari et al. 2002; Altman and Royston 2006). We previously published a GWAS of suicidal behaviour severity in bipolar disorder (BD) patients (Zai et al. 2015) and suicidality scores in major depressive disorder patients (Schosser et al. 2011). Here, we provide an updated GWAS of suicide severity and SCAN suicidality scores across bipolar disorder and major depressive disorder (MDD) patients where suicidal behaviour severity was assessed using the same instrument.

METHODS

Samples

The characteristics of the samples included in this study have been described previously (Scott et al. 2009; Schosser et al. ; Zai et al. 2015) and are shown in Table 1. BD patients (Sample CA2, N=428) at CAMH, and an independent sample of 483 BD cases (IOP) from the Institute of Psychiatry, Psychology & Neuroscience in London, UK. The participants were of self-reported European ancestry and were at least 18 years old when they were enrolled through advertisements in hospitals, family physicians' offices, clinics, or patient support groups. Their BD diagnoses according to DSM-IV and ICD-10 criteria were confirmed using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN). Exclusion criteria included a diagnosis of intravenous drug dependency, reported intravenous drug use, the presence of mood incongruent psychotic symptoms, manic episodes only in conjunction with or as a result of alcohol, substance abuse, substance dependence, medical illnesses, or medication. Their suicidality was assessed using the SCAN Suicide Severity item (6.011) as follows: 0 for non-suicidal, 1 for deliberately considering suicide or self-harm, 2 for injuring self or making an attempt without serious

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consequences; 3 for serious self-harm or attempt; 4 for an attempt at suicide designed to be lethal. We also derived SCAN Suicidality (SSU) scores as described previously (Schosser et al. 2011). SSU a combination of the SCAN Suicide Severity item (6.011) and the SCAN Loathing of Life item (6.012), where individuals who scored 1 or above in the Suicide Severity item would have the SSU score the same as the Suicide Severity item score plus three, and those who scored 0 would have the SSU score the same as the Loathing of Life score. These two measures are highly correlated within each of our three samples, with R of more than 0.90. The distributions of the Suicide Severity item and SSU scores are shown in Supplementary Figure S1. This work has been approved by the institutional review boards, and adheres to the ethical standards of the national and institutional committees on human experimentation as well as the Declaration of Helsinki in 1975 (revised in 2008).

MDD patients came from the RADIANT (RAD) studies DeCC and DeNt, with suicidal behaviour severity was assessed during a depressive episode. The DeCC (Depression Case Control) sample consists of 1346 cases (69.3% women) of recurrent depression fulfilling DSM-IV and/or ICD-10 criteria of at least moderate severity ascertained from three UK clinical sites (London, Cardiff, and Birmingham) (Cohen-Woods et al. 2009), with mean age of onset of 22.9 years (SD 10.8 years). Subjects were identified from psychiatric clinics, hospitals, general medical practices, and from volunteers responding to media advertisements. The DeNt (Depression Network) affected sibling pair linkage study (Farmer et al. 2004; McGuffin et al. 2005) consists of recurrent depression cases with moderate or more severe symptoms. Participants were enrolled from the same three UK sites as DeCC, plus four additional sites in Europe (Aarhus, Bonn, Dublin, and Lausanne) and one in the USA (St. Louis). Only the 898 probands from the families with available GWAS data were included in the present study. A further sample of 163 recurrent depression cases was included in the present study; these participants were enrolled in Bonn and Lausanne, using the same protocol as the DeNt study. Overall, all RADIANT participants fulfilled DSM-IV and/or ICD-10 criteria for moderate or more severe depression (Schosser et al. 2011). The RADIANT study coordinators were trained by AEF, thus ensuring consistency in the clinical data being collected. Exclusion criteria included a history or family history of schizophrenia or bipolar disorder, mood-incongruent psychosis, or mood symptoms that were related to alcohol or substance use. Each participant in the RADIANT study had his/her most severe episode of depression collected retrospectively using SCAN, which included the same two questions on loathing of life (6.012) and suicide severity (6.011) mentioned above (Figure S1).

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Most of the genotyping on the Samples CA2 and IOP was performed with the IlluminaSentrix Human Hap550 Beadchip (Illumina Inc., San Diego, CA, USA) at Illumina Inc. (San Diego, CA, USA), with 290 CA2 participants genotyped at the Genome Quebec facility (Montreal, Quebec, Canada). Genotyping of the RAD sample was performed with the Illumina HumanHap610-Quad BeadChip at the Centre National de Génotypage, France.

