Applying polygenic risk scoring for psychiatric disorders to a large family with bipolar disorder and major depressive disorder

Simone de Jong1,2, Mateus Jose Abdalla Diniz3,4, Andiara Saloma3,4, Ary Gadelha3, Marcos L. Santoro5, Vanessa K. Ota3,5, Cristiano Noto3, Major Depressive Disorder and Bipolar Disorder Working Groups of the Psychiatric Genomics Consortium#, Charles Curtis1,2, Stephen J. Newhouse2,6,7, Hamel Patel2,6, Lynsey S. Hall8, Paul F. O’Reilly1, Sintia I. Belangero3,5, Rodrigo A. Bressan3 & Gerome Breen1,2

Psychiatric disorders are thought to have a complex genetic pathology consisting of interplay of common and rare variation. Traditionally, pedigrees are used to shed light on the latter only, while here we discuss the application of polygenic risk scores to also highlight patterns of common genetic risk. We analyze polygenic risk scores for psychiatric disorders in a large pedigree (n ~ 260) in which 30% of family members suffer from major depressive disorder or bipolar disorder. Studying patterns of assortative mating and anticipation, it appears increased polygenic risk is contributed by affected individuals who married into the family, resulting in an increasing genetic risk over generations. This may explain the observation of anticipation in mood disorders, whereby onset is earlier and the severity increases over the generations of a family. Joint analyses of rare and common variation may be a powerful way to understand the familial genetics of psychiatric disorders.

1 MRC Social Genetic and Developmental Psychiatry Centre, Institute of Psychiatry Psychology and Neuroscience, King’s College London, London SE5 8AF, UK. 2 National Institute of Health Research Biomedical Research Centre for Mental Health, Maudsley Hospital and Institute of Psychiatry, Psychology and Neuroscience, King’s College London, London SE5 8AF, UK. 3 Department of Psychiatry, Universidade Federal de São Paulo (UNIFESP/EPM), São Paulo 04021-001, Brazil. 4 Pax Instituto de Psiquiatria, BR153, km 505, Villa Sul V, Aparecida de Goiânia 74911-516, Brazil. 5 Department of Morphology and Genetics, Universidade Federal de São Paulo (UNIFESP/EPM), São Paulo 04021-001, Brazil. 6 Department of Biostatistics and Health Informatics, Institute of Psychiatry, Psychology and Neuroscience, King’s College London, London SE5 8AF, UK. 7 Farr Institute of Health Informatics Research, UCL Institute of Health Informatics, University College London, London NW1 2DA, UK. 8 Division of Psychological Medicine and Clinical Neurosciences, MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff CF10 3AT, UK. #A full list of authors and their affiliations is shown at the end of the paper. Correspondence and requests for materials should be addressed to G.B. (email: gerome.breen@gmail.com)
The development of polygenic risk scoring (PRS) has greatly advanced the field of psychiatric genetics. This approach allows for even sub-genome-wide significant threshold results from large genome-wide meta analyses to be leveraged to explore genetic risk in smaller studies. The effect sizes at many individual single-nucleotide polymorphisms (SNPs), estimated by large genome-wide association studies (GWAS) on the disorder of interest, are used to calculate an individual level genome-wide PRS in individuals from an independent genetic dataset. The PRS based on the summary statistics of the schizophrenia (SCZ) GWAS by the Psychiatric Genomics Consortium (PGC) has proven to be most powerful in predicting not only SCZ, but also other psychiatric disorders. In addition, updated, more powerful, summary statistics from the Psychiatric Genomics Consortium from the latest GWAS for bipolar disorder (BPD) and major depressive disorder (MDD) are available via the PGC Data Access Portal.

Aside from increasing power in traditional case-control designs, PRS algorithms also open up new avenues for studying common variation. In this study, we consider the application of PRS within a family context. While pedigree studies have been traditionally used to explore rare genetic variation through linkage analyses, studying patterns of PRS throughout a pedigree would allow for assessment of phenomena like assortative mating and anticipation. Assortative (non-random) mating is a common phenomenon where mated pairs are more phenotypically similar for a given characteristic than would be expected by chance. Results from a recent study by Nordsletten et al. show extensive assortative mating within and across psychiatric, but not physical disorders. This could explain some of the features of the genetic architecture of this category of disorders. This includes anticipation, a phenomenon where later generations exhibit more severe symptoms at an earlier age, robustly reported in BPD, and recently highlighted in genetic studies of MDD.

