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A genome-wide association study of suicide severity scores in bipolar disorder

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ABSTRACT

Background: Suicide claims one million lives worldwide annually, making it a serious public health concern. The risk for suicidal behaviour can be partly explained by genetic factors, as suggested by twin and family studies (reviewed in (Zai et al. 2012)). Recently, genome-wide association studies (GWASs) of suicide attempt on large samples of bipolar disorder (BD) patients from multiple sites have identified a number of novel candidate genes. GWASs of suicide behaviour severity, from suicidal ideation to serious suicide attempt, have not been reported for BD.

Methods: We conducted a GWAS of suicide behaviour severity in three independent BD samples:212 small nuclear families with BD probands from Toronto, Canada, 428 BD cases from Toronto, and 483 BD cases from the UK. We carried out imputation with 1000 Genome Project data as reference using IMPUTE2. Quality control and data analysis was conducted using PLINK and R. We conducted the quantitative analyses of suicide behaviour severity in the three samples separately, and derived an overall significance by a meta-analysis using the METAL software.

Results: We did not find genome-wide significant association of any tested markers in any of the BD samples, but we found a number of suggestive associations, including regions on chromosomes 8 and 10 ($p < 1e\text{-}5$).

Conclusions: Our GWAS findings suggest that likely many gene variants of small effects contribute collectively to the risk for suicidal behaviour severity in BD. Larger independent replications are required to strengthen the findings from the GWAS presented here.

1. Introduction

Suicide claims 1 million lives each year worldwide, and for each completed suicide, there are twenty suicide attempts, making it an important public health issue. Over 90% of suicide victims have at least one psychiatric diagnosis, including bipolar disorder (BD) (Mann, 2002), where as much as 8% of BD followed for up to 40

Abbreviations: BD, Bipolar disorder; STEP-BD, Systematic Treatment Enhancement Program for Bipolar Disorder; WTCCC, Wellcome Trust Case Control Consortium; TGEN, Translational Genomics Research Institute; GAIN, Genetic Association Information Network; UCL, University College London; STAR*D, Sequenced Treatment Alternatives to Relieve Depression; SCAN, Schedule for Clinical Assessment in Neuropsychiatry; GWAS, genome-wide association study.

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years committed suicide (Angst et al., 2002; Nordentoft et al., 2011).

Suicide has a prominent genetic component (reviewed in (Zai et al., 2012)). Suicide attempts tend to occur more often within families (Brent et al., 2002; Johnson et al., 1998). Greater concordance was observed between monozygotic twins than between dizygotic twins (Roy and Segal, 2001; Statham et al., 1998). The concordant phenotype includes both completed and attempted suicides (Roy et al., 1995). A review of twin studies estimated the heritability of suicidal behaviour to be up to 55% (Voracek and Loibl, 2007).

A number of linkage studies have been conducted on suicide starting with Zubenko and coworkers (Zubenko et al., 2004). Their findings on the short arm of chromosome 2 were later replicated in 162 BD families (Willour et al., 2007), and more recently confirmed in the regional linkage study meta-analysis of 2p12 (Butler et al., 2010). Recent technological advances have permitted the high-throughput genotyping of hundreds of thousands of single-nucleotide polymorphisms across the genome. While no genome-wide significant findings (at significance levels of less than 5×10^{-8}) have been reported to date, a number of suggestive findings have emerged (Perroud et al., 2011; Schosser et al., 2011). Recently, a genome-wide association study (GWAS) was reported on samples of 2698 BD patients of which 1201 had a previous suicide attempt. After meta-analysis of markers with $p < 1 \times 10^{-3}$ from their discovery sample (GAIN, TGEN, German) with their replication BD sample (STEP-BD, WTCCC, UCL), the most significantly associated marker was rs300774 in an intergenic region at chromosomal region 2p25, which contains the SH3YL1, *ACP1*, and *FAM150B* genes. The association finding was supported by post-mortem prefrontal cortical gene expression analysis, where suicide completers were found to have significantly higher *ACP1* expression than non-suicide victims (Willour et al., 2012). The strongest association signal from another report of a GWAS of suicide attempt on the BD (STEP-BD, WTCCC, UCL) came from the intergenic chromosome 10 marker rs1466846; this finding was not replicated in the replication sample (GAIN, TGEN, German) (Perlis et al., 2010). Part of the reason for both lack of a strong association signal and robust replication could be that the samples are underpowered for analysis due to dichotomizing of the suicide attempt as the outcome variable. A GWAS on suicidality scores, which are derived from the Schedule for Clinical Assessment in Neuropsychiatry (SCAN) interview, was conducted with a major depression sample from the RADIANT study (Schosser et al., 2011). The suicidality score captures suicide severity from suicide ideation to attempt. The most significant findings from the RADIANT sample failed to replicate in the German replication sample.