Quality control procedures were applied to individual SNP data in the RAD sample as described previously (Lewis et al. 2010; Schosser et al. 2011). Individuals were excluded if they had more than 2% missing genotypes, mismatch between genotype-assigned and reported sex, abnormal heterozygosity, relatedness (up to 2nd-degree) with any other participants, or non-European ancestry as determined using principal components analysis with reference data from HapMap CEU, JPT, CHB, YRI, and GIH populations with EIGENSTRAT (Price et al. 2006). SNPs were excluded if they had less than 1% minor allele frequency, genotype frequencies deviating significantly from Hardy-Weinberg equilibrium ($p < 1e-6$). Principal component analysis was performed again after QC procedures, and three ancestry-informative principal components, as determined by the Scree plot, were used as covariates in the analysis. The data set of 4465 participants (2905 being depression cases) genotyped on 464,759 SNPs went through whole-genome imputation described below.

We applied comparable quality control measures for the CA2 and IOP samples separately using PLINK (Purcell et al. 2007) and R (R Development Core Team (2008). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL <http://www.R-project.org>). Briefly, participants were excluded if they had more than 5% missing genotypes, mismatch between genotype-assigned sex and reported sex, abnormal heterozygosity, relatedness to any other participants. SNPs of which genotypes deviated significantly from Hardy-Weinberg Equilibrium ($p < 1e-6$) were excluded from subsequent analyses, as were those with less than 1% minor allele frequency or more than 5% missing genotypes. We ran a principal component analysis of the genotypes to retain the discrete cluster that corresponded to European ancestry. Principal component analysis was performed again after QC procedures, and two ancestry-informative principal components, as determined by the Scree plot, were used as covariates in the analysis. After quality control, 508,883 SNPs for 313 CA2 bipolar disorder cases, and 515,024 SNPs for 406 IOP bipolar disorder cases went through whole-genome imputation.

Whole-genome imputation was performed using Minimac4 implemented on the Michigan Imputation Server with haplotype phasing using Eagle v2.4, 1000 Genomes Phase 3 data (for CA2 and IOP) or

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Haplotype Reference Consortium data (for RAD) as the reference panel, and minimum R-squared threshold of 0.3 (Das et al. 2016), with an additional filtering for SNPs with R-Squared value of at least 0.6. Whole-genome imputation and quality control yielded 8,701,619 SNPs for the 313 CA2 cases, 8,724,065 SNPs for the 406 IOP cases, and 7,472,311 SNPs for the 2,787 RAD cases.

Our total sample size of 3,506 has enough power to detect 3% of the variance of suicide severity that is accounted for by the single-nucleotide polymorphisms (SNPs; $\alpha=5e-8$, minor allele frequency 1%, additive model)(Gauderman and Morrison 2006).

For 6,737,359 SNPs that are included in all three samples, we conducted analyses of suicide severity scores and suicidality scores separately for the three sample sets using PLINK, with covariates including sex, age, and ancestry-informative principal components for all three sample sets, as well as the sub-studies within the RAD sample set. Then we performed a meta-analysis using sample size, direction of effect, and p value to derive an overall p-value for each marker (METAL software (Willer et al. 2010)). The quantile-quantile plots and the Manhattan plots were graphed in R, with the significance threshold for single-SNP analysis set at $5e-8$.

In addition to single-marker analysis, we conducted gene-based analysis for each sample separately and then meta-analyze the results across the samples using MAGMA (de Leeuw et al. 2015), with the significance threshold for 18,601 genes set at $2.7e-6$. We further obtained standardized polygenic risk scores for each sample without p-value thresholding (that is, p-value threshold of 1) using PRSice (Euesden et al. 2015), and ran linear regression analyses in R with age, sex, ancestry-informative principal components, and sub-studies as covariates. Then we ran meta-analyses using the effect estimates and standard errors from the three samples using the R *metafor* package. Previous studies reported associations between suicidality and a number of phenotypes, including impulsivity (Anestis et al. 2014), alcoholism (Darvishi et al. 2015), educational attainment (Dong et al. 2019a), insomnia (Dong et al. 2019b), loneliness (Dong et al. 2018), post-traumatic stress disorder (Krysinaka and Lester 2010), and amygdala volume (Wang et al. 2019). We used the summary statistics for 10 such phenotypes to calculate the polygenic risk scores: alcohol dependence (for Europeans (Walters et al. 2018)), bipolar disorder (Stahl et al. 2019), impulsivity [F1.50.BIS_NonP.csv – top 10K SNPs for BIS from 23&Me], insomnia (from UKB (Jansen et al. 2019)), post-traumatic stress disorder (PTSD, Freeze 1 (Duncan et al. 2018)), major depressive disorder (PGC-MDD2 excluding 23&Me data (Wray et al. 2018)), educational attainment (Lee et al. 2018), childhood maltreatment (Freeze 2 with UKB data (Dalvie et al. 2020)), loneliness (Gao et al. 2017), and amygdala volume (ENIGMA2 (Hibar et al. 2015)).

