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Most genome-wide significant susceptibility loci for schizophrenia and bipolar disorder reported to date cross-traditional diagnostic boundaries

Hywel J. Williams, Nicholas Craddock, Giancarlo Russo, Marian L. Hamshere, Valentina Moskvina, Sarah Dwyer, Rhodri L. Smith, Elaine Green, Detelina Grozeva, Peter Holmans, Michael J. Owen and Michael C. O'Donovan*

MRC Centre for Neuropsychiatric Genetics and Genomics, Department of Psychological Medicine and Neurology, School of Medicine, Cardiff University, Cardiff CF14 4XN, UK

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Recent findings from genetic epidemiology and from genome-wide association studies point strongly to a partial overlap in the genes that contribute susceptibility to schizophrenia and bipolar disorder (BD). Previous data have also directly implicated one of the best supported schizophrenia-associated loci, *zinc finger binding protein 804A* (*ZNF804A*), as showing *trans*-disorder effects, and the same is true for one of the best supported bipolar loci, *calcium channel, voltage-dependent, L type, alpha 1C subunit* (*CACNA1C*) which has also been associated with schizophrenia. We have undertaken a cross-phenotype study based upon the remaining variants that show genome-wide evidence for association in large schizophrenia and BD meta-analyses. These comprise in schizophrenia, SNPs in or in the vicinity of *transcription factor 4* (*TCF4*), *neurogranin* (*NRGN*) and an extended region covering the *MHC* locus on chromosome 6. For BD, the strongly supported variants are in the vicinity of *ankyrin 3, node of Ranvier* (*ANK3*) and *polybromo-1* (*PBRM1*). Using data sets entirely independent of their original discoveries, we observed strong evidence that the *PBRM1* locus is also associated with schizophrenia ($P = 0.00015$) and nominally significant evidence ($P < 0.05$) that the *NRGN* and the extended *MHC* region are associated with BD. Moreover, considering this highly restricted set of loci as a group, the evidence for *trans*-disorder effects is compelling ($P = 4.7 \times 10^{-5}$). Including earlier reported data for *trans*-disorder effects for *ZNF804A* and *CACNA1C*, six out of eight of the most robustly associated loci for either disorder show *trans*-disorder effects.

INTRODUCTION

For the last 100 years, psychosis occurring in the absence of an organic brain disorder has been subdivided into two categories corresponding to the modern diagnostic equivalents of schizophrenia and bipolar disorder (BD). At a mechanistic level, the causes of these disorders are almost completely unknown. Both are familial, and a substantial amount of the variance in risk for each disorder is genetic, twin studies revealing heritabilities for schizophrenia and BD of around 80% or more (1,2), with largely unknown environmental factors also being involved. Recent genetic findings, as well as findings from other areas of biomedical research, are mounting a strong challenge to the view that schizophrenia and BD are distinct entities (3). Among the key findings from epidemiology, a study from Sweden based upon over two million nuclear families showed risk of both disorders was increased in the family members of an index proband regardless of whether that proband had schizophrenia or BD (4). Moreover, a recent Danish population study of the offspring of parents, one or both of whom had schizophrenia or BD, reported patterns of recurrence in those offspring suggestive of partial overlap in genetic risk for the disorders (5).

*To whom correspondence should be addressed at: MRC Centre for Neuropsychiatric Genetics and Genomics, Henry Wellcome Building, Department of Psychological Medicine and Neurology, School of Medicine, Cardiff University, Cardiff CF14 4XN, UK. Tel: +44 2920687066; Fax: +44 2920687068; Email: odonovanmc@cardiff.ac.uk

Data from genome-wide association studies (GWASs) are also beginning to provide strong support for shared genetic risk across the disorders. For example, one study using gene-wide tests showed a significant increase in the number of genes showing evidence for association to both schizophrenia and BD than would be expected by chance (6). Highly persuasive evidence for shared genetic risk was also provided by an analysis of schizophrenia and BD GWAS data sets by the International Schizophrenia Consortium (7), which showed that sets of putative risk alleles defined on the basis of very weak trends for association in a schizophrenia GWAS were highly significantly, but weakly, predictive of schizophrenia in independent GWAS data sets. Moreover, the same sets of alleles were also predictive of risk for BD in two independent BD GWAS data sets.

