

Impact of a *cis*-associated gene expression SNP on chromosome 20q11.22 on bipolar disorder susceptibility, hippocampal structure and cognitive performance

Ming Li,* Xiong-jian Luo,* Mikael Landén, Sarah E. Bergen, Christina M. Hultman, Xiao Li, Wen Zhang, Yong-Gang Yao, Chen Zhang, Jiewei Liu, Manuel Mattheisen, Sven Cichon, Thomas W. Mühleisen, Franziska A. Degenhardt, Markus M. Nöthen, Thomas G. Schulze, Maria Grigoriou-Serbanescu, Hao Li, Chris K. Fuller, Chunhui Chen, Qi Dong, Chuansheng Chen, Stéphane Jamain, Marion Leboyer, Frank Bellivier, Bruno Etain, Jean-Pierre Kahn, Chantal Henry, Martin Preisig, Zoltán Kutalik, Enrique Castelao, Adam Wright, Philip B. Mitchell, Janice M. Fullerton, Peter R. Schofield, Grant W. Montgomery, Sarah E. Medland, Scott D. Gordon, Nicholas G. Martin, MoodS Consortium,^a The Swedish Bipolar Study Group,^a Marcella Rietschel, Chunyu Liu, Joel E. Kleinman, Thomas M. Hyde, Daniel R. Weinberger and Bing Su

Background

Bipolar disorder is a highly heritable polygenic disorder. Recent enrichment analyses suggest that there may be true risk variants for bipolar disorder in the expression quantitative trait loci (eQTL) in the brain.

Aims

We sought to assess the impact of eQTL variants on bipolar disorder risk by combining data from both bipolar disorder genome-wide association studies (GWAS) and brain eQTL.

Method

To detect single nucleotide polymorphisms (SNPs) that influence expression levels of genes associated with bipolar disorder, we jointly analysed data from a bipolar disorder GWAS (7481 cases and 9250 controls) and a genome-wide brain (cortical) eQTL (193 healthy controls) using a Bayesian statistical method, with independent follow-up replications. The identified risk SNP was then further tested for association with hippocampal volume ($n=5775$) and cognitive performance ($n=342$) among healthy individuals.

Results

Integrative analysis revealed a significant association

between a brain eQTL rs6088662 on chromosome 20q11.22 and bipolar disorder (log Bayes factor = 5.48; bipolar disorder $P=5.85 \times 10^{-5}$). Follow-up studies across multiple independent samples confirmed the association of the risk SNP (rs6088662) with gene expression and bipolar disorder susceptibility ($P=3.54 \times 10^{-8}$). Further exploratory analysis revealed that rs6088662 is also associated with hippocampal volume and cognitive performance in healthy individuals.

Conclusions

Our findings suggest that 20q11.22 is likely a risk region for bipolar disorder; they also highlight the informative value of integrating functional annotation of genetic variants for gene expression in advancing our understanding of the biological basis underlying complex disorders, such as bipolar disorder.

Declaration of interest

None.

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Bipolar disorder is a severe, chronic psychiatric disorder with a worldwide lifetime prevalence ranging from 0.5 to 1.5%.¹ Bipolar disorder is characterised by a variety of profound mood symptoms including episodes of mania, hypomania and depression, and is often accompanied by psychotic features and cognitive deficits. To date, there has been a fair amount of data from family and twin studies to highlight a strong genetic predisposition for bipolar disorder.¹ Nevertheless, bipolar disorder is a highly polygenic disorder that can vary substantially from population to population. Although linkage analysis and genetic association studies have yielded numerous candidate variants for bipolar disorder, only a few of these have been satisfactorily replicated across independent samples.^{2,3}

With advances in knowledge of human genetic variations, such as data generated by the International HapMap and 1000 Human Genome projects and several subsequent genome-wide association studies (GWAS) by a number of international collaborators, a wealth of novel susceptible variants for bipolar disorder have been reported, particularly single nucleotide polymorphisms (SNPs), in the following genes: calcium channel, voltage-dependent, L type, alpha 1C subunit (*CACNA1C*); ankyrin 3, node of Ranvier (ankyrin G) (*ANK3*); teneurin transmembrane protein 4 (*TENM4*); neurocan (*NCAN*); and tetratricopeptide repeat and ankyrin repeat containing 1 (*TRANK1*).^{4–8} These GWAS-identified risk SNPs unfortunately only account for a small portion of the genetic risk for bipolar disorder, which suggests there should be additional loci contributing to the genetic susceptibility. Previous aggregated analyses indicated there might be valid risk loci underlying genetic markers passing only nominal significance in the GWAS,⁹ a possibility confirmed by several later studies. For example, a number of schizophrenia and bipolar

*These authors contributed equally to the work.

^aA list of the additional members is provided in the online Data Supplement to this paper.

disorder susceptibility SNPs did not reach genome-wide significance in initial GWAS samples, but showed consistent replications in subsequent independent samples, thus implying that these loci might reflect weak but true risk signals.¹⁰

Genetic loci associated with clinical diagnosis are also expected to be related to so-called intermediate phenotypes implicated in the biology of genetic risk for bipolar disorder. Previous studies have reported hippocampal dysfunction (e.g. memory impairment) in patients with bipolar disorder and their unaffected relatives, implying that variation in hippocampal biology is an intermediate phenotype related to the genetic risk of bipolar disorder.¹¹ In addition, smaller hippocampal volume has been reported in patients with bipolar disorder.^{12,13} Meanwhile, functional neuroimaging studies have revealed that dysfunctions of the hippocampus and its closely related regions underpin abnormal affective responses and dysfunctional emotion regulation in bipolar disorder.¹⁴ Finally, post-mortem studies further support the hypothesis that hippocampal abnormalities are relevant to the altered synaptic plasticity and diminished resilience in bipolar disorder.¹⁵ Therefore, analysis of bipolar disorder-associated SNPs on these hippocampus-related phenotypes may provide a plausible way to uncover their functions in neurodevelopment, and possibly, their involvement in disease susceptibility.

Recent successes in integrating disease GWAS and gene expression data for several other complex diseases have been promising,^{16–18} and we wondered whether such an approach may yield novel results for bipolar disorder. Predictably, several lines of evidence have suggested an enrichment of expression quantitative trait loci (eQTL) among bipolar disorder susceptibility SNPs in the brain,¹⁹ further highlighting the importance of integrating the functional annotation of genetic variants for gene expression to advance our understanding of the biological bases of bipolar disorder. In light of these findings, we integrated bipolar disorder GWAS data from 16731 individuals and genome-wide eQTL data from 193 human cortex samples from healthy individuals, followed by a set of independent replications on both eQTL and disease associations.

Method

Discovery brain eQTL and bipolar disorder GWAS data-sets

The brain eQTL data-set used in this study was reported previously.²⁰ In brief, after excluding ethnic outliers and samples that were possibly related, a total of 193 independent human cortex samples of European origin from healthy, older individuals (age > 65) were included in the eQTL analysis. Detailed information about genotyping and expression profiling, as well as the statistical methods used, can be found in the online data supplement to this paper or the original publication.²⁰

For the bipolar disorder GWAS data, the working group of the Psychiatric Genomics Consortium (PGC) for bipolar disorder recently conducted a meta-analysis of large-scale genome-wide data on bipolar disorder among populations of European descent (PGC1 family GWAS).⁶ In this earlier study, the researchers opted to compare patients with bipolar disorder that had experienced pathologically relevant episodes of elevated mood (mania or hypomania) and control patients from the same geographical and ethnic populations. To summarise, we used 2 117 872 SNPs across the genome from the GWAS samples (7481 cases and 9250 controls), and the association significance (P -values) for these SNPs was downloaded from the PGC1 data-sharing website (www.med.unc.edu/pgc/downloads). Detailed descriptions

of the samples, data quality, genotype imputation, genomic controls and statistical analyses can be found in the original study.⁶

Integrative analysis of eQTL and bipolar disorder GWAS data

We integrated the eQTL and bipolar disorder GWAS data using a Bayesian statistical framework. Statistical analyses for the eQTL and bipolar disorder GWAS were carried out with the *Sherlock* software tool (<http://sherlock.ucsf.edu/submit.html>), which has been described elsewhere.¹⁷ In brief, *Sherlock* is based on the rationale that a risk gene for the disease may have at least one eQTL, and these eQTLs could alter gene expression, which in turn affects disease susceptibility. Given the probability that this might be true, there should be a significant overlap of the eQTL of a gene and the loci associated with the disorder, which would imply a likely functional role for the gene in that particular disease. At this juncture, *Sherlock* aligns the eQTL and bipolar disorder GWAS and considers only the shared SNPs in both data-sets. *Sherlock*'s scoring rubric both increases the total gene score for overlapping SNPs and provides a penalty in the absence of an overlap, although associations found only in the bipolar disorder GWAS do not alter the score. *Sherlock* computes individual log Bayes factors (LBFs) for each SNP pair in the alignment, and the sum of these constitutes the final LBF score for each gene.

Brain eQTL data for replication analysis

Considering that bipolar disorder is a mental disorder that originates from abnormal brain function, brain samples are presumably appropriate for replication testing of the eQTL results. We first used a brain dorsolateral prefrontal cortex (DLPFC) sample ($n=320$) consisting of White and African-American healthy controls (labelled as the 'first replication sample'), in which the sample had been previously used to identify psychiatric risk mRNA transcripts.^{21–23}

We also used other well-characterised brain expression databases for replication analysis of the eQTL associations. A brief description of the gene expression resources is provided as follows, whereas more detailed information can be found in the original studies.^{18,24–26}

- BrainCloud: BrainCloud contains genetic information and whole-transcriptome expression data from the post-mortem DLPFC of 261 healthy White and African-American individuals. The data in BrainCloud are aimed at exploring temporal dynamics and genetic control of transcription across the lifespan.²⁴ Of note, there is partial overlap between BrainCloud data and our 'first replication sample'.
- Data from the study by Webster *et al*: Webster and colleagues studied the relationship between the human brain transcriptome and genome in a series of neuropathologically normal post-mortem samples and a confirmed pathological diagnosis of late-onset Alzheimer's disease (final $n=188$ controls, 176 cases). They suggested that studying the transcriptome as a quantitative endophenotype has greater power for discovering risk SNPs that influence expression than the use of discrete diagnostic categories, such as disease presence or absence.²⁵ It should be noted that the control sample in this study was the same as our discovery brain eQTL sample.²⁰
- SNPEXpress: The authors, using Affymetrix exon arrays, analysed genome-wide SNPs that are associated with gene expression in human primary cells at the exon level, and

evaluated 93 autopsy-collected, cortical brain tissue samples with no defined neuropsychiatric conditions.²⁶

- (d) Data from the study by Zou *et al*: The authors of this study measured the expression levels of 24 526 transcripts in brain samples from the cerebellum and temporal cortex of autopsied individuals with Alzheimer's disease (cerebellar $n=197$, temporal cortex $n=202$), and conducted an expression GWAS using 213 528 *cis*-SNPs within 100 kb of the tested transcripts. Their results demonstrated the significant contributions of genetic factors to human brain gene expression, which are reliably detected across different brain regions; they also suggested that the combined assessment of expression and disease GWAS might provide complementary information in the discovery of human disease variants with functional implications.¹⁸

Bipolar disorder samples for replication analysis

Replication analyses on bipolar disorder samples were conducted in two steps (replication-I and -II), examining a total of 6056 bipolar disorder cases and 46 614 controls from 10 different geographical locations. Detailed information on each sample, including diagnostic assessment, genotyping method and quality control, are shown in the online data supplement and online Table DS1.

