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Genome wide significant locus for Research Diagnostic Criteria Schizoaffective Disorder Bipolar Type.

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Running Title: GWS association with RDC-SABP.

Abstract

Studies have suggested that Research Diagnostic Criteria for Schizoaffective disorder Bipolar type (RDC-SABP) might identify a more genetically homogenous subgroup of bipolar disorder. Aiming to identify loci associated with RDC-SABP we have performed a replication study using independent RDC-SABP cases (n=144) and controls (n=6,559), focusing on the 10 loci that P-value $<10^{-5}$ for RDC-SABP in the Wellcome Trust Case Control Consortium (WTCCC) bipolar disorder sample using 'researcher-specific SNPs' represented on the custom array, the ImmunoChip. Combining the WTCCC and replication datasets by meta-analysis (combined RDC-SABP, n=423, Controls, n=9,494) we observed genome wide significance association at one SNP, rs2352974, located within the intron of the gene TRAIP on chromosome 3p21.31. This locus did not reach genome wide significance in bipolar disorder or schizophrenia large psychiatric genomic consortium datasets, suggesting that it may be a relatively specific genetic risk for the bipolar subtype of schizoaffective disorder.

Key Words:

Schizoaffective disorder bipolar type, RDC-SABP, TRAIP, GWAS, Research Diagnostic Criteria

Introduction

In the recent years many successful large scale genome studies have identified genetic susceptibility loci, including common, rare and structural variants which confer risk individually to schizophrenia (SZ) and bipolar disorder (BD), and a combination of such disorders (PGC-BD, 2011; PGC-SZ, 2014; Kirov, 2015; Green *et al*., 2016). Often such studies of BD and/or SZ include schizoaffective disorder as part of the cases sample. Depending on the proportion of cases diagnosed as schizoaffective disorder, the inclusion of these individuals may impact on the genetic findings when considering the relationship between SZ and BD (Cardno & Owen, 2014).

Research diagnostic criteria for schizoaffective disorder bipolar type are broader than those proposed by the World Health Organisation and the American Psychiatric Association and require "some temporal overlap" of episodes of mania and psychotic symptoms, "suggestive of schizophrenia", which persist for at least 1 week in the absence of major mood symptomatology (Spitzer *et al*., 1981, Malaspina *et al*., 2013). Traditional family studies have shown evidence of familial overlap between schizoaffective disorder and both SZ and BD, which has been confirmed by Scandinavian population registered based studies (Cardno & Owen, 2014).

Genetic studies focusing on individuals rated by research diagnostic criteria as schizoaffective disorder bipolar type (RDC-SABP) have previously been performed. Examining the Wellcome Trust Case Control Consortium dataset (WTCCC, 2007), we noted that RDC-SABP stood out from other subsets of the BD sample as having a significantly excess of strong association signals ($P<10^{-5}$) and hence 'may be of particular use to for identifying common susceptibility loci GWAS' (Hamshere *et al*., 2009). In addition, variation at genes encoding $GABA_A$–receptor subunits were associated with risk of RDC-SABP and this association was relatively specific to this diagnostic subset, with no association to schizophrenia (SZ) or bipolar disorder (BD) (Craddock *et al*., 2010). This finding was replicated in an independent study (Breuer *et al*., 2011). Finally, polygenic score analysis of RDC-SABP using schizophrenia derived polygenic scores showed that the polygenic influences on schizophrenia had a greater overlap with SABP than those for the remaining bipolar disorder individuals (Hamshere *et al*., 2011).

Aiming to identify loci that are associated with RDC-SABP at statistically stringent levels of significance (P-value < $5x10^{-8}$) we have genotyped a replication sample using the Illumina Infinium HD genotyping array, the ImmunoChip, focusing on the 10 SNPs that reached a P-value threshold of < 10^{-5} in the WTCCC study (Hamshere *et al*., 2009), and combined the 2 datasets by meta-analysis (total RDC-SABP cases, n= 423 and controls, n= 9,494).

Materials and Methods

Samples

All participants were unrelated, white European, living in the British Isles. The protocols and procedures were approved by the relevant ethics review panels where patients were recruited.

Original WTCCC sample set.

The WTCC bipolar disorder sample and dataset has been previously reported, and as such the sample and collection information is not included (WTCCC, 2007). Analysesof subsets of these BD samples, including those individuals rated as schizoaffective disorder, bipolar type by Research Diagnostic criteria have also been reported (RDC-SABP) (n = 279) (Hamshere *et al*., 2009; Craddock *et al*., 2010; Green *et al*., 2010). RDC is a broader definition of SABP, and provide more delineation between individuals on the basis of the pattern of mood psychotic symptomatology than rating by DSM-IV (APA, 1994; Hamshere *et al*., 2011,).

