



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.

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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 *ANK3*, *CACNA1C* and the *ITIH3/4*-region (Schizophrenia Psychiatric GWAS Consortium, 2011). *CACNA1C* and *ANK3* have previously been found to be associated with both SCZ and BD (Athanasu 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 \pm SD) ^e			16.8	\pm 12.5	12.8	\pm 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.

Table 2
Association between schizophrenia/bipolar disorder top hit risk variant SNPs and suicide attempt.

SNP	CHR	BP	Gene	A1	Suicide attempt, SCZ/BD/MIXED N=1009 (338 cases)			Suicide attempt, SCZ/BD N=864 (292 cases)			Suicide attempt, BD N=526 (185 cases)			Suicide attempt, SCZ N=338 (106 cases)		
					FRQ	OR	p-value	FRQ	OR	p-value	FRQ	OR	p-value	FRQ	OR	p-value
rs2239547	3	52855229	ITIH3/4-region	T	0.75	1.35	0.01	0.75	1.31	0.03	0.77	1.29	0.11	0.72	1.37	0.13
rs10994359	10	62222107	ANK3	T	0.93	1.02	0.90	0.93	1.01	0.98	0.93	1.16	0.56	0.94	0.76	0.42
rs4765905	12	2349584	CACNA1C	G	0.64	1.14	0.21	0.64	1.17	0.17	0.65	1.14	0.34	0.62	1.23	0.27

Abbreviations: SNP—single nucleotide polymorphism; CHR—chromosome; BP—base pair; A1—risk allele; FRQ—frequency; OR—odds ratio.

SNPs from the Affymetrix Genome-Wide Human SNP Array 6.0 within *ANK3*, *CACNA1C* and the *ITIH3/4*-region by extracting SNPs based on UCSC coordinates ± 20 kb (hg19) (*ANK3* and *CACNA1C*) and from the *ITIH3/4* gene region based on the candidate SNP ± 250 kb were analyzed (Supplementary Table 1).

2.6. Choice of SB susceptibility loci SNPs

In the replication of the two previous GWAS on suicide attempt in patients with BD, we included SNPs obtaining *p*-values below 0.001 with MAF > 0.01 in the primary analysis of the studies on BD samples, respectively 2468 SNPs (Willour et al., 2012) and 2092 SNPs (Perlis et al., 2010) (Supplementary Table 2).

2.7. Statistical analysis

Explorative analyses of associations between suicide attempt and gender, diagnosis and duration of illness were performed using the Statistical Package for the Social Sciences (SPSS Statistics) version 17.0 (SPSS Inc., Chicago, IL, USA) to identify possible confounders to be included in the association analysis between suicide attempt and SNPs. Associations between SNPs and suicide attempt (dichotomous: yes/no) were tested through the additive model of logistic regression in PLINK. Using the genetic power calculator CATS (<http://www.sph.umich.edu/csg/abecasis/CaTS/>) our combined SCZ/BD/MIXED sample was estimated to have 63% power to detect a locus at a *p*-value of 0.001 for a minor allele frequency of 0.3 and a genotypic relative risk of 1.5. Sign tests were performed with the binomial test in R as done previously (Schizophrenia Psychiatric GWAS Consortium, 2011).

2.8. Correction for multiple testing

In the primary analysis, Bonferroni correction threshold for three independent SNPs was set at $p < 0.017$ (0.05/3 SNPs). In the secondary extended SNP analysis within the genes (509 Affymetrix SNPs), the number of independent SNPs was defined by LD blocks (139) determined by confidence bounds on the normalized measure of allelic association (*D'*) (Supplementary Table 1). Thus, threshold for significance was set at $p < 3.6 \times 10^{-4}$ (0.05/139 SNPs).

In the replication of suicide attempt susceptibility loci SNPs, the Bonferroni correction was set at $p < 1.1 \times 10^{-5}$ (0.05/4562 SNPs).

3. Results

3.1. Diagnosis and demographics

The three diagnostic groups, SCZ, BD and MIXED, did not differ significantly from each other with regard to history of suicide attempt ($p=0.489$). The suicide attempt rate was significantly higher in women than in men ($p < 0.0001$), and suicide attempters had a longer duration of illness than non-attempters ($p < 0.0001$)

(Table 1). Thus, both gender and duration of illness were included as covariates in the following regression models.

3.2. Risk variant SNPs of BD and SCZ vs. SB sub-phenotype

In the primary analysis, rs2239547 (the *ITIH3/4*-region) was significantly associated with suicide attempt after Bonferroni correction (nominal $p=0.01$) (Table 2). None of the SNPs were significantly associated with suicide attempt within the SCZ/BD, SCZ or BD subsamples (Table 2).

In the secondary analysis, 36 SNPs had a nominally significant level of association with suicide attempt ($p < 0.05$) in the SCZ/BD/MIXED sample, the lowest being $p=0.0021$ (rs12251392) (Supplementary Table 3). None of these SNPs remained significant after Bonferroni correction for multiple testing.