RESULTS

We found no genome-wide significant results in our single-marker analysis (Figure 1). The suggestive findings ($p < 1e-5$) for Suicide Severity are shown in Table 2, Supplementary Table S1, and Supplementary Figure S2, and those for SCAN Suicidality are shown in Table 2, Supplementary Table S2, and Supplementary Figure S3. We also included genes for which they are shown to be expression quantitative trait loci according to the Genotype Tissue Expression (GTEx; (Battle et al. 2017)) portal in Supplementary Tables S1 and S2. Among the top findings for SCAN Suicide Severity (6.011), a number of correlated SNPs are located in the sperm tail PG-rich repeat containing 2 (*STPG2*) gene at chromosomal location 4q23 and their genotypes are associated with *STPG2* gene expression according to the GTEx portal. Another set of correlated SNPs are located in the mitochondrial calcium uniporter regulator 1 (*MCUR1*) gene at 6p23 and their genotypes are associated with *MCUR1* gene expression (GTEx). A third set of SNPs is located in the Rho GTPase activating protein 26 (*ARHGAP26*) gene at 5q31.3. SNPs in *STPG2* and *MCUR1* are also among the top findings for SSU scores. There are also correlated SNPs in the USP6 N-terminal like (*USP6NL*) gene at 10p14 that are also associated with *USP6NL* gene expression (GTEx) and others upstream of the Thrombospondin Type Laminin G Domain And EAR Repeats (*TSPEAR*) gene at 21q22.3 that are also associated with *TSPEAR* gene expression (GTEx).

The gene-based analysis yielded a number of suggestive findings ($p < 1e-4$; Supplementary Figures S2 and S3; genes with $p < 1e-4$ are shown in Supplementary Tables S3 and S4), including the GDNF family receptor alpha 1 (*GFRA1*, at 10q25.3), *STPG2* genes for both suicide severity and suicidality score, as well as the angiotensin I converting enzyme (*ACE*, at 17q23.3) and IQ motif containing with AAA domain 1 (*IQCA1*, at 2q37.3) genes for suicide severity alone, and the Deoxyribonuclease 2 Beta (*DNASE2B* at 1p31.1) gene for suicidality score only. Polygenic risk score analyses did not yield significant findings for either suicide severity or suicidality score (Supplementary Table S5). Finally, we looked at the top genome-wide significant findings from recent GWASs of suicide attempt (Supplementary Table S6); we did not find these previously reported genome-wide significant SNPs to be nominally significant in our GWAS ($p > 0.05$).

DISCUSSION

We report here a GWAS of suicidal behaviour severity in approximately 3,500 mood disorder patients using the same instrument for assessing suicidality. The lack of statistically significant findings is likely the result of insufficient sample size to detect small effect sizes for a highly complex phenotype. The

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mechanisms of the suggestive associations are unclear. The single-SNP and gene-based findings both point to the role of the *STPG2* gene. The *STPG2* gene has been implicated in autistic spectrum disorder (Connolly et al. 2017) and neurodevelopmental disorders (Asadollahi et al. 2017). This finding supports the previously reported associations of neurodevelopment genes in suicidality (Zai et al. 2012b; Pulay and Rethelyi 2016; Sokolowski et al. 2016). In addition, a rare variant in *STPG2* (rs1727284 G allele) was associated with alcohol consumption in a recent meta-analysis (Brazel et al. 2019), and another variant (rs11933823 C allele) was associated with adventurousness (Karlsson Linner et al. 2019). The *MCUR1* gene has been associated with intelligence (Savage et al. 2018). Abnormal splicing of the *ARHGAP26* gene has been reported in schizophrenia (Glatt et al. 2011). The *USP6NL* gene has been associated with Alzheimer's disease (Jun et al. 2017). The finding with *GFRA1* was previously reported for GWAS of suicidality in the MDD sub-sample of our current study (Schosser et al. 2011). Increased *IQCA1* gene expression has been reported in Alzheimer's disease patients compared to healthy controls (Brooks and Mias 2019). As for the suggestive gene-level finding with *ACE*, a number of early genetic studies yielded mixed findings (Hong et al. 2002; Hishimoto et al. 2006; Fudalej et al. 2009; Sparks et al. 2009; Zai et al. 2012a). Since there is growing evidence of angiotensin-receptor blockers as a possible risk factor for suicide (OR = 3.52) (Callreus et al. 2007; Mamdani et al. 2019), future suicide genetic studies that control for medications such as ACE blockers may help clarify some of the mixed findings. Future work may include examination of pharmacogenetics of suicide in the context of ACE inhibitor/ blocker medications.