Replication sample set

The independent replication RDC-SABP (n=144) sample set was part of the bipolar disorder sample, the BDRN sample (n=1,849). A description of this BD collection has been detailed in Green *et al*. , (2013, 2016). WTCCC2 set was used as the control sample (n = 6,599), and the characteristics and recruitment of which have been described in WTCCC 2007. These controls are not screened to exclude the presence of psychiatric illness.

Genotyping

The genotyping was performed using the custom Illumina Infinium HD genotyping array, the ImmunoChip. The ImmunoChip BD genotyping study has been previously reported for the 1218 BD cases and 2913 controls (Green *et al*., 2013) but not for the subset of RDC SABP cases. Additional samples were genotyped at University College London (UCL) to increase the sample size, including 631 BD cases (44 RDC-SABP cases) and 3,646 WTCCC2 controls. In total, the replication RDC-SABP sample consists of 144 RDC-SABP cases and 6,556 WTCCC2 controls, which are independent of the original WTCCC GWAS.

This study focuses on 10 SNPs that were included on the ImmunoChip as part of the 'investigator-specific SNP selection for replication' and were independently associated SNPs ($r^2 < 0.2$) with an association signal of $P<10^{-5}$ for RDC-SABP cases against controls in our previous study Hamshere *et al*., 2009[12]. It is worth noting that in this study the Cochran-Armitage trend test of genotype distributions with disease was employed, whereas the data presented here was analysed using logistic regression of disease state with a genomic inflation factor (λ) of 1.06. As such the P-values and OR's stated may differ slightly from the original publication and the P-values for 2 SNPs are slightly > 10^{-5}.

Statistical analysis

A brief summary of the methodology is described here and more detailed description is available in the Supplementary Materials section. The BDRN sample set was genotyped on the ImmunoChip at either the Sanger Institute or UCL sequencing facility. The bipolar disorder dataset genotyped at the Sanger Institute has been published (Green *et al*., 2013) and this genotype calling and quality control pipeline was implemented for the sample genotyped at UCL. Briefly, the genotypes were called by GenoSNP software (Giannoulatou *et al*., 2008). Genotypes with a call probability of < 85% were scored as missing data. The data management and quality control assessment was performed using PLINK (v1.07) (Purcell et al., 2007) and a series of shell scripts initially for all BD and control samples.

We planned to combine the data genotyped at the two centres. In order to highlight any potential 'batch effects' problems that might prevent the combining of the data, we included 9 identical samples from the first centre to be genotyped by UCL. The concordance rate for the 9 samples across overlapping SNPs (n=96,184) was very high reaching 99.997%. Thus we felt confident in combining the datasets.

From the total BD dataset, 144 RDC-SABP and controls were extracted (n = 6,556) and quality control analysis performed. Principal Component Analysis (PCA) was performed with Eigenstrat on the combined sample and any individual outliers that did not cluster near to the HapMap European individuals were removed in order to maximise the ethnic homogeneity of our sample (Giannoulatou *et al*., 2008). The genomic inflation factor was calculated using 43K SNPs in relative linkage (α=1).

Meta-analysis

The RDC-SABP replication dataset was combined with the original RDC-SABP WTCCC (WTCCC 2007) dataset by fixed-effects meta-analysis using PLINK (v1.07) (Purcell *et al*., 2007) to estimate a common odds ration weighted by individual study standard errors (SE).

Results

An independent replication sample of 144 cases (RDC-SABP) and 6,559 controls SNPs were genotyped on the ImmunoChip Illumina array. We have focused on 10 SNPs that showed an independent association ($r^2 < 0.2$) signal at $P < 10^{-5}$ for research diagnostic criteria schizoaffective disorder, bipolar type against controls in our previous study of the WTCCC dataset previously (Hamshere *et al*., (2009)). We combined our replication data with the WTCCC SNP data by fixed effect meta-analysis. SNP, rs2352974, on chromosome 3p21.31 met genome-wide association (P-value = 4.37×10^{-8}, OR=0.67). This SNP resides within the intronic region of the gene, *TRAIP* (TRAF interacting protein).

A meta-analysis of all SNPs on the ImmunoChip was also performed (data not presented). No additional individual SNP was associated at levels that exceed the accepted genome-wide levels of significance ($P<5 \times 10^{-8}$).