Briefly, the bipolar disorder samples used in our replication-I analysis included: (a) Germany II (181 cases and 527 controls);⁵ (b) Germany III (490 cases and 880 controls);⁵ (c) Australia (330 cases and 1811 controls);⁵ (d) France (451 cases and 1631 controls);² (e) Sweden I (836 cases and 2093 controls);⁶ (f) Sweden II sample (1415 cases and 1271 controls);⁶ (g) Iceland (541 cases and 34 546 controls);⁶ (h) Romania (244 cases and 174 controls);⁵ and (i) China (350 cases and 888 controls).²⁷ For our replication-II analysis, we used a UK sample (1218 cases and 2913 controls).²⁸ The 10 samples from the replication-I and II analyses showed no overlap with the PGC1 bipolar disorder samples.⁶ Each of the original studies was conducted under appropriate ethical approval. Written informed consent was obtained from all participants.

Samples for analysis of hippocampal volume and cognitive performance

For the analysis of hippocampal volume, we used the data from a recent GWAS conducted by the Enhancing Neuro Imaging Genetics through Meta Analysis (ENIGMA) consortium.²⁹ The GWAS includes a total of 5775 young and healthy individuals (mean age: 34.8 years). Detailed information on the samples, imaging procedures, genotyping methods and statistical analysis can be found in the original GWAS report.²⁹

For analysis of cognitive performance, we used a Chinese sample that included 342 healthy Chinese college students from Beijing Normal University who had self-reported no known history of any neurological or psychiatric disorders (197 women and 145 men, aged 18–23). Cognitive and behavioural measures (shown in online Table DS2) included working memory, executive functions (as assessed with the Attention Network Test, the Wisconsin Card Sorting Task and a reversal-learning test) and personality traits. The institutional review board of the State Key Laboratory of Cognitive Neuroscience and Learning at Beijing Normal University, China approved this experiment. Written informed consent was obtained from all participants following a full explanation of the study procedure.

Statistical analysis

For the replication analysis of bipolar disorder, genomic control was used to correct for relatedness and potential population stratification in each sample;³⁰ association P -values and allele-specific odds ratios (ORs) for each individual sample were calculated with a logistic regression model with an additive effect using a lambda value (genomic control) as a covariate to adjust for potential population stratification. Meta-analyses were then conducted based on Z -scores by combining data from different samples in the R software package (www.r-project.org) (meta-module) using the Cochran–Mantel–Haenszel test under the fixed-effects model. As described in a previous GWAS meta-analysis,⁶ P -values for replication samples are reported as one-tailed tests, whereas P -values for all combined samples are shown as two-tailed tests. We used a forest plot to graphically present the individual ORs and their 95% confidence intervals (CIs), i.e. each sample was represented by a square in the forest plot. For the analyses on cognitive performance, two-tailed t -tests were conducted with SPSS version 16.0 (IBM Corporation, Armonk, New York, USA).

To explain the logic of the study design, a flow chart summarising the analytical methods and showing how variants were taken forward from one stage of analysis to the next is shown in Fig. 1. All protocols and methods used in this study were approved by the institutional review board of the Kunming Institute of Zoology, Chinese Academy of Sciences and adhere to all relevant national and international regulations.

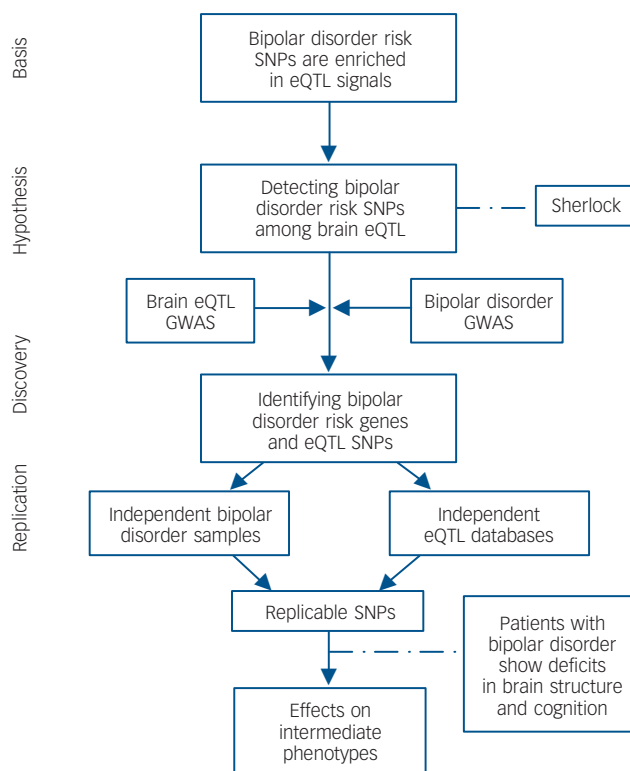


Fig. 1 Flow chart of the present study.

Based on the hypothesis that bipolar disorder risk variants are enriched among eQTL, we systematically integrated bipolar disorder GWAS and genome-wide brain eQTL data with the *Sherlock* software tool. The top genes identified by *Sherlock* were then replicated in independent bipolar disorder samples and eQTL data-sets. Finally, the successfully replicated SNP (rs6088662) was further tested for associations with bipolar disorder phenotypes including hippocampal volume and cognitive performance. SNP, single nucleotide polymorphism; eQTL, expression quantitative trait loci; GWAS, genome-wide association study.

Results

Integrative analysis of eQTL and bipolar disorder GWAS data

Sherlock identified a total 20 942 SNPs showing significant eQTL effects, and also having bipolar disorder data (e.g. *P*-values), and these SNPs were included for further analyses. Using a Bayesian statistical method to match the ‘signature’ of genes from the brain eQTL with patterns of association in the bipolar disorder GWAS, we ranked the top candidate genes for bipolar disorder risk according to their LBF scores and *P*-values. Only genes with LBF scores higher than 5.00 were shown and included for further analyses.

The integrative analysis yielded four candidate risk genes (online Table DS3). The first gene was glycosyltransferase 8 domain containing 1 (*GLT8D1*; LBF = 6.78), located on chromosome 3p21.1, which has been repeatedly reported for association with bipolar disorder.^{31,32} Detailed analysis revealed that the significant association with this gene was mainly driven by a *cis*-associated SNP (rs2251219). This SNP had already been reported in an earlier GWAS of bipolar disorder,³² and was replicated in independent bipolar disorder samples. (Their samples overlapped with our replication samples.^{33–35}) The second top-ranked gene was chemokine (C-X-C motif) ligand 16 (*CXCL16*; LBF = 6.16), which is located on chromosome 17p13. To the best of our knowledge, this gene has never been reported in genetic association studies on bipolar disorder, and we observed two *trans*-associated SNPs showing moderate associations with bipolar disorder. The third top-ranked gene was transient receptor potential cation channel, subfamily C, member 4 associated protein (*TRPC4AP*; LBF = 5.57) located on chromosome 20q11.22, with the significance mainly driven by a *cis*-associated SNP (rs6088662, $P = 5.85 \times 10^{-5}$ with bipolar disorder). The last top-ranked gene was TAF11 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 28 kDa (*TAF11*; LBF = 5.52) located on chromosome 6p21.31, with a *trans*-associated SNP (rs4482754), which also showed significant association with bipolar disorder.

Replication of eQTL effects in diverse samples

Given the many confounders in a single eQTL database, it is important and necessary to validate the eQTL associations in independent samples. The previously mentioned four candidate genes and their *cis*- or *trans*-associated SNPs were followed up in independent eQTL data-sets.

For the *cis*-associated SNP rs2251219 and *GLT8D1*, we observed significant association in one replication sample of Alzheimer’s disease source (online Table DS4),²⁵ and a marginally significant association in the BrainCloud sample.²⁴ However, as demonstrated by a previous study,³² the association of rs2251219 with *GLT8D1* expression in our discovery eQTL sample (Myers *et al* study)²⁰ may be an artifact, since the probes overlapped with other common SNPs and it could not be replicated in the original cDNA samples of our discovery eQTL data-set by quantitative polymerase chain reaction using probes not overlapping with known SNPs. In addition to *GLT8D1*, we also analysed the expression of other nearby genes around rs2251219; however, no promising findings were observed (Table DS4). For the significant *trans*-eQTL associations in our discovery sample, neither *CXCL16* nor *TAF11* could be validated in any of the replication samples (online Table DS5), implying they might have been generated by chance.

For the *cis*-association between rs6088662 and *TRPC4AP* expression, in the discovery eQTL brain sample,²⁰ the risk allele

G of rs6088662 showed significantly decreased gene expression ($P < 1.0 \times 10^{-8}$, Fig. 2(a)). This pattern was validated in one of the replication samples ($P < 1.0 \times 10^{-8}$),²⁵ but it should be noted that these replication data include our discovery sample. We therefore re-analysed the result using the non-overlapped Alzheimer’s disease patients, and it showed a nominally significant association ($P = 0.023$, Fig. 2(b)). However, rs6088662 showed an opposite effect on *TRPC4AP* expression in our ‘first replication sample’. (The risk allele G of rs6088662 showed increased gene expression.) In other replication samples, no significant association between rs6088662 and *TRPC4AP* was observed (online Table DS6).^{18,26} These inconsistencies may not be surprising, given a prior report of low-to-moderate overlap between eQTL loci across eQTL studies. (The percentage of overlapped eQTL is from 0 to approximately 35.4% between pairwise brain studies, as shown in Table 4 of the study by McKenzie *et al*³⁶). In addition, with the use of several non-brain tissue eQTL databases,^{37–39} we also observed significant and consistent associations between rs6088662 and *TRPC4AP* expression. (The *P*-values range from 0.047 to 3.60×10^{-7} ; online Figs DS1–DS3.)

To further examine whether rs6088662 is also associated with the expression of other nearby genes, we screened 14 genes in the 20q11.22 region in both discovery and replication eQTL samples (Table DS6). Intriguingly, we observed another gene, gamma-glutamyltransferase 7 (*GGT7*) showing significant association in the discovery sample ($P < 1.0 \times 10^{-7}$; Fig. 3(a)), and it remained significant in the ‘first replication sample’ with the same direction of effect ($P < 1.0 \times 10^{-8}$; Fig. 3(b)). In other replication samples, the association has also been significant (Webster *et al*²⁵ and Zou *et al*¹⁸ studies; Fig. 3(c) and Table DS6) or marginally significant (BrainCloud),²⁴ except for the study by Heinzen *et al*²⁶ ($P = 0.13$); however, in the sample analysed by Heinzen *et al*, rs6088662 still showed one of the strongest associations with *GGT7* among the genes located on chromosome 20q11.22, and the SNP showed significant or marginally significant associations with the expression of several exons in *GGT7* (online Table DS7), which was not observed in the majority of other nearby genes.

