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LETTERS TO THE EDITOR

Meta-analysis of genome-wide association data of bipolar disorder and major depressive disorder

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Substantial indirect evidence suggests overlap between bipolar disorder (BIP) and major depressive disorder (MDD). BIP and MDD have in common major depressive episodes with BIP being distinguished by the additional presence of manic (bipolar 1) or hypomanic episodes (bipolar 2). Genetic epidemiological[1] and genome-wide linkage studies[2] are also consistent with overlap between genetic risk factors for both disorders. In an attempt to identify common genetic risk factors, we conducted a meta-analysis combining data from genome-wide association studies of BIP (4387 cases and 6209 controls)[3] and MDD (1695 cases and 1761 controls).[4]

Ascertainment, diagnostic assessment, genotyping, quality control and analysis are detailed elsewhere.[3,4] Both studies were conducted under the appropriate ethical approvals, and all subjects provided written informed consent. Briefly, BIP results are obtained from a combined analysis of samples from the UK, the US and Ireland[5,6] with all subjects genotyped using Affymetrix 500K chips (Santa Clara, CA, USA). Most cases met criteria for DSM-IV (Diagnostic and Statistical Manual of Mental Disorders-IV) bipolar 1 (81%) with smaller numbers meeting criteria for bipolar 2 (16%), schizoaffective disorder/manic type (2%), or bipolar NOS (not otherwise specified) (1%). After quality control, 1 769 948 single nucleotide polymorphisms (SNPs) were analyzed (18.7% were directly genotyped and the remainder were imputed using HapMap2 CEU).[7,8] Cases meeting DSM-IV (Diagnostic and Statistical Manual of Mental Disorders-IV) criteria for MDD were ascertained from clinical and community sources, and controls at low liability for MDD were selected from a community sample.[9] Genotyping was conducted by Perlegen using a 600K platform. After quality control (with slightly stricter thresholds to maximize comparability), 1 893 617 SNPs were available (20.4% directly genotyped with the rest imputed using HapMap2 CEU).[10] In both studies, SNPs were dropped for excessive missingness, low minor allele frequencies and marked deviations from Hardy–Weinberg equilibrium. Subjects were removed for excessive missingness, unusual genome-wide heterozygosity, first- or second-degree relation to any other subject, and if empirical ancestry deviated markedly from other subjects. There was no known subject overlap across studies (BIP subjects were from the US, the UK and Ireland, and MDD subjects were from The Netherlands).

After merging SNP lists from BIP and MDD studies (with attention to strand and allele matching), there were 1 472 580 high-quality autosomal SNPs common to both studies (72.3% were imputed in both studies, 5.6% were directly genotyped in both, 11.7% were genotyped in the BIP and imputed in the MDD study, and 10.4% imputed in the BIP and genotyped in the MDD study). Genomic positions were as per NCBI (National Center for Biotechnology Information) Build 36/UCSC hg18.

Fixed-effects meta-analysis was accomplished using a weighted *z*-score method.[11] Figure 1 depicts the results and Supplementary Table S1 lists the SNPs with $P<10^{-5}$ in either primary study or in the meta-analysis. For the combined sample of 6082 cases and 7970 controls, λ_{1000} value was 1.019 (that is, λ scaled to a sample size of 1000 cases and 1000 controls, and the λ value was 1.131) (Figures 1a and b).