The evidence for shared risk from genetic epidemiology and global analyses of genome-wide sets of SNPs strongly supports the hypothesis of shared genetic risk between schizophrenia and BD, but in order to start to identify shared pathophysiology, it is necessary to demonstrate overlap in risk at the level of individual alleles. Moreover, given the still limited GWAS sample sizes available (limited in terms of power to detect specific loci), the strong case for shared genetic risk offers an important opportunity to derive confirmatory evidence for individual loci identified as being associated with schizophrenia by testing those variants in BD (and vice versa). However, with the advent of large consortia in which data sets are shared, one potential pitfall of cross-phenotype analyses is that the same controls are often used in multiple studies, a fact that has the potential to result in convergent associations across phenotypes that reflect the use of overlapping controls (8).

In the present study, we have undertaken a cross-phenotype study based upon variants that show genome-wide evidence for association (9) in the largest publicly available schizophrenia and BD data sets. Variants that have been reported at genome-wide significant levels for association with BD were tested in a fully independent schizophrenia GWAS data set, and the converse for variants that have been reported to be associated with schizophrenia at this level of support. In conducting these analyses, we have taken care to ensure that no samples, cases or controls, used to test the cross-disorder association overlap with samples used for the initial discovery. In doing so, our evaluations of variants are based upon smaller samples than were initially used by those reporting the association. Moreover, as discussed below, to ensure no overlap of controls, it was necessary to use different sets of controls for each analysis.

RESULTS

Association to the *MHC* region was detected at genome-wide levels of significance through a combined analysis of three schizophrenia GWASs (7,10,11). Although each study reported genome-wide significant association at this extended locus (each had meta-analysis of similar data sets), the study of Stefansson *et al*. (10) included an additional follow-up sample and as a result, attained the strongest evidence for association. That study therefore acts as the source of putative risk alleles at this locus. Spanning a wide region, the authors reported the most significant evidence for association at rs6932590 (Ch6, 27.4 Mb, $P = 1.4 \times 10^{-12}$). They also reported association to a second locus in the region (rs3131296, 32.3 Mb, $P = 2.3 \times 10^{-10}$) which was substantially statistically independent. Thus, we evaluated both for evidence for association to BD. For this analysis, we used the primary WTCCC GWAS BD data set (12) which had no sample overlaps with the study of schizophrenia (10). As neither SNP was on the array, we used imputed data. Quality metrics for both SNPs indicated imputation at high quality (RSQR = 0.94 and 0.99, respectively). For each locus, the associated allele reported in the source study was significantly associated with BD, and the effect size lay within the confidence interval reported in the primary study (Table 1).

We also tested *transcription factor 4* (*TCF4*) in the WTCCC BD data set. The strongest schizophrenia-associated SNP (10) was rs9960767 (Ch18, 51.3 Mb; $P = 4.1 \times 10^{-9}$), which was not on our array, but it was imputed at high quality (RSQR = 0.94). This variant showed no evidence for association (Table 1). We also note that rs10401120, a proxy ($r^2 = 0.87$) for rs9960767 used in the schizophrenia study (10), was also not associated with BD in this sample.

At *neurogranin* (*NRGN*), the most strongly schizophrenia-associated SNP was rs12807809 (Ch10, 124.1 Mb; $P = 2.4 \times 10^{-9}$) (10). Again not on the array, imputed data (RSQR = 0.63) showed significant evidence for association ($P = 0.02$) in the WTCCC BD data set to the same allele and with an effect size within the confidence interval of the discovery sample (Table 1).

From the perspective of BD, a combined analysis of data from five GWASs (largely BD but including schizoaffective disorder and major depressive disorder) and data from three replication studies (one BD, two major depressive disorders) identified genome-wide significant evidence at rs2251219 in *PBRM1* (Chr3, 52.6 Mb, $P = 1.7 \times 10^{-9}$) (13). In our UK GWAS schizophrenia data set (479 cases, 2937 controls) (14), the same allele (array data) showed strong evidence for association ($P = 0.00015$), with an effect size (OR 0.76) somewhat stronger than was reported for major mood disorder, though the 95% confidence intervals were overlapping. Since the previous meta-analysis (13) included the WTCCC BD data set with which our schizophrenia sample shares controls, this evidence is not independent of the discovery. In order to test this fully independently, we used the combined non-psychiatric disorder case samples from the WTCCC. This yielded a virtually identical effect size and also a similar degree of statistical evidence for association (Table 2), confirming that in schizophrenia, the evidence for association is entirely independent of the data originally reported.