These markers were originally identified in patients with SCZ and BD. However, even though 36 SNPs were nominally associated with suicide attempt ($p < 0.05$), the lowest being $p=0.0063$ (rs12251392) ($n=820$ – 863) (Supplementary Table 3) within the SCZ/BD group alone excluding the extended spectrum of related disorders, none of these SNPs remained significant after Bonferroni correction.

3.3. Susceptibility loci SNPs of SB vs. SB sub-phenotype

None of these SNPs remained significant after Bonferroni correction for multiple testing (Supplementary Table 4). The sample produced odds ratios in the same direction as the original studies more frequently than expected by chance. 64 of 106 independent SNPs with $p < 0.0001$ from the original studies showed a same-direction allelic association in our replication sample (sign test, $p=0.02$), as did the isolated replication of the Perlis et al. (2010) study, with 28 of 44 SNPs going in the same direction (sign test, $p=0.048$) (Supplementary Table 5).

The suicide attempt candidate SNPs were originally identified in isolated BD samples. However, none of the SNPs were significant after Bonferroni correction (Supplementary Table 4) in the BD group alone ($n=526$), nor was there evidence of aggregated same-direction allelic association (sign test, $p > 0.05$) (Supplementary Table 5).

4. Discussion

The most important finding in this study was a significant association after multiple testing corrections between a SNP in the *ITIH3/4*-region and suicide attempt in severe mental disorders. This result indicates that some of the SB sub-phenotype in patients with BD, SCZ and related psychosis spectrum disorders may be accounted for by genetic variation at the *ITIH3/4*-region, one of the strongest supported candidate gene regions for SCZ and BD (Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011; Schizophrenia Psychiatric GWAS Consortium, 2011).

The underlying mechanism of the association between the *ITIH3/4*-region and SB in these psychiatric disorders is unknown. *ITIH3* is expressed both in liver and brain, while *ITIH4* is only expressed in liver (Daveau et al., 1998). The *ITIH3/4*-associated SNP is in perfect LD with a coding variant in *ITIH4* (rs4687657) (Schizophrenia Psychiatric GWAS Consortium, 2011). The ITIH proteins are involved in the inflammatory acute phase response (Bost et al., 1998; Hamm et al., 2008), and the ITIH4 protein has been suggested as a biomarker of neuroinflammation (Kashyap et al., 2009; Yang et al., 2012) but a possible involvement of the inflammatory function of the ITIH proteins in SB is yet to be investigated. Interestingly, epidemiological studies show correlation between allergic inflammation and suicide (Qin et al., 2013). Another study also linking the immune system with SB showed that a polymorphism in the gene regulating the acute phase reactant C-reactive protein was associated with both impulsiveness and SB (Suchankova et al., 2013). The involvement of neuroinflammation in BD and SCZ is already well documented (Najjar et al., 2013; Stefansson et al., 2009) but further studies are warranted to explore a possible similar underlying mechanism in SB.

We did not find any evidence supporting associations between suicide attempt and *ANK3* and *CACNA1C*, suggesting that these other two candidate genes of BD and SCZ are less involved in the genetic risk of SB in patients with BD and SCZ.

We were not able to replicate the results for any of the previously identified susceptibility loci for suicide attempt in BD, originating from two GWA-studies (Perlis et al., 2010; Willour et al., 2012). Failure to replicate previous results of suicide attempt susceptibility loci SNPs suggests that the heritability of the suicide attempt sub-phenotype is not due to large effects of any of these susceptibility loci. However, the significant result of the sign test indicated that an aggregate of these SNPs was in alignment with the original studies more often than would be expected by chance. This suggests a polygenic model with additive effects of several risk alleles to SB. Thus, these gene variants might be found significantly associated in larger studies with adequate power.

4.1. Strengths and limitations

The strength of this study is the sample of representative psychiatric patients from all social classes receiving standard clinical treatment with a common platform for study inclusion from the ethnically homogenous Norwegian population.

The sample size limited the power to replicate true susceptibility loci of SB. The complex SB trait with polygenic risk factors and the retrospective assessment of SB may have resulted in underestimation of suicide attempts due to recall bias. Also, patients who committed suicide before a possible inclusion to the study might have had a different and perhaps stronger genetic risk of SB than those who were included here. Suicidal ideation could be closer related to the familial transmission of psychiatric disease liability (Brent et al., 1996) and future studies with the ability to differentiate results between impulsivity, suicidal ideation, suicide attempt and committed suicide, would elucidate this further.

4.2. Conclusion

We detected a novel association between a SNP in the *ITIH3/4*-region and suicide in a combined group of patients with BD, SCZ and related disorders in the psychosis spectrum. This warrants further replication attempts, preferably in larger samples, and may be useful in understanding molecular mechanisms of SB in severe mental disorders.

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We are not concerned that our author agreement may be incompatible with archiving requirements specified by our funding body that supports our research.

Conflict of interest

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Ole Andreas Andreassen has received speakers' honoraria from GSK, Lundbeck and Eli Lilly.

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All other authors declare that they have no conflicts of interest.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.jad.2013.12.018>.

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