In the present study, to address the issue of power with the dichotomous variable, we carried out a similar GWAS using the quantitative variable of suicide severity in three samples of BD patients.

2. Methods

The characteristics of the samples included in this study have been described previously (Scott et al., 2009; Xu et al., 2014). For the first sample, two hundred and twelve small nuclear families (Sample CA1) were recruited at the Centre for Addiction and Mental Health (CAMH) in Toronto, Canada. Suicidality was assessed using the semi-structured interview for DSM-IV, with the Suicide Specifier Score: 0 for non-suicidal, 1 for having thoughts of own death, 2 for having suicidal ideation, 3 for having planned suicide, and 4 having attempted suicide (Supplementary Fig. 1a). We also recruited a second independent sample consisting of 428 BD patients (Sample CA2) at CAMH, and a third sample of 483 BD cases (Sample IOP) from the Institute of Psychiatry in London, UK. Details on the CA2 and IOP samples have been described previously (Scott et al., 2009). The participants were at least 18 years of age at time of enrolment and European ancestry by self-report. They were recruited through advertisements in family doctors' offices, clinics, hospitals, and patient support groups. Their diagnoses for BD according to DSM-IV and ICD-10 criteria were confirmed using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN). Exclusion criteria included a diagnosed or reported dependence on intravenous drugs, the presence of mood incongruent psychotic features, and the presence of manic episodes that are only concurrent with or as a result of alcohol, substance abuse or dependence, medication, or medical conditions. Their suicidality was assessed using the Suicide Severity item within the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) as follows: 0 for non-suicidal, 1 for deliberately considering suicide or self-harm, 2 for injuring self or making an attempt without serious consequences; 3 for serious self-harm or attempt; 4 for an attempt at suicide designed to be lethal (Supplementary Fig. 1b and c). More details on sample characteristics are shown in Table 1. All procedures contributing to this work abide by the Declaration of Helsinki in 1975 (revised in 2008), and the ethical standards of the national and institutional committees on human experimentation.

Sample CA1 was genotyped with the Affymetrix 5.0 arrays (Affymetrix, Santa Clara, CA, USA) at the London Regional Genomics Centre (London, Ontario, Canada). Samples CA2 and IOP were genotyped with the IlluminaSentrix Human Hap550 Beadchip (Illumina Inc., San Diego, CA, USA) mostly at Illumina Inc. (San Diego, CA, USA), with 290 subjects from the CA2 sample being genotyped at the Genome Quebec facility (Montreal, Quebec, Canada).

We applied the same quality control measures for all three samples separately using PLINK (Purcell et al., 2007) and R (R Development Core Team, 2008). Briefly, individuals with less than 95% of the markers genotyped were removed, and markers that were less than 95% genotyped or had a minor allele frequency of less than 5% were excluded. Cryptic relatedness was assessed and one individual of each pair of related individuals (defined as pairs with PI^HAT>0.05) was removed if there is more missing

Table 1
Demographic information on the bipolar disorder samples included in the genome-wide association study of suicide behaviour severity in the present study.

Bipolar Disorder Sample	CA1	CA2	IOP
Site	CAMH	CAMH	IOP
Number of Cases	189	308	462
Genotyping platform	Affymetrix SNP 5.0	Illumina Sentrix Human Hap550 Beadchip	Illumina Sentrix Human Hap550 Beadchip
Suicide Measure	SCID Suicide Specifier	SCAN 6.011	SCAN 6.011
Number of SNPs before imputation	209824	438625	439032
Average Age (Std Dev)	33.27 ± 9.48	43.06 ± 12.41	47.84 ± 11.29
Sex Ratio (% Male)	63%	40%	33%