Genome-wide significant evidence for *ankyrin 3, node of Ranvier* (*ANK3*) in BD comes from a meta-analysis of GWASs combining a total 4387 cases and 6209 controls with a maximum *P*-value of 9.1×10^{-9} for rs10994336 (15). As the meta-analysis of *ANK3* used the WTCCC BD data set, we used the combined non-psychiatric disorder case samples from the WTCCC to test the evidence for association in schizophrenia. We were unable to directly test rs10994336 as there are no imputed or array data available to us for this

Table 1. Genome-wide significant schizophrenia loci tested in bipolar disorder

Original study results						Bipolar disorder		
Study	Locus	SNP	*P*-value	OR	(95% CI)	*P*-value	OR	(95% CI)
Stefansson *et al.* (10)	*MHC*	rs6932590	1.4×10^{-12}	1.15	(1.05–1.26)	0.04[a]	1.09	(0.99–1.18)
Stefansson *et al.* (10)	*MHC*	rs3131296	2.3×10^{-10}	1.21	(1.08–1.36)	0.01[a]	1.14	(1.02–1.25)
Stefansson *et al.* (10)	*TCF4*	rs9960767	4.1×10^{-9}	1.30	(1.11–1.51)	0.92	0.99	(0.80–1.18)
Stefansson *et al.* (10)	*NRGN*	rs12807809	2.4×10^{-9}	1.15	(1.10–1.20)	0.02[a]	1.14	(1.01–1.27)

Study, source of genome-wide significant finding; *P*-value, Armitage trend test; OR, odds ratio; CI, confidence interval.
[a]One-tailed *P*-value where OR is in the same direction as the original study.

Table 2. Genome-wide significant bipolar disorder loci tested in schizophrenia

Original study results						Schizophrenia		
Study	Locus	SNP	*P*-value	OR	(95% CI)	*P*-value	OR	(95% CI)
McMahon *et al.* (13)	*PBRM1*	rs2251219	1.7×10^{-9}	0.88	(0.85–0.92)	1.3×10^{-4a}	0.77	(0.68–0.89)
Ferreira *et al.* (15)[b]	*ANK3*	rs1938526	1.3×10^{-8}	1.40	–	0.82	0.97	(0.72–1.29)

Study, source of genome-wide significant finding; *P*-value, Armitage trend test; OR, odds ratio; CI, confidence interval.
[a]One-tailed *P*-value where OR is in the same direction as the original study.
[b]No details of 95% CI given in the original manuscript.

control set. However, we had data available for rs1938526, which was also genome-wide significant in the study of Ferreira and colleagues ($P = 1.3 \times 10^{-8}$). For this marker, the results were not-significant ($P = 0.82$) (Table 2).

As we have already published cross-disorder data on *ZNF804A* and *calcium channel, voltage-dependent, L type, alpha 1C subunit* (*CACNA1C*) across the disorders (16,17), we do not represent those analyses here.

DISCUSSION

The present study was designed with the explicit goal of testing a very restricted number of genetic hypotheses, namely, that variants implicated at genome-wide levels of significance by the largest available studies of schizophrenia are associated with susceptibility to BD, and that those similarly identified as associated with BD are associated also with schizophrenia. In contrast with much of the earlier work in this area, our own included, the genes we evaluate for cross-disorder effects have very strong prior support for involvement in one of the disorders, allowing a more secure interpretation of the relevance of the findings in the secondary phenotype. To test these hypotheses independently of the discovery data sets, we were unable to use a number of publically available data sets (e.g. the GAIN schizophrenia and BD data sets) as those include cases and or controls that contributed to the original discoveries. Future replication analyses will therefore require new, independent data sets for both disorders to become available. Nevertheless, at the general level, there is clear evidence for an excess of *trans*-disorder associations over and above chance expectations. Under the assumption of six independent tests (allowing for two independent tests at the extended chromosome 6 locus), the probability for the observed distribution of *trans*-disorder association *P*-values under the null hypothesis is $P = 4.7 \times 10^{-5}$ (Fisher's test for combining independent *P*-values, conservatively assigning values of $P = 1$ for association to those hypothesized risk alleles where any trend for association is in the opposite direction to that predicted). The evidence is also strong ($P = 4.2 \times 10^{-4}$), allowing for only a single independent test of the *MHC* locus, that being rs6932590 for which the evidence was strongest in the discovery sample (10). Thus, in aggregate, the present study provides further support for the burgeoning and increasing body of evidence that points to an overlap in genetic susceptibility to schizophrenia and BD.