The other genes located on chromosome 20q11.22, *ACSS2*, *MYH7B* and *EDEM2i*, also showed associations in some of the eQTL samples, but the associations were not consistent and these genes are unlikely to be the associated genes (Table DS6). To summarise, from the eQTL analyses in both discovery and replication samples, we have been able to show that rs6088662 is likely to be an authentic eQTL SNP, and we found two potential genes (*GGT7* and *TRPC4AP*) showing an association with this risk SNP.

rs6088662 is associated with bipolar disorder across cohorts

Given the replication of significant associations between rs6088662 and *TRPC4AP* expression, we opted to further analyse this SNP with regard to bipolar disorder risk. In the stage I replication analysis, we analysed rs6088662 in nine independent case–control samples. Although the association between rs6088662 and bipolar disorder did not achieve even nominal significance ($P = 0.05$) in any single cohort, it did show a trend of association in the Germany II and Sweden II samples ($P = 0.08$ and $P = 0.07$ respectively). In the Chinese sample, there was no difference in allele frequencies of this SNP between Han Chinese and Europeans (0.165 *v.* 0.171 for the risk allele G), and the effect size (OR) in the Chinese sample was even higher than in our discovery sample (1.17 *v.* 1.12), the non-significant result being likely due to the limited sample size. When all the replication-I samples were combined, the association *P*-value reached nominal significance level ($P = 4.95 \times 10^{-2}$), with the

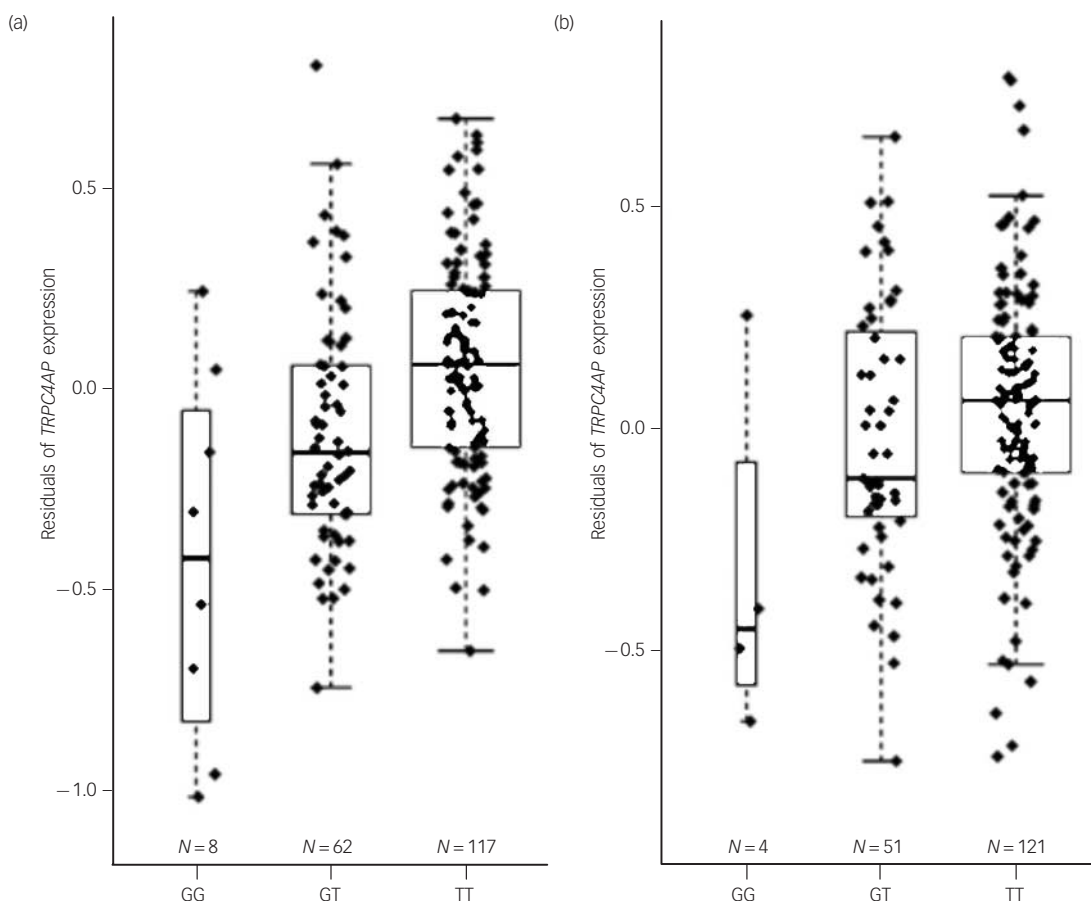


Fig. 2 The risk SNP rs6088662 is significantly associated with *TRPC4AP* mRNA expression. (a) Results in 193 neuropathologically normal human brain (cortical) samples from European individuals. (b) Results in 176 Alzheimer's disease human brain (cortical) samples from European individuals. SNP, single nucleotide polymorphism.

OR being 1.06 (95% CI = 0.99–1.13), consistent with the discovery PGC1 GWAS. There was no significant heterogeneity among the replication-I samples ($P=0.77$). Detailed results for each individual sample are shown in Table 1. The forest plot of the meta-analysis of all replication-I samples is shown in Fig. 4.

Notably, a previous study²⁸ reported a significant association of a proxy SNP of rs6088662 (rs13041792, $r^2=1.00$ with rs6088662 in Europeans) with bipolar disorder in an independent UK sample (1218 cases and 2913 controls), which is in agreement with our results and was also included in our analysis, denoted as the 'replication-II' sample. Meta-analysis by combining PGC1 GWAS, replication-I and replication-II samples yielded a genome-wide significant association of rs6088662 with bipolar disorder ($P=3.54 \times 10^{-8}$, OR = 1.12, 95% CI = 1.07–1.16, Table 1). We used the fixed-effects model for meta-analysis because there was no significant heterogeneity among the samples ($P>0.05$).

Considering the genetic overlap between bipolar disorder and other psychiatric disorders,¹ we also tested the association of rs6088662 with two other mental disorders, schizophrenia and major depressive disorder. It showed a nominally significant association with schizophrenia in the latest PGC2 GWAS ($P=0.0037$, OR = 1.04, 95% CI = 1.00–1.08, $n=35\,476/46\,839$);⁴⁰ however, it did not show any significant associations with major depressive disorder when using data from the PGC1 major depressive disorder GWAS plus the PsyCoLaus study samples (10 541/11 208) (online Table DS8),^{41,42} implying that rs6088662 is likely a psychosis risk SNP rather than a risk SNP for a broader spectrum of mood disorders.

A proxy search for SNPs in high linkage disequilibrium with rs6088662 was performed on the SNP Annotation and Proxy

Search (SNAP) database, version 2.2 (www.broadinstitute.org/mpg/snap/ldsearch.php) with the European panel from the 1000 Human Genome project (pilot 1) data-set. This identified 43 SNPs in high linkage disequilibrium ($r^2>0.8$) with rs6088662, all of which are located within the *MYH7B* and *TRPC4AP* regions (Fig. 5). Among these, there are one non-synonymous SNP, three synonymous SNPs, one SNP in the 3' untranslated region (3' UTR) and one SNP located in the non-coding RNA (ncRNA) region (online Table DS9). However, to identify causal variants for bipolar disorder, further studies are needed.

rs6088662 is associated with hippocampal volume and cognitive performance

To move beyond statistical association with clinical diagnosis and to obtain convergent evidence for an association between rs6088662 and bipolar disorder-related biology, we also performed a series of convergent experiments testing risk-associated SNPs on several intermediate biological phenotypes. The hippocampus is located under the cerebral cortex and it is a region frequently reported to show dysfunction among patients with bipolar disorder.^{18,23} We therefore hypothesised that if the identified risk-associated SNP (e.g. rs6088662) affects the anatomy or function of this brain region, then related cognitive deficits, regardless of illness status, should be associated with it. In an exploratory manner, we tested the effects of rs6088662 on the biological phenotypes related to the hippocampus (hippocampal volume and cognitive performance) in healthy individuals.

In the ENIGMA sample, rs6088662 was significantly associated with hippocampal volume across multiple cohorts

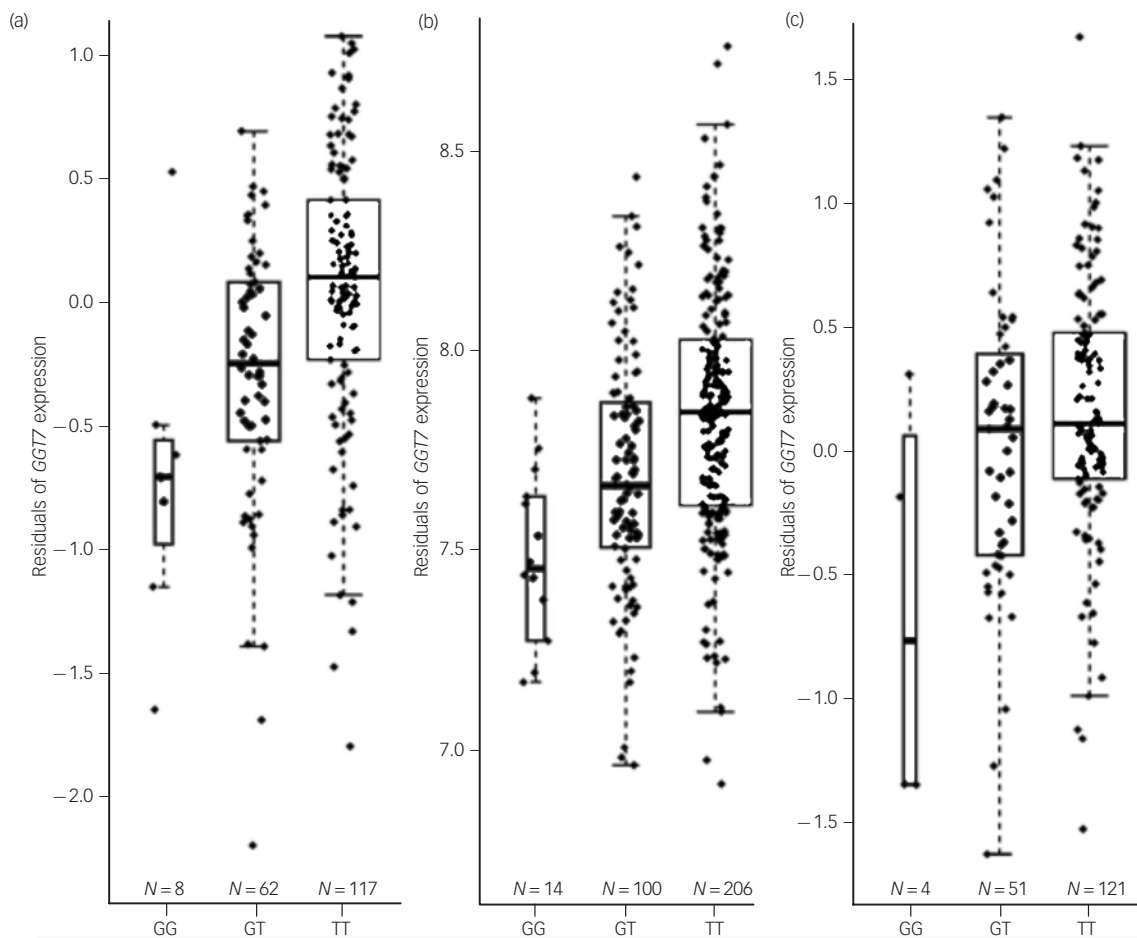


Fig. 3 The risk SNP rs6088662 is significantly associated with *GGT7* mRNA expression. (a) Results in 193 neuropathologically normal human brain (cortical) samples from European individuals. (b) Results in 320 healthy human brain DLPFC samples from White and African-American individuals. (c) Results in 176 Alzheimer's disease human brain (cortical) samples from European individuals. DLPFC, dorsolateral prefrontal cortex.

