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Meta-analysis of two genome-wide association studies of bipolar disorder reveals important points of agreement

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Two genome-wide association studies (GWAS) of bipolar disorder have been published to date, one in this journal (1) and one in *Nature* (2). Cursory consideration of the top findings in the two studies does not show obvious overlap; some may even have concluded there is no agreement. Yet, simulations show that true positive findings have only a 26% chance of falling into the top 1000 top-values in a GWAS, even when power to detect is 85% (3). We wish to draw attention to the need to look in-depth at GWAS datasets, rather than focusing simply on "top hits." Closer analysis reveals several points of agreement between the two bipolar disorder GWAS published so far.

The Baum et al. study used the Illumina HumanHap550 platform to screen pooled DNA from two independent samples totaling 1233 bipolar I cases and 1439 matched controls (1). Baum et al. reported 88 SNPs near 80 distinct genes that met replication criteria in both samples. The WTCCC study used the Affymetrix 500k platform to individually genotype 1838 bipolar cases and 2938 controls (2). The WTCCC reported 14 SNPs associated with bipolar disorder at $p < 10^{-5}$. The use of different, largely non-overlapping genotyping platforms between these two studies restrict current comparisons to the imputed HapMap genotypes generated from the WTCCC data set, which have been shown to be very reliable (2). A total of 407,875 SNPs present on the Illumina HumanHap550 platform exceeded a minor allele frequency threshold of 5% and had < 50% estimated missing data in the imputed data. We will refer to this as the "total imputation dataset." Because Baum et al. did not individually genotype most SNPs, this set was compared to a total of 80 SNPs that have now been genotyped individually in at least one of the Baum et al. study samples.

We first asked: Does the set of SNPs implicated by Baum et al. show more evidence of association in the WTCCC sample than would be expected by chance? Imputed genotypes

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were available in the WTCCC dataset for 76 of Baum et al.'s individually genotyped SNPs. Of these, five were associated in the same direction with bipolar disorder, with at least nominal significance in both studies. We compared this observed set of 76 p-values against the distribution expected under the null hypothesis by randomly sampling 10^6 sets of 76 SNPs each from the total imputation dataset of the WTCCC. The number of randomly sampled SNP sets in which the best 5 p-values were less than or equal to the best 5 p-values in the observed SNP set was tallied. About 700 random sets of SNPs met this criterion, for an empirical $p = 7 \times 10^{-5}$. Because this procedure tests only one hypothesis, we can confidently reject the null hypothesis of no common genetic signals between the two studies.

Next we examined the 27 SNPs that had been individually genotyped in both Baum *et al* samples (Supplemental Table). Fourteen were significantly associated with bipolar disorder in two or more of the three samples (NIMH, German, WTCCC), and ten of those were associated to the same allele. We report in Table 1 the sample-specific p-values and odds ratios, overall p-values and random-effects odds ratios, and heterogeneity scores of these SNPs. The most consistently associated SNPs, based on the I^2 heterogeneity test (4), lie near genes with known roles in synaptic transmission (Zn^{2+} transporter ZIP3/SLC39A3 (5)) and cell-cell adhesion in the brain (junctional adhesion molecule 3, OMIM: 606871). Interestingly, JAM3 lies in a region syntenic to a quantitative trait locus for behavioral despair in the rat (6).

We recognize that stringent levels of statistical significance are required for confirmation of any risk gene or polymorphism identified through a GWAS. Substantial further work may be required to achieve this in bipolar disorder, including the study of additional large samples and the verification of imputed genotypes. Nevertheless, the genes shown in Table 1 are strong candidates given the available data.

The above analyses were restricted to SNPs that showed consistency across both studies at the allelic level, as recommended by Chanock et al (7), but SNPs that do not follow this pattern are not uninteresting. For example, both studies identified strongly associated SNPs near the gene DFNB31 (Baum *et al*, rs942518 and rs16929770; WTCCC, rs10982256). Genotyping in the NIMH and German samples revealed that the opposite alleles were associated with bipolar disorder in each study, but this does not necessarily invalidate this gene as an interesting candidate (8). Another example is the gene diacylglycerol kinase eta (DGKH), in which Baum et al. reported their most significant findings (rs1012053, combined sample $p = 1.5 \times 10^{-8}$). Although rs1012053 shows little or no evidence of association in the WTCCC imputed dataset (Table 1), at least 6 SNPs within 2 kb of DGKH show significant evidence of association in the WTCCC sample, with p-values as low as 0.006. Could this reflect allelic heterogeneity at the same risk locus?

In conclusion, this meta-analysis reveals several points of agreement between the two GWAS of bipolar disorder published to date. There is significant overlap in association signals, and modest but consistent evidence of association across both studies for two SNPs near two distinct genes. Detailed consideration of the wider distribution of association signals across studies, rather than an unjustified focus on “top hits,” may prove to be a valuable strategy in complex genetics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Random effects meta-analysis results for selected SNPs

				NIMH		German		Wellcome Trust	DerSimonian-Laird (random effects) OR (95% CI)	Random effects p-value	I^2 (%)
SNP	Allele	Nearest gene	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)			
rs10791345	G	JAM3	0.0510	1.27 (0.99-1.62)	0.0146	1.28 (1.05-1.57)	0.0001	1.23 (1.14-1.34)	1.25 (1.14-1.36)	1E-06	0
rs4806874	G	SLC39A3/ZIP3	0.0030	1.35 (1.11-1.63)	0.0136	1.22 (1.04-1.42)	0.0004	1.17 (1.12-1.22)	1.20 (1.12-1.29)	5E-06	0
rs17125698	C	CHES1/FOXN3	0.0299	1.31 (1.03-1.66)	0.0488	1.23 (1.00-1.50)	0.1374	1.09 (1.01-1.18)	1.16 (1.04, 1.28)	0.007	15
rs1010554	C	STAB1	0.0006	1.35 (1.13-1.61)	0.0539	1.15 (1.00-1.33)	0.0467	1.08 (1.00-1.18)	1.17 (1.04-1.32)	0.01	60
rs4411993	C	SORCS2	0.0036	1.52 (1.14-2.04)	0.0296	1.27 (1.02-1.59)	0.4105	1.05 (0.93-1.19)	1.23 (1.00-1.52)	0.054	69*
rs13414801	C	BRE	0.0016	1.35 (1.12-1.64)	0.9130	0.99 (0.85-1.15)	0.0268	1.10 (1.01-1.20)	1.12 (0.97, 1.30)	0.109	69*
rs9513877	G	VGCNL1	0.0006	1.38 (1.15-1.66)	0.0209	1.19 (1.03-1.38)	0.5667	1.02 (0.98-1.07)	1.18 (0.99-1.39)	0.071	79*
rs1170191	G	DGKH	0.0026	1.46 (1.14-1.86)	0.0003	1.41 (1.17-1.70)	0.3854	1.05 (0.98-1.12)	1.26 (1.01-1.61)	0.043	81**
rs1012053	A	DGKH	0.0001	1.66 (1.27-2.18)	1.5E-05	1.57 (1.28-1.92)	0.2761	1.06 (0.95-1.19)	1.38 (1.01, 1.89)	0.044	88**
rs9315885	T	DGKH	0.0037	1.33 (1.10-1.61)	0.0062	1.24 (1.06-1.44)	0.3833	1.04 (0.99-1.09)	1.18 (1.01-1.37)	0.042	88*

* p <0.05

** p <0.005