Our findings need to be considered with caution due to a number of limitations. Our sample size is likely insufficient to detect effects at single-marker, gene, or polygenic risk score levels. For polygenic risk score analysis of impulsivity, we only have the top 10,000 SNPs available, so we may not be getting the full picture of the genetic sharing between impulsivity and suicidality from this analysis. Our phenotypes of suicide severity and suicidality score pertain to the most severe depressive episode for each patient; and might have missed some lifetime suicidal ideation or suicide attempts that did not occur in the most severe depressive episodes. Thus, our preliminary findings encourage additional studies on the role of neurodevelopment and medication use in suicidality.

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STATEMENT OF INTEREST

JLK: has received honoraria from Novartis, Roche and Eli Lilly corporations, and is an unpaid member of the scientific advisory board of AssureRx Corp. JLK & CCZ: authors in patents on suicide markers. CF,

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AKT, EK, GMH, RSZ, VdL, JS, NK, CML, GB, AF, PM, IJ, LJ, and JBV reported no conflict of interest related to this manuscript.

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Table 1. Demographic information for the 3 sample sets of European ancestry included in the current study.

Sample	CA2 (Canada)	IOP (UK)	RAD (RADIANT)
Diagnosis	Bipolar Disorder	Bipolar Disorder	Major Depressive Disorder
Total N	313	406	2787
% Female (N)	0.60 (188)	0.67 (270)	0.71 (1973)
Age (mean \pm SD)	43.67 \pm 12.41	47.32 \pm 11.04	44.89 \pm 12.11
% Ever \geq 5 alcoholic drinks almost every day (N)	0.36 (112)	0.32 (128)	N/A
SCAN Suicide Severity (6.011) (N (%))			
0	112 (36%)	119 (29%)	1188 (43%)
1	108 (34%)	162 (40%)	1134 (41%)
2	52 (17%)	59 (15%)	249 (9%)
3	13 (4%)	16 (4%)	64 (2%)
4	28 (9%)	50 (12%)	152 (5%)
SCAN Suicidality (SSU) Score (N(%))			
0	36 (12%)	52 (13%)	373 (13%)
1	22 (7%)	11 (3%)	133 (5%)
2	21 (7%)	23 (5%)	347 (13%)
3	33 (10%)	33 (8%)	335 (12%)
4	108 (34%)	162 (40%)	1134 (41%)
5	52 (17%)	59 (15%)	249 (9%)
6	13 (4%)	16 (4%)	64 (2%)
7	28 (9%)	50 (12%)	152 (5%)