($P=0.00063$, $\beta=27.29 \text{ mm}^3$; online Table DS10), supporting the prior hypothesis that bipolar disorder-associated SNPs will likely affect hippocampal structure, although detailed analysis found that the risk allele G led to larger hippocampal volume. As a *post hoc* exploratory test, we then investigated the potential impact of rs6088662 on cognitive performance and found that rs6088662 showed a nominally significant association with executive functions (the alert attention task) ($P=0.0094$; online Table DS11) and language abilities (visual/auditory) ($P=0.012$; online Table DS11). Again, the risk allele G indicated a better cognitive performance.

Analysis of bipolar disorder-related phenotypes further confirmed the role of the risk SNPs in bipolar disorder susceptibility and implied it may be functional in the brain. However, as the association results on these intermediate phenotypes (especially for cognitive performance) may not survive multiple correction, further validation in larger samples is needed. In addition, the discrepancy of allelic directionality between clinical diagnosis and intermediate phenotypes suggests that the molecular mechanism at work may be more complicated than we had initially expected when undertaking this study.

Discussion

Findings relating to the 20q11.22 region

In this study, using an integrative analysis that involved both expression and bipolar disorder data, we identified a potential risk

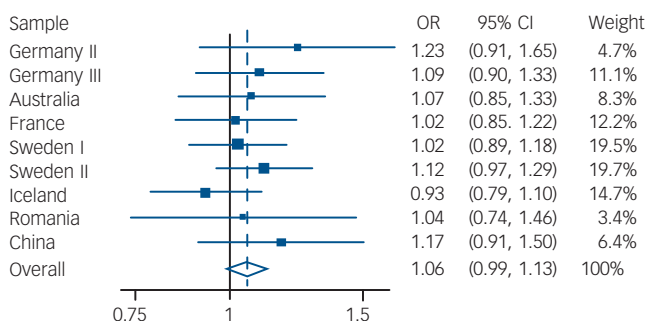
locus on chromosome 20q11.22 for bipolar disorder, although it remains unclear which SNPs are actually responsible. This genomic region contains an extensive area of high linkage disequilibrium spanning approximately 276 kb, including at least five protein coding genes (Fig. 5). Of the 43 common SNPs in high linkage disequilibrium ($r^2 > 0.8$) with rs6088662, there is one non-synonymous SNP, three synonymous SNPs, one SNP in the 3' UTR area and one SNP located in the ncRNA region, all of which are potentially functional but have, as of yet, unknown roles (online Table DS9).

We found a nominally significant association of bipolar disorder risk SNPs with hippocampal volume and cognitive performance, which is consistent with the prevalent perspective that many bipolar disorder-related genes also affect brain structures and cognitive functions. Rather perplexingly though, the rs6088662 risk allele actually seemed to be associated with larger hippocampal volume and better cognition, running entirely opposite to the conventional view that risk alleles generally lead to smaller hippocampal volume and worse cognition. One potential speculative explanation is that the risk genes (*GGT7* or *TRPC4AP*) may play diverse roles in neural development, and the SNP has pleiotropic effects – some detrimental and some beneficial. Another possible explanation is that gene-behaviour association differs by diagnosis status, as previous studies also reported other similar situations: for example, the psychosis risk allele rs1344706 in *ZNF804A* is associated with better cognitive performance in

Table 1 Summary of logistic regression results for rs6088662 across cohorts

Sample	Ethnicity	Cases	Controls	Effect allele	Additive P^a	Odds ratio	95% CI	Data source
Discovery PGC1	European	7481	9250	G	5.85×10^{-5}	1.12	1.06–1.19	Sklar <i>et al</i> ⁶
Replication-I								
Germany II	German	181	527	G	0.08	1.23	0.91–1.65	This study
Germany III	German	490	880	G	0.16	1.09	0.90–1.33	This study
Australia	Australian	330	1811	G	0.29	1.07	0.85–1.33	This study
France	French	451	1631	G	0.42	1.02	0.85–1.22	This study
Sweden I	Swedish	836	2093	G	0.37	1.02	0.89–1.18	This study
Sweden II	Swedish	1415	1271	G	0.07	1.12	0.97–1.29	This study
Iceland	Icelandic	541	34 426	G	0.19	0.93	0.79–1.10	This study
Romania	Romanian	244	174	G	0.42	1.04	0.74–1.46	This study
China	Han Chinese	350	888	G	0.11	1.17	0.91–1.50	This study
Total ^b		4838	43 701	G	4.95×10^{-2}	1.06	0.99–1.13	
Replication-II								
UK	British	1218	2913	G	1.06×10^{-6}	1.34	1.19–1.51	Green <i>et al</i> ²⁸
Discovery + replication samples ^c		13 537	55 864	G	3.54×10^{-8}	1.12	1.07–1.16	

CI, confidence interval; PGC, Psychiatric Genomics Consortium.
a. P -values are two-sided for the discovery cohort and combined analysis; one-sided P -values are listed for the replication-I samples.
b. Heterogeneity test: all replication-I cohorts: $P=0.77$, $I^2=0\%$; meta-analysis was conducted under a fixed-effects model.
c. Heterogeneity test: discovery + replication samples: $P=0.07$, $I^2=41.8\%$; meta-analysis was conducted under a fixed-effects model.

**Fig. 4** Forest plot of odds ratios (ORs) with a 95% confidence interval (CI) for total replication-I bipolar disorder samples included in the meta-analysis of rs6088662.

The risk allele G of rs6088662 is overrepresented in bipolar disorder cases in all of the tested cohorts (except for the Icelandic sample).

patients with schizophrenia as seen in two independent samples.^{43,44} Likewise, another psychosis risk SNP (rs1006737) in *CACNA1C* was shown to be associated with larger grey matter volume for those with the risk allele.^{45,46}

Additional evidence of *GGT7* and *TRPC4AP* in bipolar disorder

TRPC4AP is known to be a substrate-specific adapter of a double-cortin (DCX; DDB1-CUL4-X-box) E3 ubiquitin ligase complex required for cell-cycle control, and *GGT7* is a member of a gene family that encodes enzymes involved in the metabolism of glutathione and in the transpeptidation of amino acids; however, their roles in bipolar disorder susceptibility are still unclear. Here we studied the spatial expression profiling of *GGT7* and *TRPC4AP* in multiple human tissues to see whether their expression was enriched in brain tissues, as bipolar disorder is a mental disorder that mainly originates from abnormal brain function, and if these genes are preferentially expressed in the brain, which would make more sense when considering them as potential risk genes for bipolar disorder. We used the expression data from the Genotype-Tissue Expression project,⁴⁷ in which 3797 tissues from 150 post-mortem donors have been collected and subsequently analysed using an RNA sequencing-based gene expression

approach. Notably, we found that *GGT7* is abundantly expressed in human brain tissues, such as the cerebellum (online Fig. DS4(a)), whereas the expression level of *GGT7* is generally low in non-neural tissues. However, the expression of *TRPC4AP* in brain tissue is relatively lower than in other tissues (online Fig. DS4(b)), but this gene has been previously reported in association with Alzheimer's disease,^{48,49} a neurological disorder showing a high comorbidity with affective disorders, such as bipolar disorder and major depressive disorder, in geriatric populations.⁵⁰

Implications

Alongside our specific findings for genetic susceptibility to bipolar disorder, our results highlight several advantages of convergent analysis using bipolar disorder and eQTL GWAS data-sets (Fig. 1) over conventional analytical strategies aimed at uncovering susceptibility genes. First, analyses such as ours may identify genes that may be missed by traditional univariate analytical approaches, because these genes tend to be authentic risk genes but with small effects. Second, the identification of eQTL effects of the risk SNPs could provide insights for future focused studies, since conventional analyses often observe a large linkage disequilibrium region containing numerous genes showing association with the illness, but actually determining which one is the susceptibility gene is, at best, difficult. Third, significant association between eQTL and illness has been consistently replicated across independent data-sets, providing convergent validity for findings and suggesting potentially higher reproducibility for this kind of system level analysis. Given these advantages, it is likely that further studies using similar methods will strengthen the case for such studies in trying to uncover genetic risk factors for psychiatric diseases.

Study limitations

Although this study offers some interesting observations, it should be noted that the present evidence is limited, and we are therefore cautious in interpreting these results:

- In the integrative analysis of bipolar disorder and eQTL GWAS data, we arbitrarily selected genes that were scored higher than 5.0 (LBF score). As such, it is possible that some genes that

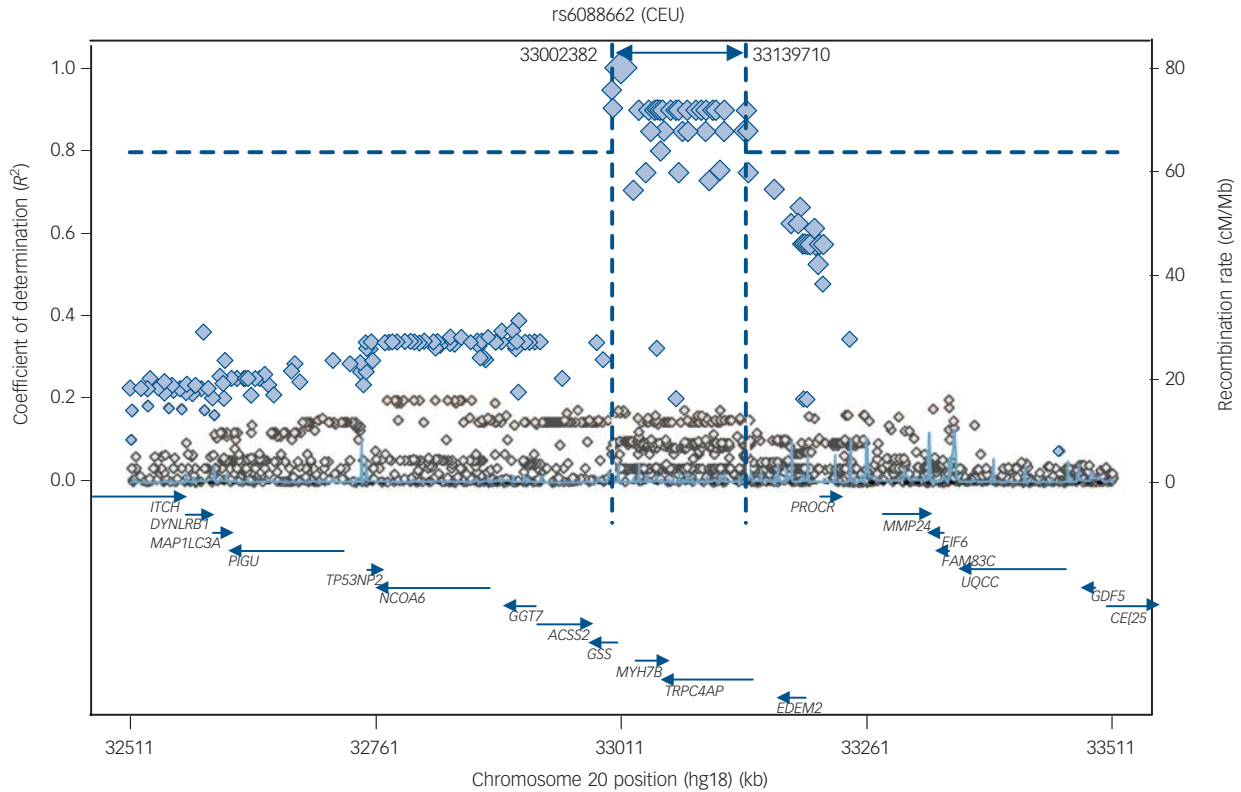


Fig. 5 Plot of chromosome region showing a genomic area of high linkage disequilibrium with rs6088662 in European populations. CEU, Northwestern Europe.

may contribute to bipolar disorder risk but did not meet our selection criteria could have been missed.

