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Brief report

Association analysis between suicidal behaviour and candidate genes of bipolar disorder and schizophrenia

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ABSTRACT

Background: The present study investigated associations between the strongest joint genetic risk variants for bipolar disorder (BD) and schizophrenia (SCZ) and a history of suicide attempt in patients with BD, SCZ and related psychiatric disorders.
Methods: A history of suicide attempt was assessed in a sample of 1009 patients with BD, SCZ and related psychosis spectrum disorders, and associations with the joint genetic risk variants for BD and SCZ (rs2239547 (*ITIH3*/4-region), rs10994359 (*ANK3*) and rs4765905 (*CACNA1C*)) were investigated. Previously reported susceptibility loci for suicide attempt in BD were also investigated. Associations were tested by logistic regression with Bonferroni correction for multiple testing.
Results: The risk allele in rs2239547 (*ITIH3*/4-region) was significantly associated with a history of suicide attempt ($p=0.01$) after multiple testing correction (p threshold <0.017). The previous suicide attempt susceptibility loci were only nominally associated, but had the same direction of risk in the replication sample (sign test, $p=0.02$).
Limitations: Relatively small sample size and retrospective clinical assessment.
Conclusions: We detected a novel association between suicide attempt and the *ITIH3*/4-region in a combined group of patients with BD, SCZ and related psychosis spectrum disorders. This may be useful in understanding molecular mechanisms of suicidal behaviour in severe mental disorders, although replication is warranted.

1. Introduction

Patients with bipolar disorder (BD) and schizophrenia (SCZ) have several overlapping clinical characteristics including suicide that causes excess mortality with a large impact on early death (Nordentoft et al., 2013). Both BD and SCZ are understood in relation to diagnostic spectrums (Ivleva et al., 2008), and there is a growing body of evidence supporting that clinical and genetic risk factors are shared (Hamshere et al., 2011; Lichtenstein et al., 2009). BD, SCZ and suicidal behaviour (SB) are all influenced by genetic factors (Baldessarini and Hennen, 2004; Roy et al., 1999). Nevertheless, it remains unclear whether the association between SB and these disorders is due to shared genetic risk factors (Brent and Mann, 2005; Goodwin and Jamison, 2007; Qin et al., 2002; Schizophrenia Psychiatric GWAS Consortium, 2011), thus warranting studies investigating if BD and SCZ risk genes also predispose to SB (Baldessarini and Hennen, 2004; McGuffin et al., 2010).

Large genome-wide association studies (GWAS) on BD and SCZ have provided promising results on common genetic risk factors (Andreassen et al., 2013; Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011; Schizophrenia Psychiatric GWAS Consortium, 2011). Despite these recent findings, each genetic locus has a small effect size, and much unexplained variance

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('missing heritability') remains. SB may be a sub-phenotype that reflects more genetic homogeneity beyond diagnostic categories of neuropsychiatric disorders (Craddock and Sklar, 2009). A molecular genetic relationship between SB and BD and SCZ may lead to new insight in biological pathways of the disorders, thereby forming a basis for improved prediction and thus prevention.

To our knowledge, only two studies have performed GWAS on SB in patients with BD (Perlis et al., 2010; Willour et al., 2012) and none in patients with SCZ. Several candidate susceptibility loci were identified but no common genetic variants of any large effect. The low odds ratios and the lack of significant findings suggest a high level of polygenicity in the genetic risk of SB in BD.

Recently, a large joint GWAS of BD and SCZ identified three significant risk loci for BD and SCZ, located in *ANK*3, *CACNA*1*C* and the *ITIH*3/4-region (Schizophrenia Psychiatric GWAS Consortium, 2011). *CACNA*1*C* and *ANK*3 have previously been found to be associated with both SCZ and BD (Athanasiu et al., 2010; Ferreira et al., 2008; Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011). Since SB is prevalent in SCZ and BD, these disease risk genes may also be associated with SB in these disorders.

