

Genome-wide association study reveals two new risk loci for bipolar disorder

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Abstract

Bipolar disorder (BD) is a common and highly heritable mental illness and genome-wide association studies (GWAS) have robustly identified the first common genetic variants involved in disease aetiology. The data also provide strong evidence for the presence of multiple additional risk loci, each contributing a relatively small effect to BD susceptibility. Large samples are necessary to detect these risk loci. Here we present results from the largest BD GWAS to date by investigating 2.3 million single-nucleotide polymorphisms (SNPs) in a sample of 24,025 patients and controls. We detect 56 genome-wide significant SNPs in five chromosomal regions including previously reported risk loci *ANK3*, *ODZ4* and *TRANK1*, as well as the risk locus *ADCY2* (5p15.31) and a region between *MIR2113* and *POU3F2* (6q16.1). *ADCY2* is a key enzyme in cAMP signalling and our finding provides new insights into the biological mechanisms involved in the development of BD.

Subject terms: Biological sciences Genetics Neuroscience

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References

1. Lichtenstein, P. *et al.* Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. *Lancet* **373**, 234–239 (2009).

2. Nöthen, M. M., Nieratschker, V., Cichon, S. & Rietschel, M. New findings in the genetics of major psychoses. *Dialogues Clin. Neurosci.* **12**, 85–93 (2010).
3. Baum, A. E. *et al.* A genome-wide association study implicates diacylglycerol kinase eta (DGKH) and several other genes in the etiology of bipolar disorder. *Mol. Psychiatry* **13**, 197–207 (2008).
4. Sullivan, P. F., Daly, M. J. & O'Donovan, M. Genetic architectures of psychiatric disorders: the emerging picture and its implications. *Nat. Rev. Genet.* **13**, 537–551 (2012).
5. Craddock, N. & Sklar, P. Genetics of bipolar disorder. *Lancet* **381**, 1654–1662 (2013).
6. The International Schizophrenia Consortium. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature* **460**, 748–752 (2009).
7. Psychiatric GWAS Consortium Bipolar Disorder Working Group. Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. *Nat. Genet.* **43**, 977–983 (2011).
8. Cichon, S. *et al.* Genome-wide association study identifies genetic variation in neurocan as a susceptibility factor for bipolar disorder. *Am. J. Hum. Genet.* **88**, 372–381 (2011).
9. Chen, D. T. *et al.* Genome-wide association study meta-analysis of European and Asian-ancestry samples identifies three novel loci associated with bipolar disorder. *Mol. Psychiatry* **18**, 195–205 (2013).
10. Ferreira, M. A. R. *et al.* Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder. *Nat. Genet.* **40**, 1056–1058 (2008).
11. Hindorf, L. A. *et al.* Potential etiologic and functional implications of genome-wide association loci for human diseases and traits. *Proc. Natl Acad. Sci. USA* **106**, 9362–9367 (2009).
12. Green, E. K. *et al.* Replication of bipolar disorder susceptibility alleles and identification of two novel genome-wide significant associations in a new bipolar disorder case-control sample. *Mol. Psychiatry* **18**, 1302–1307 (2012).
13. Adzhubei, I. *et al.* A method and server for predicting damaging missense mutations. *Nat. Methods* **7**, 248–249 (2010).
14. Bernstein, B. E. *et al.* An integrated encyclopedia of DNA elements in the human genome. *Nature* **489**, 57–74 (2012).
15. Karolchik, D., Hinrichs, A. S. & Kent, W. J. The UCSC Genome Browser. *Curr. Protoc. Bioinformatics* **Chapter 1**, 4 (2012).
16. GTEx Consortium. The Genotype-Tissue Expression (GTEx) project. *Nat. Genet.* **45**, 580–585 (2013).
17. Ramos, E. M. *et al.* Phenotype-Genotype Integrator (PheGenI): synthesizing genome-wide association study (GWAS) data with existing genomic resources. *Eur. J. Hum. Genet.* **22**, 144–147 (2013).
18. Boyle, A. P. *et al.* Annotation of functional variation in personal genomes using RegulomeDB. *Genome Res.* **22**, 1790–1797 (2012).
19. Xia, K. *et al.* seeQTL: a searchable database for human eQTLs. *Bioinformatics* **28**, 451–452 (2012).
20. Luciano, M. *et al.* Whole genome association scan for genetic polymorphisms influencing information processing speed. *Biol. Psychol.* **86**, 193–202 (2011).
21. Craddock, N., O'Donovan, M. C. & Owen, M. J. The genetics of schizophrenia and bipolar disorder: dissecting psychosis. *J. Med. Genet.* **42**, 193–204 (2005).
22. Kwan, K. Y., Sestan, N. & Anton, E. S. Transcriptional co-regulation of neuronal migration and laminar identity in the neocortex. *Development* **139**, 1535–1546 (2012).
23. Ostrom, R. S., Bogard, A. S., Gros, R. & Feldman, R. D. Choreographing the adenylyl cyclase signalosome: sorting out the partners and the steps. *Naunyn Schmiedebergs Arch. Pharmacol.* **385**, 5–12 (2012).
24. Delghandi, M. P., Johannessen, M. & Moens, U. The cAMP signalling pathway activates CREB through PKA, p38 and MSK1 in NIH 3T3 cells. *Cell Signal.* **17**, 1343–1351 (2005).
25. Kang, H. J. *et al.* Spatio-temporal transcriptome of the human brain. *Nature* **478**, 483–489 (2011).