- (b) Similarly, although we used GWAS data in our analysis, SNP coverage is still relatively low and other true risk SNPs may have been missed. Due to the dearth of functional data, it is difficult to identify the causative variant(s).
- (c) Likewise, we cannot exclude the possibility that the positive association signal was actually caused by the hitchhiking effect of rare missense mutations, copy number variations or variants in a distant region. Further focused studies may provide a more complete survey.
- (d) The SNPs in the discovery eQTL sample were not imputed, thus reducing the overlap between eQTL and GWAS datasets and the power of our method, although we believe the obtained results are valuable.
- (e) The gene expression coverage in the discovery eQTL data-set is relatively low, and we cannot exclude the possibility of other missing risk genes during the integrative analyses, although we conducted a comprehensive replication and fine mapping analyses to localise the actual risk genes. Further studies using a high coverage array or RNA sequencing are warranted.
- (f) It also should be acknowledged that the eQTL databases we used are highly variable, in terms of expression platforms and tissue quality, age and diagnoses. It is highly likely that biological factors mediating eQTL associations, such as epigenetic regulation, transcription factor binding and microRNA dynamics will vary across age and diagnosis.
- (g) We would also like to note that our results reached genome-wide significance in the final meta-analysis of our ten new samples added to the public bipolar disorder data-set. Our

understanding of the association of rs6088662 with bipolar disorder and with gene expression and hippocampal biology might have started first with the combined GWAS result, but this was not our strategy.

In conclusion, our data from large-scale samples support that SNPs located on chromosome 20q11.22 are significantly associated with bipolar disorder. We observed associations with *GGT7* and *TRPC4AP* mRNA expression, hippocampal volume and cognitive performance. Although the actual risk gene(s) for bipolar disorder in this genomic region are yet to be determined, future studies may give a more compelling picture on the association between these potential risk factors and genetic susceptibility to bipolar disorder.

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Ming Li, PhD, State Key Laboratory of Genetic Resources and Evolution, Kunming Institute of Zoology, Chinese Academy of Sciences, Kunming, Yunnan, China, and Lieber Institute for Brain Development, Johns Hopkins University, Baltimore, Maryland, USA; **Xiong-jian Luo**, PhD, Key Laboratory of Animal Models and Human Disease Mechanisms of the Chinese Academy of Sciences and Yunnan Province, Kunming Institute of Zoology, Kunming, Yunnan, China; **Mikael Landén**, MD, PhD, Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, and Section of Psychiatry and Neurochemistry, Sahlgrenska Academy at Gothenburg University, Gothenburg, Sweden; **Sarah E. Bergen**, PhD, Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden, and Stanley Center for Psychiatric Research, Broad Institute of Harvard and MIT, Cambridge, Massachusetts, USA; **Christina M. Hultman**, PhD, Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden; **Xiao Li**, MSc, **Wen Zhang**, PhD, **Yong-Gang Yao**, PhD, Key Laboratory of Animal Models and Human Disease Mechanisms of the Chinese Academy of Sciences and Yunnan Province, Kunming Institute of Zoology, Kunming, Yunnan, China; **Chen Zhang**, PhD, Schizophrenia Program, Shanghai Mental Health Center, and Shanghai Jiao Tong University School of Medicine, Shanghai, China; **Jiewei Liu**, MSc, State Key Laboratory of Genetic Resources and Evolution, Kunming Institute of Zoology, Chinese Academy of Sciences, Kunming, Yunnan, and Kunming College of Life Science, University of Chinese Academy of Sciences, Kunming, Yunnan, China; **Manuel Mattheisen**, MD, Department of Biomedicine, Aarhus University, Aarhus C, Denmark; **Sven Cichon**, PhD, Division of Medical Genetics, University of Basel, Basel, Switzerland, Institute of Human Genetics and Department of Genomics, Life and Brain Center, University of Bonn, Bonn, and Institute of Neuroscience and Medicine (INM-1), Structural and Functional Organization of the Brain, Genomic Imaging, Research Centre Jülich, Germany; **Thomas W. Mühleisen**, PhD, Institute of Human Genetics and Department of Genomics, Life and Brain Center, University of Bonn, Bonn, and Institute of Neuroscience and Medicine (INM-1), Structural and Functional Organization of the Brain, Genomic Imaging, Research Centre Jülich, Germany; **Franziska A. Degenhardt**, MD, Institute of Human Genetics and Department of Genomics, Life and Brain Center, University of Bonn, Bonn, Germany; **Markus M. Nöthen**, MD, Institute of Human Genetics and Department of Genomics, Life and Brain Center, University of Bonn, Bonn, and German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany; **Thomas G. Schulze**, MD, Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim/University of Heidelberg, Mannheim, Section on Psychiatric Genetics, Department of Psychiatry and Psychotherapy, University Medical Center, Georg-August-University, Göttingen, and Institute of Psychiatric Phenomics and Genomics (IPPG), Ludwig-Maximilians-University Munich, Munich, Germany; **Maria Grigoriou-Serbanescu**, PhD, Biometric Psychiatric Genetics Research Unit, Alexandru Obregia Clinical Psychiatric Hospital, Bucharest, Romania; **Hao Li**, PhD, **Chris K. Fuller**, MSc, Department of Biochemistry and Biophysics, University of California at San Francisco, San Francisco, California, USA; **Chunhui Chen**, PhD, **Qi Dong**, PhD, State Key Laboratory of Cognitive Neuroscience and Learning & IDG/McGovern Institute for Brain Research, Beijing Normal University, Beijing, and Center for Collaboration and Innovation in Brain and Learning Sciences, Beijing Normal University, Beijing, China; **Chuansheng Chen**, PhD, Department of Psychology and Social Behavior, University of California, Irvine, California, USA; **Stéphane Jamain**, PhD, Inserm U 955, IMRB, Psychiatrie Génétique, Créteil, Université Paris Est, Faculté de Médecine, and Fondation Fondamentale, Créteil, France; **Marion Leboyer**, MD, PhD, Inserm U 955, IMRB, Psychiatrie Génétique, Créteil, Université Paris Est, Faculté de Médecine, Fondation Fondamentale, Créteil, and AP-HP, Hôpital A. Chenevier – H. Mondor, Pôle de Psychiatrie, Créteil, France; **Frank Bellivier**, MD, PhD, Inserm U 955, IMRB, Psychiatrie Génétique, and Fondation Fondamentale, Créteil, AP-HP, Groupe hospitalier Lariboisière – F. Widal, Pôle de Psychiatrie, Paris, and Université Paris Diderot, Paris, France; **Bruno Etain**, MD, PhD, Inserm U 955, IMRB, Psychiatrie Génétique, Créteil, Université Paris Est, Faculté de Médecine, Créteil, Fondation Fondamentale, Créteil, and AP-HP, Hôpital A. Chenevier – H. Mondor, Pôle de Psychiatrie, Créteil, France; **Jean-Pierre Kahn**, MD, PhD, Fondation Fondamentale, Créteil, and Département de Psychiatrie et de Psychologie Clinique, CHU de Nancy, Hôpital Jeanne d'Arc, Toul, France; **Chantal Henry**, MD, PhD, Inserm U 955, IMRB, Psychiatrie Génétique, Créteil, Université Paris Est, Faculté de Médecine, Créteil, Fondation Fondamentale, Créteil, and AP-HP, Hôpital A. Chenevier – H. Mondor, Pôle de Psychiatrie, Créteil, France; **Martin Preisig**, MD, MPH, Department of Psychiatry, Centre Hospitalier Universitaire Vaudois, Prilly, Switzerland; **Zoltán Kutalik**, PhD, Institute of Social and Preventive Medicine, Centre Hospitalier Universitaire Vaudois, Lausanne, and Swiss Institute of Bioinformatics, Lausanne, Switzerland; **Enrique Castelao**, MSc, Department of Psychiatry, Centre Hospitalier Universitaire Vaudois, Prilly, Switzerland; **Adam Wright**, PhD, **Philip B. Mitchell**, MD, School of Psychiatry, University of New South Wales, Sydney, and Black Dog Institute, Prince of Wales Hospital, Sydney, Australia; **Janice M. Fullerton**, PhD, **Peter R. Schofield**, PhD, Neuroscience Research Australia, Sydney and School of Medical Sciences, Faculty of Medicine, University of New South Wales, Sydney, Australia; **Grant W. Montgomery**, PhD, **Sarah E. Medland**, PhD, **Scott D. Gordon**, PhD, **Nicholas G. Martin**, PhD, MoodS Consortium and The Swedish Bipolar Study Group, Queensland Institute of Medical Research, Brisbane, Australia; **Marcella Rietschel**, MD, PhD, Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim/University of Heidelberg, Mannheim, Germany; **Chunyu Liu**, PhD, Department of Psychiatry, University of Illinois at Chicago, Chicago, Illinois, USA; **Joel E. Kleinman**, MD, **Thomas M. Hyde**, MD, **Daniel R. Weinberger**, MD, Lieber Institute for Brain Development, Johns Hopkins University, Baltimore, Maryland, USA; **Bing Su**, PhD, State Key Laboratory of Genetic Resources and Evolution, Kunming Institute of Zoology, Chinese Academy of Sciences, Kunming, Yunnan, China

Correspondence: Bing Su, Kunming Institute of Zoology, Chinese Academy of Sciences, 32 East Jiao-chang Road, Kunming 650223, Yunnan, China. Email: sub@mail.kiz.ac.cn; Ming Li, Lieber Institute for Brain Development, Johns Hopkins University, Baltimore, MD, USA. Email: limingkiz@gmail.com

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Additional members from the Bipolar Disorder Group of the MooDS Consortium

Jana Strohmaier,¹ René Breuer,¹ Sandra Meier,¹ Per Hoffmann,²⁻⁵ Stefan Herms,²⁻⁴ Markus Schwarz,⁶ Helmut Vedder,⁶ Jutta Kammerer-Ciernioch,⁶ Andreas Reif,⁷ Johanna Sasse,⁸ Michael Bauer,⁸ Sandra Zwick,⁸ Martin Hautzinger,⁹ Piotr M. Czerski,¹⁰ Joanna Hauser,¹⁰ Johannes Schumacher,³ Wolfgang Maier,¹¹ Peter Propping³

¹Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, University of Heidelberg, Mannheim, Germany

²Division of Medical Genetics, University of Basel, Basel, Switzerland

³Institute of Human Genetics, University of Bonn, Bonn, Germany

⁴Department of Genomics, Life and Brain Center, University of Bonn, Bonn, Germany

⁵Institute of Neuroscience and Medicine (INM-1), Structural and Functional Organization of the Brain, Genomic Imaging, Research Centre Jülich, Jülich, Germany

⁶Psychiatric Center Nordbaden, Wiesloch, Germany

⁷Department of Psychiatry, University of Würzburg, Würzburg, Germany

⁸Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus, Dresden, Germany

⁹Department of Clinical and Developmental Psychology, Institute of Psychology, University of Tübingen, Tübingen, Germany

¹⁰Department of Psychiatry, Poznan University of Medical Sciences, Poznan, Poland

¹¹Department of Psychiatry, University of Bonn, Bonn, Germany

Members of the Swedish Bipolar Study Group

Lena Backlund,¹ Louise Frisé,¹ Catharina Lavebratt,² Martin Schalling,² Urban Ösby¹

¹Department of Clinical Neuroscience Neurogenetics Unit, Stockholm, Sweden

²Department of Molecular Medicine and Surgery, Karolinska Institute, Stockholm, Sweden

Description about discovery eQTL database

The brain eQTL dataset used in this study was reported previously.¹ In brief, human cortex samples were collected from the National Institute of Aging Alzheimer Centers and the Miami Brain Bank and the original subjects met several criteria: (a) self-defined as being ethnically of European descent; (b) had no clinical history of stroke, cerebrovascular disease, Lewy bodies or co-morbidity with neurological disease; (c) were assessed by board certified neurologists who made a determination on their condition; and (d) had an age at death greater than 65 years. After excluding ethnic outliers and samples that were possibly related, a total of 193 independent subjects' samples remained for subsequent analysis.