At the level of specific loci, we provide the first support ($P = 1.3 \times 10^{-4}$) for the involvement in schizophrenia of variation at or around *PBRM1*. Considering the level of statistical support in the original (13) and our own independent study, the evidence implicating this locus in schizophrenia and BD is now very strong. *Polybromo-1* (*PBRM1*) encodes polybromo-1, a gene that is important in chromatin remodelling, but given the extensive LD in the region, as noted by the authors of the previous study (13), it is not clear the signal specifically points to that gene. Thus, functional interpretation is premature until the source of the signal is better localized. We also provide the first independent support for the involvement of both the *MHC* region and *NRGN* in BD, albeit at levels of significance that are weaker than that for schizophrenia and the region surrounding *PBRM1*. Although the levels of statistical significance for these regions are only nominally significant, and do not survive correction for multiple testing within this study, we note the enhanced prior probability for each of these as schizophrenia-associated from genome-wide studies and the overlap of confidence intervals for estimated effect sizes in the two phenotypes. We, therefore, consider that our data add important evidence that those original findings represent true associations, and that the loci additionally confer risk to BD. The potential implications of those findings for understanding the pathophysiology of psychosis are discussed in the original schizophrenia manuscripts. Noting that the functional interpretations are necessarily speculative since the true functional variants are still unknown, the associations between psychosis and the extended

MHC locus potentially lend support to long-held hypotheses of the importance in psychosis of either infective agents and/or autoimmunity (11). This support is not strong given that the association signal spans several megabases which contain large numbers of genes with no known role in immunity. Under the assumption that the association on chromosome 11 at around 124.1 Mb points to the gene encoding neurogranin, that finding is intriguing since it might functionally converge with the cross-disorder associations at *CACNA1C* (17). Thus, *CACNA1C* encodes the major constituent of the brain L-type voltage-gated calcium channels that are critical to dendritic calcium influx (18) while neurogranin has been proposed to act as a sensor of dendritic calcium concentration. In response to rising Ca^{2+} levels, neurogranin releases calmodulin, which is then free to trigger a number of processes central to the induction of long-term potentiation and regulation of synaptic sensitivity (19).

Including *ZNF804A* and *CACNA1C*, the data for which have been presented elsewhere, six (two *MHC* loci, *ZNF804A*, *CACNA1C*, *NRGN*, *PBRM1*) of eight loci that have now been implicated at genome-wide levels of significance by large combined studies of either schizophrenia or BD have now been demonstrated to show at least nominally significant *trans*-disorder effects, the exceptions being *TCF4* (associated so far in schizophrenia but not BD) and *ANK3* (associated so far in BD but not schizophrenia). It might be argued that apparent shared effects across loci are trivially the result of the misapplication of diagnostic categories that are actually of fundamental biological validity, that is, *trans*-disorder associations simply arise because the BD samples are contaminated by schizophrenic cases and/or vice versa. However, given that the schizophrenia-associated alleles have similar effect sizes in BD, and vice versa (Tables 1 and 2), this would require assignment to the diagnostic category to be virtually random. Given that most, if not all, samples used to date in GWASs have been subjected to stringent research diagnostic criteria and practices, this does not seem as plausible an explanation as the existence of true overlap in genetic susceptibility.

The observation that some alleles impact on both schizophrenia and BD does not imply the existence of a unitary condition (3). For example, while it may be the case that some cross-disorder associations reflect alleles that cause a non-specific rise in risk of major psychiatric syndromes, others might exert effects on the function of brain networks, perturbation of which result in domains of psychopathology and/or alterations of behaviour that occur in subsets of people who are correctly (under present diagnostic schemes) assigned to the diagnostic categories schizophrenia and BD. For example, psychotic symptoms, depressed mood and altered drive and activity are frequent occurrences in people with either disorder. Therefore, if there are alleles that impact on those domains, those alleles may appear as risk factors for both disorders. It is our expectation that exploring the relationships between risk alleles and clinical phenotypes, for example, phenotypes that appear hybrids of both disorders such as schizoaffective disorder, psychopathological domains (e.g. depressive symptoms, presence of psychotic features) as well as other types of phenotypes (e.g. cognitive and brain imaging endophenotypes), may ultimately lead to classification systems that are quite different from those currently in place. How those will look can obviously at this point not be known; the main point we wish to make here is that overlap in risk alleles does not imply homogeneity; rather that current diagnostic classifications do not divide cases neatly on the basis of distinct underlying aetiologies.