In the current study, we aim to discuss the application of polygenic risk scoring for SCZ, MDD, and BPD to explore patterns of common risk variation within a family context. We illustrate our discussion by investigating the relationship between PRS and apparent assortative mating, and anticipation within a complex multigenerational pedigree affected with mood disorders.

**Results**

**Study overview.** We identified a large pedigree in Brazil, the Brazilian Bipolar Family (BBF), after examination of a 45-year-old female who presented with severe Bipolar Type 1 (BPI) disorder. She stated there were dozens of cases of mood disorders in the family, most of whom lived in a small village in a rural area of a large state north of São Paulo (see Methods for details). We conducted 308 interviews using the Portuguese version of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/16 for family members over the age of 16 and the Portuguese version of Kiddie-SADS-Present and Lifetime Version (K-SADS-PL) for family members aged 6–16. Following diagnostic interviews, we conducted genotype analysis of all interviewees using the Illumina Infinium PsychArray-24. Polygenic risk scores (PRS) were assigned to each family member using PRS thresholds most predictive in discriminating affected from unaffected family members (see Methods).

**Affection status.** The PRS thresholds were selected to optimally discriminate between affected (n = 78) versus unaffected (n = 147) family members with a higher score in affecteds for SCZ:PRS (Beta = 0.069, SE = 0.032, Z-ratio = 2.117, p = 0.035, R² = 0.021), and BPD:PRS (Beta = 0.094, SE = 0.030, Z-ratio = 3.123, p = 0.002, R² = 0.039). None of the PRS significantly discriminated between individuals having experienced a psychotic episode at some point in their lives (n = 25) versus the unaffected group (n = 147). Visualization of PRS in different diagnostic categories is shown in Supplementary Figure 1.

**Assortative mating.** Married-in individuals were defined as individuals married to a BBF member, but having no parents in the family themselves. Of the 70 married-in individuals ascertained (irrespective of having genotype data) 19 (27%) were affected with a psychiatric disorder. This is significantly higher than the 17% population prevalence of the most common of the three disorders: MDD (Fisher’s exact p = 0.02). The unaffected married-in group does not differ from the general healthy population as evidenced by no significant differences in PRS as compared to the population control group (BRA; see Methods).

The above led us to investigate whether we can observe assortative mating on a genetic level, using PRS. In spouse pairs, we were unable to predict the PRS of the husband, using that of his wife, even when selecting concordant (both affected or both unaffected) pairs only. We considered the possibility that the married-in individuals might confer a different genetic predisposition to mood disorders to their offspring than the original family members. The number of children contributed per spouse pair to each offspring category is shown in Supplementary Table 1. Demographics of the offspring in the different offspring categories (no affected parents (n = 54); one affected family member parent (n = 69); one affected married-in parent (n = 15) and two affected parents (n = 38)) are given in Supplementary Tables 2 and 3. Indeed, we find that offspring of an affected married-in parent show increased SCZ:PRS (Beta = 0.209, SE = 0.064, Z-ratio = 3.288, p = 0.002, R² = 0.186, Fig. 1) and BPD:PRS (Beta = 0.172, SE = 0.066, Z-ratio = 2.613, p = 0.013, R² = 0.126, Fig. 1) as compared to having no affected parents.