This study uses a sample of patients with BD, SCZ and related psychosis spectrum disorders to (1) test for association between joint BD and SCZ risk variant SNPs and SB (Schizophrenia Psychiatric GWAS Consortium, 2011) testing the hypothesis that these SNPs are associated to higher risk of patient suicide attempt, and (2) replicate SB susceptibility loci SNPs previously identified in BD cases (Perlis et al., 2010; Willour et al., 2012) testing the hypothesis that these susceptibility loci SNPs for SB in BD would be replicated in our combined sample, since a high fraction of the genetic risk of BD, SCZ and related psychosis spectrum disorders is shared (Andreassen et al., 2013).

2. Methods

2.1. Sample

A total number of 1009 psychiatric patients (526 BD cases, 338 SCZ cases and 145 cases with related psychosis spectrum disorders (MIXED)) were included (Table 1). The terms BD, SCZ and MIXED are used to define these groups. All were of European, the majority Norwegian, ethnicity recruited from several Norwegian hospitals and out-patient clinics. All patients met DSM-IV criteria for their respective diagnosis using the Structured Clinical Interview for DSM-IV (SCID-I) (American Psychiatric Association, 1994; First et al., 1997).

2.2. Ethics

Written, informed consent was obtained from all participants. The Regional Committees for Research Ethics and the Norwegian Data Inspectorate approved the study.

2.3. Clinical assessment

Diagnostic evaluation was performed by trained senior psychiatrists and psychologists. All patients participated in semi-structured interviews with trained clinicians, which included life-time history of at least one suicide attempt. Based on these data the patients were grouped dichotomously; suicide attempters and non-attempters. Clinical risk factors of SB in the sample have been described in detail previously (Finseth et al., 2012; Mork et al., 2012).

2.4. Genotyping and imputation

The sample was genotyped using the Affymetrix Genome-Wide Human SNP array 6.0 (Affymetrix Inc, Santa Clara, CA, USA). Quality control was performed using PLINK (Purcell et al., 2007). Individuals with genotyping below 95% were excluded, as were SNPs with minor allele frequency (MAF) < 1%, low yield (< 95%) and deviation from Hardy–Weinberg equilibrium ($p < 0.001$).

Candidate SNPs and SB susceptibility SNPs not present on the Affymetrix Genome-Wide Human SNP array 6.0 were imputed with MACH that applies a Markov Chain Haplotyping algorithm (Li et al., 2010), using the European samples available in the Phase I release of the 1000 genomes project (http://www.sph.umich.edu/csg/abecasis/MACH/download/1000G-PhaseI-Interim.html) after quality control. For further description on genotyping and imputation procedures, see Supplementary Material.

2.5. Choice of joint BD and SCZ risk variant SNPs

In the primary analysis, the three top SNP hits from the largest joint GWAS on BD and SCZ to date were included (Schizophrenia Psychiatric GWAS Consortium, 2011) as defined by the conservative inclusion criterion of *p*-values meeting genome-wide significance (cut-off $< 5 \times 10^{-8}$) (Table 2). In the secondary analysis,

Table 1
Demographics of suicide attempters vs. non-attempters.

	Total		Suicide attempters		Non-attempters		χ^2/z	df	*p*-value
	N	%	N	%	N	%			
Total	1009	100	338	33.5	671	66.5			
Diagnostic group[a]							1.43	2	0.489
BD[b]	526	52.1	185	35.2	341	64.8			
SCZ[c]	338	33.5	106	31.4	232	68.6			
MIXED[d]	145	14.4	47	32.4	98	67.6			
Gender[a]							12.5	1	< 0.0001
Female	518	48.7	200	38.6	318	61.4			
Male	491	51.3	138	28.1	353	71.9			
Duration of illness, years (mean ± SD)[e]			16.8	± 12.5	12.8	± 11.7	−5.4		< 0.0001

Abbreviations: df—degrees of freedom, SD—standard deviation.

[a] Chi-square test.
[b] BD I: 304 cases, BD II: 197 cases and BD NOS: 25 cases.
[c] Schizophrenia: 258 cases, Schizophreniform disorder: 24 cases and Schizoaffective disorder: 56 cases.
[d] Related BD and SCZ spectrum disorders: Other psychosis: 94 cases and Major depressive disorder: 51 cases.
[e] Mann–Whitney test.