We also note that the underlying true proportion of susceptibility alleles for the individual disorders that confer risk across disorders remains to be determined. It is certainly not our contention that all genetic risk is shared across diagnostic groups; indeed, recent family study data using very large samples indicate non-shared as well as shared genetic risk factors for schizophrenia and BD (4,5), and it is possible that the currently observed high proportion may be inflated due to ascertainment bias in the susceptibility alleles discovered so far. The reasoning is that if multiple overlapping pathogenic pathways contribute to the spectrum of mood and psychotic illness, power considerations dictate that it is likely that the alleles with broadest phenotypic effect will be those discovered earliest because their detection is least sensitive to phenotypic variation in samples and, hence, will be well represented in most samples studied.

In summary, the present study adds strong support for the hypothesis of shared genetic risk between schizophrenia and BD. We also provide evidence for the involvement of specific loci in these disorders, in particular, strong evidence for a locus in the vicinity of *PBRM1*, but also support for *NRGN1* and the *MHC* locus. Further studies will be required to identify whether these associations map on to particular clinical (or endophenotype) variables that might usefully be used to classify these disorders on more aetiologically relevant grounds.

MATERIALS AND METHODS

Tested variants

In order to rigorously test the hypothesis of *trans*-disorder, we restricted our analysis to variants which have strong prior evidence for association to one or other disorder. Thus, we only tested variants that surpass a widely accepted benchmark for genome-wide significance ($P \leq 7.2 \times 10^{-8}$) (9) in large meta-analyses. These comprise in schizophrenia, SNPs in or in the vicinity of *zinc finger binding protein 804A* (*ZNF804A*) (16), *TCF4* (10), *NRGN* (10) and an extended region covering the *MHC* locus on chromosome 6 (7,10,11). For BD, the strongly supported variants are in or in the vicinity of *CACNA1C* (15), *ANK3* (15) and *PBRM1*, the latter showing genome-wide support in a composite phenotype of BD, schizoaffective disorder and major depressive disorder (13). Cross-disorder analyses involving the samples included in the present study already support evidence for association for *ZNF804A* and *CACNA1C* across the disorders (16,17).

GWAS data sets

Full details of the GWAS samples (all white and of UK origin) and the conduct of the GWAS analyses are fully described in the primary schizophrenia (14) and BD (12) manuscripts. Since both primary GWASs exploited the same sets of controls, where the sourced evidence for association included one of the UK GWAS samples, it was necessary to use an alternative control data set for the present analysis to ensure the

cross-disorder test was fully independent of the discovery. To achieve this, we adopted an approach reported by the WTCCC (12) in which a 'control' population was derived by combining the data from the six other (non-psychiatric disorder) case samples used in that study, all of which were genotyped contemporaneously using the same pipeline as our primary GWAS data sets. Although these samples were not screened for presence of psychiatric illness, this does not have an appreciable effect on the outcome of association analyses when the rate of the disorder in the general population is low (8). These six case samples gave a total sample size of 11 374 subjects.

Imputation

Genome-wide imputation was performed using Mach 1.0 (20) with the 1000 genomes-Sanger 2009-08 data release (http://www.sph.umich.edu/csg/yli/mach/download/1000G-Sanger-0908.html) as the reference source for the variants to be imputed. That source comprises the variation derived from 112 haploid genomes and contains over eight million SNPs. Following the authors recommendations (http://www.sph.umich.edu/csg/yli/mach/tour/imputation.html), Step 1 of the imputation process was based on a subset of 450 individuals (150 BD subjects, 150 schizophrenia subjects and 150 controls selected at random from our data sets) from which the sample recombination parameters were derived for use in imputing the whole sample, therefore removing the chance that one data set could bias the imputation parameters. Also, following the guidelines, only SNPs with an RSQR above 0.3 were retained. Tests for association were with a likelihood ratio test using mach2dat (21). Note that imputed data were not available for the 'controls' derived from the six sets of non-psychiatric disorder cases reported by the WTCCC.

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Conflicts of Interest statement. None declared.

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