**Anticipation.** The BBF shows patterns of anticipation, with individuals having an earlier age at onset (AAO) in later generations. For 104 individuals (irrespective of having genotype data), the average age at onset significantly decreases over generations with G2 (n = 1, AAO = 8), G3 (n = 23, AAO = 30.2 yrs ± 21.1), G4 (n = 53, AAO = 31.2 yrs ± 12.3), G5 (n = 23, AAO = 19.7 yrs ± 9.5), and G6 (n = 4, AAO = 13 yrs ± 3.6) (Supplementary Figure 2) with older participants recalling their AAO directly and younger participants confirmed using clinical records or parental recall (Beta = −4.549, SE = 1.793, Z-ratio = −2.537, p = 0.013, R² = 0.059). We hypothesized that this decrease in AAO would be reflected in a negative correlation with PRS, subsequently resulting in a pattern of increased PRS over generations. Because of a limited sample size of affected individuals per generation, a direct correlation of AAO and PRS does not reach significance, although the youngest generation (G5) does show trends towards negative correlations for SCZ:PRS and MDD:PRS (Supplementary Figure 3). The SCZ:PRS does show a significant increase over generations (Fig. 2) where n = 197 family members were included (46 married-in individuals were excluded from the analysis to capture inheritance patterns of SCZ:PRS) in a linear regression with generation as independent variable (Beta = 0.131, SE = 0.049, Z-ratio = 2.668, p = 0.008, R² = 0.025). The presence of such an effect when comparing generations suggests ascertainment effects such as relying on the recall of older family member with very long duration of illness in previous generations may be masking an overall effect across the entire family.
standardized PRS, unaffected family members have been demonstrated recently17, common genetic variation within a traditional pedigree design. The current study is one of the duals (Supplementary Figure 5). PRS for rs1862975 genotypes in affected and unaffected individuals over generations is given in Supplementary Figure 4. The number of individuals carrying the TT genotype equivalent to the rs1862975 TT risk genotype. of the 57 BRA controls, 9 individuals (15%) carried the GG genotype equivalent to the rs1862975 TT risk genotype. The distribution of the rs1862975 genotypes in affected and unaffected individuals over generations is given in Supplementary Figure 4. The number of individuals carrying the TT does not significantly change over generations in either group. None of the PRS showed a significant difference when comparing PRS for rs1862975 genotypes in affected and unaffected individuals (Supplementary Figure 5).

Discussion
The current study is one of the first the first to probe patterns of common genetic variation within a traditional pedigree design. While increased polygenic scores in patients as compared to unaffected family members have been demonstrated recently17, we aimed to illustrate the possibilities of this approach by investigating apparent assortative mating and anticipation in a large multigenerational pedigree affected with mood disorders through polygenic risk scores for SCZ5, MDD18, and BPD19, and thereby improve mechanistic understanding of common genetic risk for psychiatric disorders.

Highlighting the possibilities of PRS applications within a family context, we set out to utilize patterns of common variation to illuminate phenomena within the family that are out of reach from traditional case/control studies. Assortative mating is one of the features in this family, where many married-in-affected individuals are more affected with a mood disorder than the general population. As opposed to the family members, the married-in-individuals were more often affected with (r)MDD instead of BP. As diagnoses were determined after the couples were married, we cannot rule out that this could be a result from a causal effect of a spouse’s mental health on that of their partner. However, non-random mating patterns have been reported in the population regarding body type, socio-economic factors and psychiatric traits8,10. The BBF provides a unique opportunity to look at the genetic correlation between spouse pairs and the contribution of married-in-individuals to overall psychiatric morbidity. A recent study has found genetic evidence for assortative mating when studying BMI and height in spouse pairs11. In the BBF; the affected married-in-individuals have a higher, though non-significant, polygenic score than affected or unaffected family members but it appears that we observe significant consequences of this in that the offspring of an affected married-in parent collectively show significantly increased SCZ:PRS and BPD:PRS. However, it is puzzling we do not see an effect on offspring of two affected parents (which would include a married-in-parent), which could indicate this finding to be of limited statistical robustness.

A contribution of the married-in parents to a genetic driven anticipation in age of onset is supported by the increase in SCZ:PRS over generations, although our cross sectional study dataset was less well powered to find an association with age at onset within affected family members. We did observe a trend for association between age at onset and PRS in the youngest generation in this study but not when combining sample across generations. Age at onset can be considered a proxy for severity20,21 and has been previously associated with genetic risk in MDD13,14. However, this variable needs to be interpreted with caution, especially when analyzing patterns over time since it is dependent on context and memory22. Ascertainment bias can be a confounding factor in studies of psychiatric traits, with older generations having less access to psychiatric care and possibly misremembering the onset or nature of their first episode. In addition, although currently classified as “unaffected” or “unknown”, members of the youngest generations can still develop a psychiatric disorder in the future.