Genotyping of the 193 cortex samples was conducted using Affymetrix GeneChip Human Mapping 500K Array Set, and mRNA expression measurements were performed using Illumina HumanRefseq-8 Expression BeadChip using standard manufacturer's protocols. The PLINK program was used to carry out as a one-degree-of-freedom allelic test of association, and the associations results were further separated into *cis* and *trans* significantly associated SNP-transcript pair sets. *Cis* SNPs were defined as SNPs within either 1 Mb of the 5' or 3' end of the transcript and within the transcript. Sherlock considers both *cis* and *trans* eQTL SNPs. Detailed information about genotyping and expression profiling as well as statistical methods can be found in the original publication.¹

Description about non-brain tissue replication eQTL databases

The non-brain tissue eQTL databases were retrieved through Genevar,² which have ever been reported by Nica *et al*,³ Dimas *et al*,⁴ and Stranger *et al*⁵ In brief, Nica *et al* explored in depth the roles of genetic variation on gene expression in three human tissues: lymphoblastoid cell lines (LCL), skin, and adipose, and the samples (156 LCL, 160 skin, 166 adipose) derived simultaneously from a subset of healthy female twins of the MuTHER resource;³ Dimas *et al* conducted the genome-wide expression analysis in three types of cells (fibroblast, LCL and T-cell) from 75 Geneva GenCord Caucasian individuals;⁴ Stranger *et al* analyzed genome-wide gene expression in LCL from 8 global populations of the HapMap3 project and correlated gene expression levels with HapMap3 SNPs located in cis to the genes. We used the data from the Caucasian samples (N=109) reported by Stranger *et al*⁵ In these three datasets, all the statistical analysis between SNPs and gene expression were conducted using Spearman's correlation.

Replication-I sample information (see Table DS1)

Germany II and III sample

Cases for Germany II and III samples were again ascertained from consecutive admissions to the inpatient units of the Department of Psychiatry and Psychotherapy at the University of Bonn and at the Central Institute for Mental Health in Mannheim, University of Heidelberg, as well as at other collaborating psychiatric university hospitals in Germany. DSM-IV lifetime diagnoses of bipolar disorder were assigned using a consensus best-estimate procedure, based on all available information, including structured interviews (SCID-I, SADS-L; Germany III) or semi-structured interviews (AMDP; Germany II), medical records, and the family history method. In addition, the OPCRIT system was used for the detailed polydiagnostic documentation of symptoms.⁶

Controls for Germany II were ascertained from the population-based Heinz Nixdorf Recall Study.⁷ Study protocols were reviewed and approved in advance by Institutional Review Boards of the participating institutions. All subjects provided written informed consent. This includes a clause that all data may be shared with collaborating partners such as the PGC. However, consents do not include permission for depositing of de-identified individual GWAS genotype and phenotype data into the NIMH genetics initiative repository, although these data may be used in specific collaborations for studies of neuropsychiatric disorders. All subjects were genotyped using the Illumina platform.

The controls for Germany III were recruited at the Max Planck Institute of Psychiatry in Munich, Germany, and were selected randomly from a Munich-based community sample. They were collected in the course of genetic studies of major depression, and were therefore screened for the presence of anxiety and affective disorders using the Composite International Diagnostic Screener (WHO-CIDI). Only individuals negative for the above-named disorders were included in the sample. All included controls were Caucasian, 93.04% were of German origin. These subjects thus represent a group of healthy individuals with regard to depression and anxiety. The study was approved by the ethics committee of the Ludwig Maximilians University in Munich, Germany, and written informed consent was obtained from all subjects.

Australia sample

Subjects were ascertained through two studies: (a) a bipolar disorder pedigree sample (described in McAuley *et al*)⁸ and (b) a specialized Sydney Black Dog Institute bipolar disorder clinic sample (described in Mitchell *et al* 2009).⁹ All subjects were interviewed by trained research staff using the DIGS or SCID, using best-estimate DSM-IV diagnoses derived from those instruments, medical records and FIGS. First, for the pedigree sample, only one bipolar disorder subject per family was included in the case sample. Pedigrees were only included in the original genetic study if there was unilineal inheritance, and at least two bipolar disorder subjects including at least one with bipolar I disorder. Subjects were ascertained through clinical presentations to the Mood Disorders Unit at the Prince of Wales Hospital in Sydney, direct referrals from Australian clinicians, and bipolar disorder consumer organizations. Second, for

the clinic sample, subjects comprised consecutive subjects referred by psychiatrists or general practitioners for specialized clinical review. All patients provided written informed consent to participate in this study and the study was approved by the local ethics committee. Patients were included in the BOMA study and genotyped at the Life & Brain Centre in Bonn.

Australia controls were drawn from families participating in the Brisbane Longitudinal Twin Study, an unselected community sample recruited to take part in studies of melanoma risk factors, cognition, and other phenotypes. Subjects were not screened for any phenotype relevant to bipolar disorder. The study was approved by the ethic committee and all proband gave written informed consent. All subjects were genotyped as a single project by deCODE and have been through an extensive QC process including exclusion for non-European ancestry. The sample is overwhelmingly of northern European origin, predominately from the British Isles.

France sample

Patients with bipolar disorder and controls were recruited as part of a large study on genetics of bipolar disorder in France (Paris-Creteil, Bordeaux, Nancy) with a protocol approved by relevant IRBs and with written informed consent. Cases were of French descent for more than three generations and were all been assessed by a well-trained psychiatrist or psychologist with the DIGS¹⁰ and the FIGS. Diagnoses were based on structured interviews supplemented by medical case notes, mood scales and a self-rating questionnaire assessing dimensions. Genotyping of controls were provided by the Centre National de Génotypage (M Lathrop, Evry). Patients and controls were genotyped on the Illumina platform (HumanHap300, HumanHap550, HumanHap 610-quad).

Sweden I sample

SBP Bipolar cases were recruited from St. Göran's Hospital in Stockholm, Sweden. All participants provided written informed consent to participate in a genetic study of bipolar disorder, and the study was approved by the Regional Ethics Committee of Stockholm. Diagnoses were based on physician administered ADE¹¹ and MINI.¹²

Bipolar disorder cases were identified from the Swedish Bipolar Quality Assurance Registry. Patient information within the registry includes disease sub-classification, psychosis, age at onset, number of manic and depressive episodes, number of hospitalizations and family history. Participants provided written informed consent to participate in a genetic study of psychiatric disease, and the study was approved by the Regional Ethics Committee of Stockholm.

Hospital Discharge Registry (HDR) bipolar cases were identified from the Swedish Hospital Discharge Registry if they a) have at least two admissions with discharge diagnoses of bipolar disorder and b) were born in Sweden or another Nordic country. The register contains a nearly complete record of all individuals hospitalized in Sweden since 1973. Diagnoses were established by an attending physician and were shown to have high sensitivity and specificity.¹³ The study was approved by the Regional Ethics Committee of Stockholm. All participants provided written informed consent to participate in genetic studies of psychotic disorders and were interviewed by a research nurse about other medical conditions.

The SBP bipolar disorder cases were recruited from the Stockholm County catchment area. All patients provided written informed consent to participate in a genetic study of bipolar disorder, and the study was approved by the Regional Ethics Committee of Stockholm. Diagnoses were made according to the DSM-IV criteria.

Sweden control samples were obtained from the Swedish Hospital Discharge Registry on the condition they had never received discharge diagnoses of bipolar disorder, schizophrenia and/or schizoaffective disorder.

Sweden II sample

This sample consisted of 1415 patients with bipolar disorder (62.5% female, age \pm s.d. = 53 ± 14 , bipolar disorder type I = 578, bipolar disorder type II = 517, NOS = 281, SAB = 39, unknown subtype = 4), and 1271 healthy controls (50.3% female, age \pm s.d. = 59 ± 11 years). All subjects were unrelated to each other and ethnically Swedish. Patients with bipolar disorder were collected from the Swedish National Quality Assurance Registry for bipolar disorder (Bipolär), to which all patients with a DSM-IV diagnosis of bipolar I, II, NOS, or schizoaffective disorder are considered for registration at the participating clinics.¹⁴ There were no other inclusion or exclusion criteria. Diagnoses were made by the treating physician with longitudinal access to all available clinical information. Controls were also identified from national population registers, and had never received a discharge diagnosis of SCZ or bipolar disorder. Controls were contacted directly in a similar procedure as the cases, gave written informed consent, were interviewed about other medical conditions and visited their family doctor or local hospital laboratory for blood donation. Patients and controls were genotyped on the Illumina Omni Express array, and the genomic inflation factor (λ) is 1.03.

Iceland sample

The Iceland sample consisted of 541 subjects with bipolar disorder and 34,546 population controls. Patients and controls were Icelandic and were recruited throughout the country. Diagnoses were assigned according to RDC through the use of the SADS-L for 303 subjects. DSM-IV BD diagnoses were obtained through the use of the Composite International Diagnostic Interview (CIDI-Auto) for 82 subjects. In addition, there were 150 subjects with ICD-9 or ICD-10 bipolar disorder diagnoses and nine subjects with DSM-III bipolar disorder diagnoses.

The 34,546 controls were recruited as a part of various genetic programs at deCODE and were not screened for psychiatric disorders. Approval for the study was granted by the National Bioethics Committee of Iceland and the Icelandic Data Protection Authority and written informed consent was obtained for all participants.

Romania sample

All patients were recruited from consecutive hospital admissions and were directly interviewed with the Structured Clinical Interview for DSM-IV-TR-Axis I Disorders - Patient Version (SCID-I, 1994) and the Diagnostic Interview for Genetic Studies (DIGS) version 3.0 (1999). Information provided by medical records and interviews of family members was also used in a best estimate procedure of diagnosis on the basis of DSM-IV-TR criteria. The control sample was population-based, drawn from the same population as the patients, and was screened for major psychiatric disorders. The

ethnicity of the patients and control subjects was determined by genealogical investigation to the grandparental generation. Only the patient sample was previously reported in other collaborative studies.¹⁵⁻¹⁷ The 174 controls were genotyped on Illumina OMNI-Express chips in Bonn, and the patients were also genotyped on Illumina chips (partly on Quad Omni-1).