We note four findings from the meta-analysis: (A) two SNPs in a 10.5-kb region of *CACNA1C* exceeded a genome-wide significance level of 5×10^{-8}:[12] rs1006737 ($P_{\text{fixed}}=3.1\times10^{-8}$) and rs7297582 ($P_{\text{fixed}}=3.4\times10^{-8}$) (Figure 1c). These SNPs reached genome-wide significance in the initial BIP report and multiple SNPs in this region had $P<0.05$ in the MDD study. For rs1006737*A, the case frequency/odds ratio estimates were: for BIP sample: 0.36/1.18 and for MDD sample: 0.32/1.10 (similar to the findings from a different MDD sample had values 0.36/1.15).[13] Second, two *ANK3* SNPs exceeded genome-wide significance in the initial BIP report but were not supported in the MDD genome-wide association study (rs10994336 and rs10994338 with *P*-values $\sim$0.9). Third, support for the *PCLO* SNP of particular interest in the MDD genome-wide association study (rs2522843) was not increased with meta-analysis although several SNPs had *P*-values <0.05. Fourth, as shown in Supplementary Table S1, several areas were of modest significance in each primary genome-wide association study and of considerably greater significance in the meta-analysis (although none reached the genome-wide significance level): intergenic regions on chromosome 2: 175.95–175.99 Mb and chromosome 13:49.96–49.98 Mb along with SNPs in *SYNE1*, *FAT4*, *DMTF1*, *C7orf23* and *C15orf53*. *SYNE1* (a gene mutated in spinocerebellar ataxia) is of immediate interest as it contains a spectrin-binding domain, suggesting a connection with the function of the BIP susceptibility locus *ANK3*.

In conclusion, this analysis provides support for a role of *CACNA1C* risk variants for both bipolar and