Finally, we explored the balance of common and rare risk variation through combining our current PRS results with
Table 1 Demographics of the Brazilian bipolar family members and the Brazilian population control dataset (BRA controls) in the current study

| Diagnosis     | n  | Male, female | Age (±sd) | Age of onset (±sd) | Married-in | Psychosis |
|---------------|----|--------------|-----------|-------------------|------------|-----------|
| BPI           | 17 | 6, 11        | 50.4 (±18.9) | 24.9 (±14.6)      | 0          | 13        |
| BPII          | 11 | 4, 7         | 38.7 (±15.2) | 24.2 (±13.8)      | 1          | 4         |
| BPNS          | 8  | 6, 2         | 29.6 (±19.9) | 17.0 (±18.7)      | 0          | 1         |
| rMDD          | 17 | 5, 12        | 50.2 (±16.7) | 27.3 (±14.1)      | 3          | 4         |
| MDD           | 21 | 11, 10       | 43.8 (±17.8) | 34.5 (±15.5)      | 6          | 1         |
| SADB          | 1  | 0, 1         | 73         | 44                | 0          | 1         |
| Schizophrenia | 1  | 1, 0         | 44         | 36                | 0          | 1         |
| Cyclothymia   | 1  | 0, 1         | 40         | 25                | 0          | 0         |
| Dysthymia     | 0  | 1, 1         | 52         | —                 | 1          | 1         |
| Unaffected    | 147| 89, 58       | 36.8 (±20.0) | —                 | 35         | 0         |
| Unknown       | 18 | 14, 4        | 5.7 (±7.1)  | 0                 | —          | —         |
| Total         | 243| 136, 107     | 37.3 (±21.0) | 28.3 (±15.5)      | 46         | 25        |
| BRA controls  | 57 | 33, 24       | 27.1 (±7.2)  | —                 | —          | —         |

The first column contains the number of individuals affected with the disorder. A breakdown of gender, age, age at onset (with ± standard deviation) is given in the next columns. The married-in column contains the number of individuals in each diagnostic category married-in to the family. The last column contains counts of individuals in each category who have experienced a psychiatric episode during their lifetime.

Diagnoses are BPI bipolar I, BPII bipolar II, BPNS bipolar not otherwise specified, rMDD recurrent major depressive disorder, MDD major depressive disorder, SADB schizoaffective disorder, schizophrenia, cyclothymia and dysthymia.

previously performed linkage analyses. We did not find a decrease in potential rare risk allele genotypes over generations contrasting the increase in SCZ:PRS, and PRS profiles for individuals carrying rare risk genotypes are not significantly different. This indicates that these factors separately confer independent disease risk. We recognize the limitations in sample size of our pedigree and therefore the power to draw statistically robust conclusions, especially in the offspring and combined linkage and PRS analyses. Even though the BBF might not be sufficiently powered, our point is to use this dataset to illustrate our approach and emphasize the unique nature of the family enabling the study of patterns of PRS and the balance of common and rare genetic risk for psychiatric disorders conferred within families. We encourage replication in similar pedigrees including affected married-in individuals when available to fully utilize the potential of PRS in this setting.

In conclusion, our study is an exploration of PRS as a tool for investigating patterns of common genetic risk in a traditional pedigree context. The SCZ and BPD scores appear best suited in this setting.

Methods

Subject description. The Brazilian bipolar family (BBF) was ascertained via a 45-year-old female proband who presented with severe Bipolar Type 1 (BPI) disorder and stated there were dozens of cases of mood disorders in the family, most of whom lived in a small village in a rural area of a large state north of São Paulo. Cooperation from the family and a 2003 self-published book about their history was invaluable for our ascertainment. Historically, the entire BBF consists of 960 members. Living family members > 16 years of age underwent semi-structured interview. In the rare event of discrepancies, two independent psychiatrists final consensus diagnosis was assigned. All affected and unaffected family members self-reported mixed Southern European ancestry, confirming by genome-wide principal components analysis showing that family members clustered closely with the Northern and Western European and Tuscan Italian populations in Hapmap3, with a relative lack of African or Native American ancestry (Supplementary Figure 6). The principal components appear to represent within-family structure, with most PC1 seemingly separating subfamilies (Supplementary Figures 7 and 8).