China sample

The patients who met DSM-IV criteria for bipolar disorder type 1 or type 2 were recruited from the Division of Mood Disorders at Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine between November 2006 and October 2010. Each patient was independently interviewed and diagnosed by a consensus of at least two experienced psychiatrists. Diagnoses were further confirmed with an Extensive Clinical Interview and a Structured Clinical Interview for DSM-IV Axis/Disorders, Patient Version (SCID-P) given by a research psychiatrist. Subjects with comorbid diagnosis of other psychiatric disorders or chronic physical illness were excluded in this study to mitigate the potential for compounding factors during our analysis. The Extensive Clinical Interview contains items to assess demographics, mental status, and ages at onset for the bipolar disorder patients. To avoid the biases due to the low reliability of retrospective evaluation of prodromal symptoms, we defined age at onset as the first reliably diagnosed hypo/manic or depressive episode according to DSM-IV criteria.

Control subjects were enrolled from hospital staff and students of the School of Medicine in Shanghai that were interviewed by a specialized psychiatrist with SCID-P. Subjects with any psychiatric disorder and chronic physical disease were excluded from our analysis. All subjects were of Han Chinese origin and provided written informed consent before any study-related procedures were performed. This sample has been reported in a previous study.¹⁸

Replication-II sample information (see Table DS1)

UK sample

The cases consisted of 1218 individuals of which 29% were male. The mean age of recruitment was 46 (s.d.=12) years, with a mean age at first impairment because of bipolar disorder of 22 (s.d.=9) years. A lifetime diagnosis was made according to Research Diagnostic Criteria and the 1218 individuals were categorized as follows: bipolar I disorder/mania: 63% cases, bipolar II disorder/hypomania: 29% cases, schizoaffective disorder, bipolar type: 8% cases. Of those individuals for whom we were able to make a definite rating, 65% of the cases had a lifetime experience of psychotic symptoms (defined as a score over 9 on the Bipolar Affective Disorder Dimension Scale (BADDs)) and 25% had a lifetime experience of predominantly mood-incongruent psychotic symptoms (defined as a score over 29 on the BADDs mood incongruence scale). There were 2913 controls in the independent sample, of which 47% were male. This sample has been reported in a previous study.¹⁹

Analysis of hippocampal volume and cognitive performance

To analyse hippocampal volume, we used the data from a recent large-scale GWAS conducted by the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) consortium.²⁰ The GWAS comprised 17 samples of European ancestry of which genome-wide SNP data and hippocampal volume data were collected, including a total of 5,775 young healthy individuals (mean age: 34.8 years). Evidence for potential association was assessed using the allelic dosage of the SNP and covariates controlling for population stratification (four MDS components), intracranial volume, age, age², sex and the interactions between age and sex, and age² and sex. Detailed information on the samples, imaging procedures, genotyping methods and statistical analysis can be found in the original GWAS report.²⁰

For cognitive analysis, we utilized a Chinese sample that included 342 healthy Chinese college students from Beijing Normal University who had self-reported no known history of any neurological or psychiatric disorders (197 females and 145 males, aged 18-23). Cognitive and behavioral measures included working memory, executive functions (as assessed with the Attention Network Test, the Wisconsin Card Sorting Task, and a reversal learning test), and motivation traits etc. Detailed cognitive functions examined in this study are listed in Table DS2. This cognitive sample was previously used in several studies and shown to be effective in detecting authentic risk effects.²¹⁻²³ Genotyping was performed by Affymetrix 6.0 array using standard protocols. Since homozygotes for the rs6088662 minor allele (GG) are rare in this sample, we combined GG and GA genotypes as a single group denoted 'G carrier', and statistical analysis using two-tailed t-test was done with SPSS 16.0 (SPSS, Chicago, USA). This particular experiment was approved by the Institutional Review Board of the State Key Laboratory of Cognitive Neuroscience and Learning at Beijing Normal University, China. Written consent form was obtained from all participants following a full explanation of the study procedure.

Table DS1 Description of individual samples included in this study

Sample	Cases	Case diagnosis	Diagnosis	Interview	Controls	Genotyping	λ	Ref.
Discovery								
PGC1	7,481	BPD1,BPD2,SAB,BPD-NOS	DSMIIR,DSM-IV,RDC	multiple	9,250	multiple	1.15	24
Replication-I								
Germany II	181	BPD1,BPD2	DSM-IV	AMDP	527	Illumina	1.05	17,25
Germany III	490	BPD1,BPD2,SAB,BPD-NOS	DSM-IV	SCID-I,SADS-L	880	Illumina	1.00	17,25
Australia	330	BPD1,BPD2,SAB,BPD-NOS	DSM-IV	SCID,DIGS	1,811	Illumina	1.00	9,26
France	451	BPD1,BPD2,BPD-NOS	DSM-IV	DIGS	1,631	Illumina	1.03	27,28
Sweden I	836	BPD1,BPD2,BPD-NOS	DSM-IV	ADE,MINI	2,093	Affymetrix 6.0	1.07	27
Sweden II	1,415	BPD1,BPD2,SAB,BPD-NOS	DSM-IV	/	1,271	Affymetrix 6.0	1.03	14
Iceland	541	BPD1,BPD2,BPD-NOS	DSM-IV,ICD-10,	CID-I,SADS-L	34,426	Affymetrix 6.0	1.11	17
Romania	244	BPD1	DSM-IV	SCID-I-P/DIGS	174	Illumina	/	15-17
China	350	BPD1,BPD2	DSM-IV	SCID-P	888	SNaPSHOT	/	18
Total	4,838				43,701			
Replication-II								
UK	1,218	BPD1,BPD2,SAB	RDC	/	2,913	ImmunoChip	1.02	19
Grand Total	13,537				55,864			

BPD1, bipolar disorder type 1; BPD2, bipolar disorder type 2; BPD-NOS, bipolar disorder not otherwise specified; SCZ, schizophrenia; SAB, schizoaffective disorder (bipolar type); λ = genomic control lambda.

We primarily used the Illumina (San Diego, CA, USA), Affymetrix and SNaPSHOT platforms to genotype rs6088662. For the genotyping in UK and Romania samples we used proxy SNP rs13041792 in UK ($r^2=1.00$ with rs6088662 in Europeans using data from 1000-Human-Genome) and rs6088667 in Romania samples ($r^2=0.90$ with rs6088662) instead, as rs6088662 is not covered.

Table DS2 Cognitive performance assessment in Chinese sample

Domain	Task	Brief description	Index
Memory	Wechsler Memory Scale -3rd Edition (WMS-III)	Two subscales: Picture recall (Subjects were showed pictures of 20 simple objects for 30 seconds and then asked to recall as many as possible) and picture recognition (Subjects were showed pictures of 8 simple objects for 30 seconds and then asked to pick them out from 28 pictures).	Number of items correctly recalled or recognized
	Working memory	In the 2-back working memory task, subjects judged whether the current item was the same (or related) to the one presented two trials earlier. Three sessions involved morphological, phonological, and semantic judgment.	Overall accuracy
Executive function	Attention network test	Subjects saw several small arrows on the computer screen and had to judge the direction of the arrow in the middle (left or right). The 6 peripheral arrows can either in the same or inverse direction to the middle one. There were also cues to alert subjects or point to the position where arrows will be presented	Alert, orientation, conflict
	Wisconsin card sort task	Subjects had to select one from four cards that fits a rule. Rules included color, form, and amount of items on the cards, and rules changed during the experiment	Preserved error (Nelson)
Personality	Temperament and Character Inventory-Re	7 aspects of personality: Novelty Seeking, Harm Avoidance, Reward Dependence, Persistence, Self-Directedness, Cooperativeness, Self-Transcendence	7 subscales scores
Language abilities	Visual-auditory learning, from Woodcock Reading Mastery test Revised, Forms G.	This task consists of several sessions. In each session, subjects were asked to learn a few symbol-word pairs. Afterwards, they were asked to read out some sentences written in symbols using corresponding words they just learned.	Number of correct responses

Table DS3 Results of integrative analysis using brain eQTL and bipolar disorder GWAS data

Gene	Gene LBF	Gene p-val	SNP	Location	Proximity	eQTL p-val	BPD p-val	SNP LBF
<i>GLT8D1</i>	6.78	2.22e-06						
			rs2251219	3:52559827	cis	2.84e-17	5.45e-07	6.95
			rs17073273	6:144330243	trans	8.55e-06	0.73	-0.093
			rs2070968	10:73251566	trans	6.20e-06	0.67	-0.075
<i>CXCL16</i>	6.16	2.22e-06						
			rs12634640	3:187552259	trans	6.92e-07	1.63e-03	2.38
			rs810517	10:80612626	trans	1.14e-06	2.12e-04	3.78
<i>TRPC4AP</i>	5.57	8.89e-06						
			rs9883745	3:133715013	trans	2.86e-06	0.46	-0.13
			rs10501340	11:55439371	trans	6.73e-06	2.75e-02	0.28
			rs11049310	12:28100068	trans	8.31e-06	0.77	-0.056
			rs6088662	20:33011294	cis	5.44e-09	5.85e-05	5.48
<i>TAF11</i>	5.52	1.11e-05						
			rs4482754	4:87230328	trans	7.57e-06	3.62e-06	4.40
			rs7263316	20:19632036	trans	5.94e-07	2.37e-02	1.12

Table DS4 Association of rs2251219 with gene expression in 3p21.1 region

Author (Ref.)	Myers <i>et al</i> ¹	Unpublished data	Colantuoni <i>et al</i> ²⁹	Webster <i>et al</i> ³⁰		Zou <i>et al</i> ³¹		Heinzen <i>et al</i> ³²
Region	Brain	DLPFC	DLPFC	Brain		Cerebellar	Temporal cortex	Frontal cortex
Dx (Number)	Control (N=193)	Control (N=320)	Control (N=261)	Control + AD (N=369)	AD (N=176)	AD (N=197)	AD (N=202)	Control (N=93)
<i>STAB1</i>	n.s.	/	n.s.	n.s.	n.s.	n.s.	n.s.	0.095
<i>NT5DC2</i>	/	/	n.s.	/	/	n.s.	n.s.	n.s.
<i>PBRM1</i>	/	n.s.	0.085	/	/	n.s.	n.s.	n.s.
<i>GNL3</i>	/	/	0.017	/	/	n.s.	n.s.	/
<i>GLT8D1</i>	<1.0×10 ⁻¹⁶	n.s.	0.048	<1.0×10 ⁻³⁰	<1.0×10 ⁻¹⁸	n.s.	n.s.	n.s.
<i>SPCS1</i>	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
<i>NEK4</i>	/	0.051	n.s.	/	/	n.s.	n.s.	n.s.
<i>ITIH1</i>	/	/	n.s.	/	/	n.s.	n.s.	0.055
<i>ITIH3</i>	/	/	n.s.	/	/	n.s.	n.s.	n.s.
<i>ITIH4</i>	<1.0×10 ⁻³	/	<1.0×10 ⁻²	<1.0×10 ⁻⁴	<1.0×10 ⁻²	n.s.	n.s.	n.s.
<i>TMEM110</i>	/	0.083	/	/	/	n.s.	n.s.	n.s.