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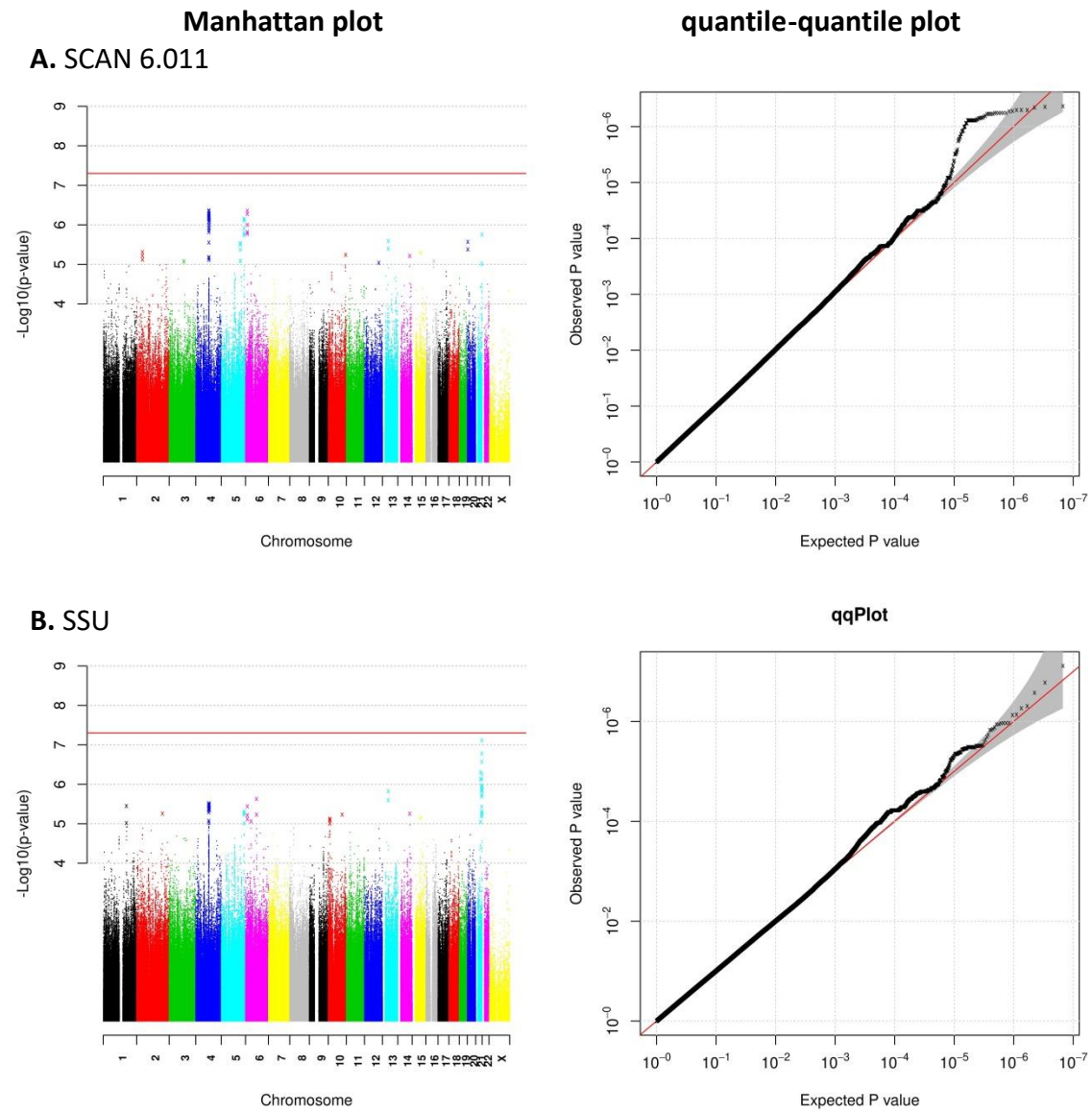


Figure 1. Manhattan and quantile-quantile plots for the analysis of (A) the SCAN Suicide Severity (6.011) and (B) SCAN Suicidality SSU scores.

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Table 2. Summary of results from our genome-wide association study of SCAN Suicide Severity (6.011) and SCAN Suicidality (SSU) scores. The upper panel shows the top five SNPs for each phenotype, and the bottom panel shows the top suggestive gene-based findings for these phenotypes.

Phenotype	SNP	Gene	eQTL*	CHR	BP	Zscore	P	Direction
6.011	rs9654143	<i>STPG2</i>	<i>STPG2/</i> <i>RAP1GDS1</i>	4	98689152	-5.054	4.33E-07	---
6.011	rs9647614		<i>MCUR1</i>	6	13843271	4.892	9.98E-07	+++
6.011	rs61246028		<i>LINC00400</i>	13	43756955	4.703	2.57E-06	+++
6.011	rs79099900	<i>RASSF2</i>		20	4804781	-4.692	2.71E-06	---
6.011	rs74961332	<i>POFUT2</i>	<i>POFUT2</i>	21	46702822	4.779	1.76E-06	++
SSU	rs9654143	<i>STPG2</i>	<i>STPG2/</i> <i>RAP1GDS1</i>	4	98689152	-5.054	4.33E-07	---
SSU	rs9647614			6	13843271	4.892	9.98E-07	+++
SSU	rs61246028		<i>LINC00400</i>	13	43756955	4.703	2.57E-06	+++
SSU	rs77916371	<i>PTPN21</i>		14	88969691	-4.522	6.13E-06	---
SSU	rs11071625	<i>LOC107984782</i>		15	61967903	-4.562	5.07E-06	---

*according to GTEx portal.

Phenotype	GENE_NAME	GENE	NSNPS	CHR	N	ZSTAT	P	NPERM
6.011	<i>ACE</i>	1636	61	17	3506	3.7384	9.26E-05	1000
6.011	<i>GFRA1</i>	2674	666	10	3506	4.1658	1.55E-05	1000
6.011	<i>STPG2</i>	285555	1887	4	3506	3.9027	4.76E-05	1000
6.011	<i>IQCA1</i>	79781	373	2	3506	4.1165	1.92E-05	1000
SSU	<i>GFRA1</i>	2674	666	10	3506	3.9624	3.71E-05	1000
SSU	<i>STPG2</i>	285555	1887	4	3506	3.8058	7.07E-05	1000
SSU	<i>DNASE2B</i>	58511	92	1	3506	3.7905	7.52E-05	1000

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