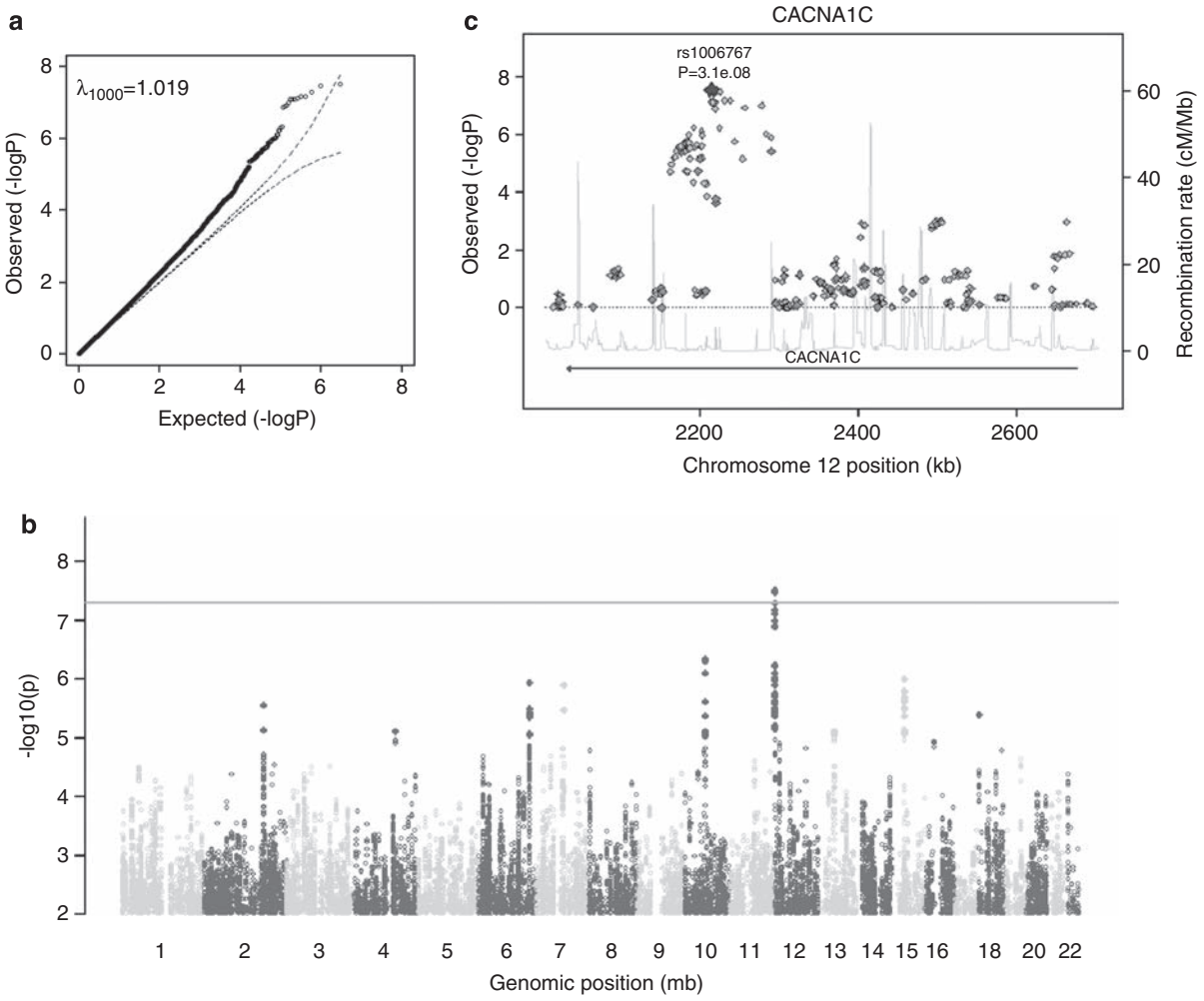

Figure 1 Results of genome-wide association study (GWAS) meta-analysis for bipolar disorder (BIP) and major depressive disorder (MDD). (**a**) Quantile–quantile plot of the meta-analytic results (observed × expected *P*-values on $-\log_{10}$ scale). (**b**) Manhattan plot ($-\log_{10}$ of fixed-effects *P*-value × genomic position). (**c**) The *CACNA1C* region (red diamonds indicate single nucleotide polymorphisms (SNPs) genotyped in both studies, gold SNPs genotyped in one study and imputed in the other, and gray SNPs imputed in both studies).

unipolar major mood disorders. Among the possible explanations, genetic variation in *CACNA1C* might be common, subtle and pleomorphic risk factor for mood disorders. Alternatively, the overlap could be due to misclassification—for example, if some portion of the MDD group was truly ''bipolar-like'', but was misclassified due to diagnostic or nosological error (despite the use of standard and careful methodologies), or if some portion of the BIP group was similarly misclassified.[14] In contrast, the bipolar risk locus *ANK3* did not find support in this meta-analysis, suggesting that its effect may be specific to BIP or that power was insufficient to detect an effect. Finally, our analysis had insufficient power definitively to establish or to exclude the role of several biologically interesting candidate genes (for example, *PCLO* and *SYNE1*), and further insights into their roles in mood disorders await larger-scale mega-analyses.[15]

Conflict of interest

In the interests of full disclosure, Dr Sullivan reports receiving unrestricted research funding from Eli Lilly for genetic research in schizophrenia. Dr Perlis has received speaking or consulting fees from Astra Zeneca, Eli Lilly, GlaxoSmithKline, Pfizer, and Proteus, LLC. Dr Nolen reports receiving unrestricted research funding and Speaker's fee from Astra Zeneca, Eli Lilly, GlaxoSmithKline, Pfizer, Servier and Wyeth. The other authors report no conflicts.

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Life events moderate variation in cognitive ability (*g*) in adults

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The heritability of general cognitive ability (*g*) in adults is estimated to lie approximately between 75 and 85%.[1] Despite this overwhelming indirect evidence of 'genes for *g*', only a handful of genes have been identified so far, together explaining $< \sim 5\%$ of the genetic variation.[2] Several reasons have been suggested for this 'missing heritability',[3] including the presence of gene–environment interactions (GEI). We have investigated the presence of GEI for measured Life Events and *g*, in a population-based sample of adult twins and their siblings ($N = 560$).

The reported large heritability estimates for *g* are derived from classical twin studies, in which additivity of genetic and environmental effects is assumed; implying heritability estimates are equal across environmental conditions. Non-additivity of genetic and environmental effects (that is, GEI), conversely, implies that genes control an individual's sensitivity to environmental influences, or environmental factors moderate gene expression. If GEI is present, the extent to which genes and environment cause variation in *g* varies across environmental conditions, and a single heritability estimate is no longer accurate.[4] Consequently, assuming the absence of GEI may lead to biased estimates of the relative importance of genetic and environmental influences.[4] Moreover, when genetic effects vary across environmental conditions, an environmentally stratified design might seriously improve gene-finding success when researchers focus on those environmental conditions wherein the genetic effects are largest. Gene-finding attempts for *g* would thus benefit from studies that elucidate the environmental circumstances for which genetic effects are largest.