SNP	CHR	BP	A1	A2	WTCCC RDC-SABP data				Immunochip, RDC_SABP data				Meta-analysis		Gene
					Cases MAF	Controls MAF	P-Value	OR	Cases MAF	Controls MAF	P	OR	P	OR	
rs4027132	2	12037492	G	A	0.357	0.459	7.69E-06	0.65	0.486	0.457	0.332	1.12	0.0038	0.81	*LPIN1* (70 kb)
rs2352974	3	49890613	T	C	0.387	0.499	1.01E-06	0.63	0.413	0.493	0.0084	0.73	**4.37E-08**	**0.67**	***TRAIP*** (0 kb)
rs7680321	4	47145107	C	T	0.136	0.079	1.02E-05	1.83	0.118	0.090	0.109	1.34	7.03E-06	1.64	*GABRB1* (0 kb)
rs4279178*	4	47068580	A	G	0.401	0.509	2.96E-06	0.65	0.444	0.482	0.208	0.86	8.24E-06	0.72	*GABRB1* (0 kb)
rs13154602	5	76395917	A	C	0.363	0.269	3.59E-06	1.58	0.267	0.282	0.574	0.93	6.35E-04	1.31	*ZBED3-AS1* (0 kb)
rs1171115	6	84229623	C	T	0.357	0.264	9.81E-06	1.52	0.302	0.275	0.308	1.14	3.00E-05	1.38	*PRSS35* (0 kb)
rs7990962	13	43399245	G	A	0.253	0.173	6.92E-06	1.62	0.163	0.180	0.474	0.89	8.83E-04	1.34	*LINC01050*|*LINC00428* (24.5kb|17.3kb)
rs16942644	15	89612736	A	G	0.171	0.102	2.00E-06	1.82	0.135	0.111	0.197	1.25	4.00E-06	1.60	*ABHD2* (18.7 kb)
rs4786811	16	6132787	G	A	0.041	0.014	1.10E-05	2.98	0.010	0.018	0.368	0.59	2.25E-04	2.32	*RBFOX1* (0 kb)
rs4818065	21	41037723	A	G	0.272	0.182	6.97E-07	1.69	0.184	0.187	0.905	0.98	5.63E-05	1.42	*B3GALT5* (2.9 kb)

Table 1. Meta-analysis of WTCCC RDC-SABP (cases n=279, controls n=2 938) and ImmunoChip RDC-SABP data (cases n=144, controls n=9 497).

Abbreviations: A1, allele 1; A2, allele 2; CHR, chromosome; BP, position in base pairs for UCSC Build hg19; WTCCC, Wellcome Trust Case Control Consortium; MAF, minor allele frequency; OR, odds ratio; RDC, research diagnostic criteria; SABP, Schizoaffective disorder, bipolar type; Gene, gene symbol is followed by the distance between the SNP and the reference sequence gene location.
The SNPs listed are those with an independent association ($r^2 < 0.2$) signal at $P < 10^{-5}$ for research diagnostic criteria (RDC) schizoaffective disorder, bipolar type against controls previously reported by Hamshere et al., 2009[12] analysed originally using the Cochran-Armitage Trend test, here an updated analysis of the WTCCC RDC-SABP dataset has been performed using logistic regression of disease state with a genomic inflation factor (l) of 1.06, as such P-values and OR's may alter slightly from the original publication. Note: rs4786811 is included in the meta-analysis although the MAF is < 0.05 in both cases and controls. Rs6414684 was merged with rs4279178*.

Discussion

Combining an independent sample with our previous dataset (Hamshere *et al*., 2009), we report a novel locus reaching genome-wide significant association with schizoaffective disorder bipolar type at the intronic SNP rs2352974 (P-Value = 4.37×10^{-8}, OR= 0.67) on chromosome 3p21.31 at *TRAIP* (TRAF interacting protein). In comparison, this loci was not genome-wide significantly associated in either the large Psychiatric GWAS Consortium (PGC) bipolar disorder (P=0.39, OR=1.01) or schizophrenia (SZ) meta-analysis data (P=0.037, OR=0.98) (PGC-BD, 2011, PGC-SZ, 2014), suggesting that it may be a relatively specific genetic risk for bipolar subtype of schizoaffective disorder. The gene *TRAIP* encodes an E3 RING ubiquitin ligase. A recent study has reported that mutations within *TRAIP* are associated with microcephalic primordial dwarfism, and identified *TRAIP* as a component of the DNA damage response replication blocking DNA lesions (Harley *et al*., 2016).

There is much debate around the clinical usefulness and the nosological status of diagnostic category schizoaffective disorder. Discussions include whether schizoaffective disorder is a form of schizophrenia, affective disorder, a combination of the two or should be regarded as a separate disease entity (Craddock *et al*., 2009). To add to this there are concerns over the poor reliability of diagnosis (Maj *et al*. 2000; Santelmann *et al*., 2015) and apparent low diagnostic stability over time (Schwartz *et al*., 2000; Laursen *et al*., 2005). Our findings here, of a susceptibility locus specific (i.e. not identified in BD or SZ datasets) for RDC-SABP, combined with our previous genetic findings for SABP do further support the notion that SABP is a partly independent diagnostic category, with some specific biological characteristics not shared with other phenotypes (Craddock *et al*., 2009, 2010; Hamshere *et al.*, 2009). Larger well phenotypically defined samples, although challenging to collect, we envisage will enable the identification of additional risk loci that are specific to SABP, and loci that also confer risk to both or either BD and/or SZ.

In summary, within our UK RDC-SABP sample we have identified a genome-wide significantly associated locus at an intronic SNP in *TRAIP*. Our findings further indicate the importance of research examining clinical diagnostic phenotypes, which in turn will be ultimately important for clinical practice.

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