N.A., not available; Dx, diagnosis; AD, Alzheimer's disease; n.s., not significant; DLPFC, Dorsolateral prefrontal cortex

Table DS5 Replication of *trans* eQTL association in different samples

Author (Ref.)	Myers <i>et al</i> ¹	Unpublished data	Colantuoni <i>et al</i> ²⁹	Webster <i>et al</i> ³⁰		Zou <i>et al</i> ³¹		Heinzen <i>et al</i> ³²
Region	Brain	DLPFC	DLPFC	Brain		Cerebellar	Temporal cortex	Frontal cortex
Dx (Number)	Control (N=193)	Control (N=320)	Control (N=261)	Control + AD (N=369)	AD (N=176)	AD (N=197)	AD (N=202)	Control (N=93)
<i>CXCL16</i> rs12634640	<1.0×10 ⁻⁶	n.s.	n.s.	<1.0×10 ⁻²	n.s.	n.s.	n.s.	n.s.
rs810517	<1.0×10 ⁻⁵	n.s.	n.s.	0.023	n.s.	n.s.	n.s.	n.s.
<i>TAF11</i> rs4482754	<1.0×10 ⁻⁵	/	n.s.	<1.0×10 ⁻²	n.s.	n.s.	n.s.	n.s.

Dx, diagnosis; AD, Alzheimer's disease; n.s., not significant; DLPFC, Dorsolateral prefrontal cortex

Table DS6 Association of rs6088662 with gene expression in 20q11.22 region

Author (Ref.)	Myers <i>et al</i> ¹	Unpublished data	Colantuoni <i>et al</i> ²⁹	Webster <i>et al</i> ³⁰		Zou <i>et al</i> ³¹		Heinzen <i>et al</i> ³²
Region	Brain	DLPFC	DLPFC	Brain		Cerebellar	Temporal cortex	Frontal cortex
Dx (Number)	Control (N=193)	Control (N=320)	Control (N=261)	Control + AD (N=369)	AD (N=176)	AD (N=197)	AD (N=202)	Control (N=93)
<i>AHCY</i>	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
<i>ITCH</i>	n.s.	0.067	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
<i>DYNLRB1</i>	/	n.s.	n.s.	/	/	n.s.	n.s.	n.s.
<i>PIGU</i>	/	n.s.	n.s.	/	/	n.s.	n.s.	n.s.
<i>NCOA6</i>		n.s.	0.036	n.s.	n.s.	n.s.	n.s.	n.s.
<i>GGT7</i>	<1.0×10 ⁻⁷	<1.0×10 ⁻⁸	0.054	<1.0×10 ⁻⁷	<1.0×10 ⁻²	n.s.	<1.0×10 ⁻²	0.13
<i>ACSS2</i>	/	n.s.	0.098	/	/	<1.0×10 ⁻²	<1.0×10 ⁻⁵	n.s.
<i>GSS</i>	n.s.	/	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
<i>MYH7B</i>	n.s.	n.s.	<1.0×10 ⁻³	n.s.	n.s.	<1.0×10 ⁻¹⁵	n.s.	n.s.
<i>TRPC4AP</i>	<1.0×10 ⁻⁸	<0.005	/	<1.0×10 ⁻⁸	0.023	n.s.	n.s.	n.s.
<i>EDEM2</i>	0.040	0.067	<1.0×10 ⁻²	<1.0×10 ⁻²	0.010	n.s.	n.s.	n.s.
<i>PROCR</i>	/	/	n.s.	/	/	n.s.	n.s.	n.s.
<i>MMP24</i>	/	0.098	n.s.	/	/	n.s.	n.s.	0.11
<i>UQCC1</i>	/	n.s.	n.s.	/	/	n.s.	n.s.	n.s.

N.A., not available; Dx, diagnosis; AD, Alzheimer's disease; n.s., not significant; DLPFC, Dorsolateral prefrontal cortex

Table DS7 Association of rs6088662 with GGT7 exon expression in Heinzen *et al*³²

Probe_Type	Gene_Symbol	Transcript	Transcript_Probe_ID	Exon_Probe_ID	Start	End	P-val
transcript	GGT7	NM_178026	3903598	-	32884010	32924318	0.128
exon	GGT7	NM_178026	3903598	3903603	32896517	32896683	0.2386
exon	GGT7	NM_178026	3903598	3903604	32896819	32896919	0.4164
exon	GGT7	NM_178026	3903598	3903606	32901439	32901524	<u>0.02122</u>
exon	GGT7	NM_178026	3903598	3903610	32902247	32902276	0.2765
exon	GGT7	NM_178026	3903598	3903611	32902349	32902375	0.2827
exon	GGT7	NM_178026	3903598	3903613	32902716	32902761	0.2265
exon	GGT7	NM_178026	3903598	3903614	32902789	32902817	0.2122
exon	GGT7	NM_178026	3903598	3903616	32903626	32903723	<u>0.07463</u>
exon	GGT7	NM_178026	3903598	3903618	32903901	32903942	<u>0.08682</u>
exon	GGT7	NM_178026	3903598	3903619	32903951	32903990	0.6926
exon	GGT7	NM_178026	3903598	3903620	32906001	32906080	0.2708
exon	GGT7	NM_178026	3903598	3903621	32906278	32906381	0.5625
exon	GGT7	NM_178026	3903598	3903623	32908286	32908357	0.6493
exon	GGT7	NM_178026	3903598	3903624	32910932	32911062	0.8358
exon	GGT7	NM_178026	3903598	3903626	32911433	32911460	<u>0.05013</u>
exon	GGT7	NM_178026	3903598	3903629	32911733	32911766	0.1856
exon	GGT7	NM_178026	3903598	3903633	32912864	32912890	0.1768
exon	GGT7	NM_178026	3903598	3903634	32912953	32913023	0.5577
exon	GGT7	NM_178026	3903598	3903636	32914307	32914408	0.2789
exon	GGT7	NM_178026	3903598	3903638	32914781	32914926	0.7815
exon	GGT7	NM_178026	3903598	3903643	32924120	32924243	0.938
exon	GGT7	NM_178026	3903598	3903644	32924280	32924317	0.2398

Table DS8 Association of rs6088662 with schizophrenia and major depression

Disorder	Sample	Cases	Controls	Allele	P-value	Odds ratio	95% CI
Schizophrenia	PGC2 ³³	35,476	46,839	G	0.0037	1.04	1.00-1.08
Depression	PGC1 ³⁴	9,240	9,519	G	0.27	1.03	0.98-1.08
	PsyCoLaus study ³⁵	1,301	1,689	G	0.90	0.99	0.88-1.12

Table DS9 SNPs in the LD area with potentially functional role on genes

SNP	Position	Distance (bp)	R^2	MAF	Function	Gene Name
rs3746444	33041912	30618	0.848	0.20	ncRNA	MIR499A
rs7268266	33045550	34256	0.898	0.20	cds-synon	MYH7B
rs3746436	33049854	38560	0.898	0.20	cds-synon	MYH7B
rs3746435	33050859	39565	0.898	0.20	missense	MYH7B
rs36003887	33052768	41474	0.898	0.20	cds-synon	MYH7B
rs8501	33054245	42951	0.898	0.20	3' UTR	TRPC4AP

Table DS10 Association of rs6088662 with hippocampal volume in Europeans²⁰

SNP	Position	Allele	Frequency	β (mm ³)	SE (mm ³)	P-value
rs6088662	20:33547633	G	0.1937	27.29	7.99	0.00063

SE, standard error; β represents the difference in hippocampal volumes per copy increase of effect allele.

The association analysis in 5,775 healthy European subjects was corrected for intracranial volume, sex, age, age², sex \times age, sex \times age² and four MDS components.

Table DS11 Association analysis between rs6088662 and cognitive performance in the Chinese sample

Cognitive function	Test or subscale	Mean (s.d.)		t	P-value
		G carrier	TT		
Executive function	Attention alert	0.013 (0.027)	0.0047 (0.025)	2.612	0.0094
Language abilities	Visual-auditory	124.81 (7.76)	121.73 (10.56)	2.539	0.012

Before performing two-tailed t-test, F-test was conducted to compare the variances between two genotype groups.

F-test in the analysis of visual-auditory was significant ($p < 0.005$), i.e., assuming the two groups do not have equal standard deviations, thus we used unpaired t-test with Welch's correction.

F-test in the analysis of attention alert was not significant ($p > 0.3$), i.e., assuming both groups have the same standard deviation, we used unpaired t-test with no correction.

Fig. DS1 Association of rs6088662 with *TRPC4AP* mRNA expression in Europeans in Dimas *et al* study ($n=75$).⁴

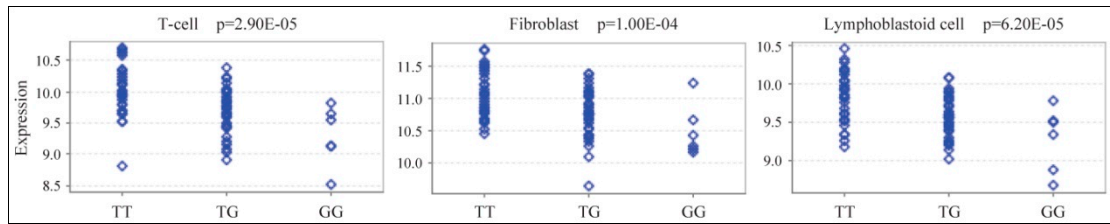


Fig. DS2 Association of rs6088662 with *TRPC4AP* mRNA expression in Europeans in Nica *et al* study ($n=160$).³

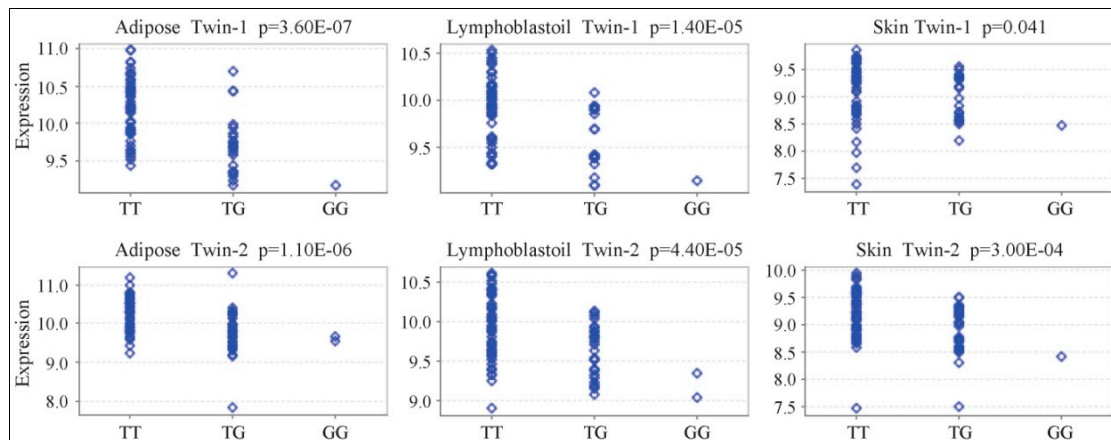
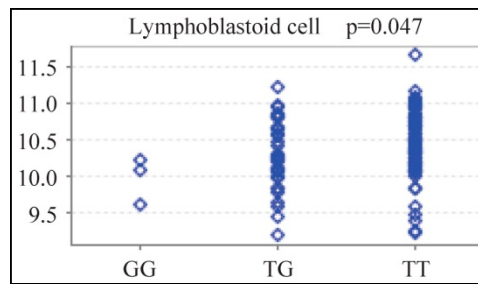


Fig. DS3 Association of rs6088662 with *TRPC4AP* mRNA expression in Europeans in Stranger *et al* study ($n=109$).⁵



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