26. Stefansson, H. *et al.* Common variants conferring risk of schizophrenia. *Nature* **460**, 744–747 (2009).
27. Perroud, N. *et al.* Genome-wide association study of increasing suicidal ideation during antidepressant treatment in the GENDEP project. *Pharmacogenomics J.* **12**, 68–77 (2012).
28. Lee, S. H. *et al.* Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat. Genet.* **45**, 984–994 (2013).
29. Higgs, B. W., Elashoff, M., Richman, S. & Barci, B. An online database for brain disease research. *BMC Genomics* **7**, 70 (2006).
30. Adler, C. M., DelBello, M. P. & Strakowski, S. M. Brain network dysfunction in bipolar disorder. *CNS Spectr.* **11**, 312–320 (2006).
31. Martinowich, K., Schloesser, R. J. & Manji, H. K. Bipolar disorder: from genes to behavior pathways. *J. Clin. Invest.* **119**, 726–736 (2009).
32. Daban, C. *et al.* Is processing speed a valid cognitive endophenotype for bipolar disorder? *J. Affect. Disord.* **139**, 98–101 (2012).
33. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders* Fourth Edn (DSM-IV) APA (1994).
34. Leckman, J. F., Sholomskas, D., Thompson, W. D., Belanger, A. & Weissman, M. M. Best estimate of lifetime psychiatric diagnosis: a methodological study. *Arch. Gen. Psychiatry* **39**, 879–883 (1982).
35. Spitzer, R. L., Williams, J. B., Gibbon, M. & First, M. B. The structured clinical interview for DSM-III-R (SCID). I: history, rationale, and description. *Arch. Gen. Psychiatry* **49**, 624–629 (1992).
36. Farmer, A. E., Wessely, S., Castle, D. & McGuffin, P. Methodological issues in using a polydiagnostic approach to define psychotic illness. *Br. J. Psychiatry* **161**, 824–830 (1992).
37. Schmermund, A. *et al.* Assessment of clinically silent atherosclerotic disease and established and novel risk factors for predicting myocardial infarction and cardiac death in healthy middle-aged subjects: rationale and design of the Heinz Nixdorf RECALL Study. *Am. Heart J.* **144**, 212–218 (2002).
38. Muglia, P. *et al.* Genome-wide association study of recurrent major depressive disorder in two European case-control cohorts. *Mol. Psychiatry* **15**, 589–601 (2010).
39. Moffatt, M. F. *et al.* A large-scale, consortium-based genomewide association study of asthma. *New Engl. J. Med.* **363**, 1211–1221 (2010).
40. McKay, J. D. *et al.* A genome-wide association study of upper aerodigestive tract cancers conducted within the INHANCE consortium. *PLoS Genet.* **7**, e1001333 (2011).
41. Miller, S. A., Dykes, D. D. & Polesky, H. F. A simple salting out procedure for extracting DNA from human nucleated cells. *Nucleic Acids Res.* **16**, 1215 (1988).
42. McAuley, E. Z. *et al.* A genome screen of 35 bipolar affective disorder pedigrees provides significant evidence for a susceptibility locus on chromosome 15q25-26. *Mol. Psychiatry* **14**, 492–500 (2009).
43. Mitchell, P. B., Johnston, A. K., Corry, J., Ball, J. R. & Malhi, G. S. Characteristics of bipolar disorder in an Australian specialist outpatient clinic: comparison across large datasets. *Aust. N. Z. J. Psychiatry* **43**, 109–117 (2009).
44. Medland, S. E. *et al.* Common variants in the trichohyalin gene are associated with straight hair in Europeans. *Am. J. Hum. Genet.* **85**, 750–755 (2009).
45. Herold, C., Steffens, M., Brockschmidt, F. F., Baur, M. P. & Becker, T. INTERSNP: genome-wide interaction analysis guided by a priori information. *Bioinformatics* **25**, 3275–3281 (2009).
46. Purcell, S. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am. J. Hum. Genet.* **81**, 559–575 (2007).
47. Howie, B. N., Donnelly, P. & Marchini, J. A flexible and accurate genotype imputation method for the next generation of

- genome-wide association studies. *PLoS Genet.* **5**, e1000529 (2009).
48. Marchini, J., Howie, B., Myers, S., McVean, G. & Donnelly, P. A new multipoint method for genome-wide association studies by imputation of genotypes. *Nat. Genet.* **39**, 906–913 (2007).
 49. Abecasis, G. R. A map of human genome variation from population-scale sequencing. *Nature* **467**, 1061–1073 (2010).
 50. Meesters, C. Quick, 'imputation-free' meta-analysis with proxy-SNPs. *BMC Bioinformatics* **13**, 231 (2012).
 51. De Bakker, P. I. W. *et al.* Practical aspects of imputation-driven meta-analysis of genome-wide association studies. *Hum. Mol. Genet.* **17**, R122–R128 (2008).
 52. De Lara, C. L. Implication of synapse-related genes in bipolar disorder by linkage and gene expression analyses. *Int. J. Neuropsychopharmacol.* **13**, 1397–1410 (2010).
 53. Mamdani, F. *et al.* Lithium response and genetic variation in the CREB family of genes. *Am. J. Med. Genet. B. Neuropsychiatr. Genet.* **147B**, 500–504 (2008).
 54. Johnson, A. D. *et al.* SNAP: a web-based tool for identification and annotation of proxy SNPs using HapMap. *Bioinformatics* **24**, 2938–2939 (2008).
 55. AMDP. The AMDP-System Association of Methodology and Documentation in Psychiatry. *Manual for the Assessment and Documentation of Psychology* 4th Edn Springer (1982).
 56. Wittchen, H. U. *et al.* Screening for mental disorders: performance of the Composite International Diagnostic—Screenener (CID–S). *Int. J. Methods Psychiatr. Res.* **8**, 59–70 (1999).
 57. Nurnberger, J. I. Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH Genetics Initiative. *Arch. Gen. Psychiatry* **51**, 849–859 (1994).
 58. Maxwell, M. E. Family Interview for Genetic Studies.. Clinical Neurogenetic Branch, Intramural Research Program, NIMH (1992).
 59. Sheehan, D. V. *et al.* The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J. Clin. Psychiatry* **59**, (Suppl 2): 22–33 (quiz 34–57) (1998).
 60. Spitzer, R. L., Endicott, J. & Robins, E. Research diagnostic criteria: rationale and reliability. *Arch. Gen. Psychiatry* **35**, 773–782 (1978).
 61. Endicott, J. & Spitzer, R. L. A diagnostic interview: the schedule for affective disorders and schizophrenia. *Arch. Gen. Psychiatry* **35**, 837–844 (1978).
 62. Wing, J. K. SCAN. Schedules for Clinical Assessment in Neuropsychiatry. *Arch. Gen. Psychiatry* **47**, 589–593 (1990).

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Competing financial interests

The authors declare no competing financial interests.

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Supplementary information

PDF files

1. Supplementary Figures, Tables and References (1,402 KB)
Supplementary Figures 1-2, Supplementary Tables 1-8 and Supplementary References

Excel files

1. Supplementary Data 1 (16 KB)
Quality control procedure for the genotype and the imputed MoodS data.

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