Polygenic risk scores. Polygenic risk scores for each family member (n = 243) and population control (n = 57) were generated in the same run using the PRSice v1.25 software with the publically available PGC schizophrenia GWAS as a base dataset (36,989 SCZ cases, 113,075 controls), in addition to MDD (51,865 MDD cases, 113,220 controls, not including 23andme individuals) and BPD (20,352 BPD cases, 31,358 controls) summary statistics from the latest PGC meta analyses (unpublished data). We performed p-value-informed clumping on the genotype data with a cut-off of r² = 0.25 within a 200-kb window, excluding the MHC region on chromosome 6 because of its complex linkage disequilibrium structure. We rejected the possibility of over-fitting as we selected the PRS thresholds most predictive in discriminating affected from unaffected family members through linear regression in PRSice for SCZ:PRS (p < 0.0005, 1218 SNPs), MDD:PRS (p < 0.0032) and BPD:PRS (p < 0.0005).
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Author contributions

M.J.A.D., A.C.S.R., A.G., R.B.: family phenotyping and sample collection. M.L.S., V.K.O., C.N., R.B., S.I.B.: Brazilian controls phenotyping and sample collection. M.D.D. and B.I. P. working groups of PGC: providing summary statistics. C.C., H.P.: sample processing and genotyping. L.S.H., P.F.O., S.D.J.: statistical analysis and advice. G.B., S.D.J.: study design, drafting manuscript.

Additional information

Competing Interests: G.B. has been a consultant in preclinical genomics and has received grant funding from Eli Lilly ltd within the last 3 years. A.G. has participated in advisory boards for Janssen-Cilag and Daiichi-Sankyo. The remaining authors declare no competing interests.

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Major Depressive Disorder and Bipolar Disorder Working Groups of the Psychiatric Genomics Consortium

Naomi R. Wray\textsuperscript{9,10}, Stephan Ripke\textsuperscript{1,12,13}, Manuel Mattheisen\textsuperscript{14,15,16,17,18}, Maciej Trzaskowski\textsuperscript{9}, Enda M. Byrne\textsuperscript{9}, Abdel Abdellaoui\textsuperscript{19}, Mark J. Adams\textsuperscript{20}, Esben Agerbo\textsuperscript{18,21,22}, Tracy M. Air\textsuperscript{23}, Till F.M. Andlauer\textsuperscript{24,25}, Silviu-Alin Bacanu\textsuperscript{26}, Marie Baekvtd-Hansen\textsuperscript{18,27}, Aart\textipa{T}. F. Beekman\textsuperscript{28}, Tim B. Bigdell\textsuperscript{26,29}, Elisabeth B. Binder\textsuperscript{24,30}, Douglas H.R. Blackwood\textsuperscript{20}, Julien Bryois\textsuperscript{31}, Henriette N. Buttenschøn\textsuperscript{14,18,32}, Jonas Bybjerg-Grauholm\textsuperscript{27}, Na Cai\textsuperscript{33,34}, Enrique Castelao\textsuperscript{35}, Jane Hvarregaard Christensen\textsuperscript{14,15,18}, Toni-Kim Clarke\textsuperscript{20}, Jonathan R.I. Coleman\textsuperscript{1}, Lucía Colodro-Conde\textsuperscript{36}, Baptiste Couvy-Duchesne\textsuperscript{10,37}, Nick Craddock\textsuperscript{8}, Gregory E. Crawford\textsuperscript{38,39}, Gail Davies\textsuperscript{40}, Ian J. Deary\textsuperscript{40}, Franziska Degenhardt\textsuperscript{41,42}, Eske M. Derks\textsuperscript{36}, Nese Direk\textsuperscript{43,44}, Conor V. Dolan\textsuperscript{19}, Erin C. Dunn\textsuperscript{45,46,47}, Thalia C. Eley\textsuperscript{1}, Valentina Escott-Price\textsuperscript{47}, Farnush Farhadi Hassan Kiadeh\textsuperscript{48}, Hilary K. Finucane\textsuperscript{49,50}, Andreas J. Forstner\textsuperscript{41,42,51,52}, Josef Frank\textsuperscript{53}, Hélénia A. Gaspar\textsuperscript{1}, Michael Gill\textsuperscript{54}, Fernando S. Goes\textsuperscript{55}, Scott D. Gordon\textsuperscript{36}, Jakob Grove\textsuperscript{14,15,18,56}, Christine Saholm Hansen\textsuperscript{18,27}, Thomas F. Hansen\textsuperscript{18,57,58}, Stefan Herms\textsuperscript{41,42,43}, Ian B. Hickie\textsuperscript{59}, Per Hoffmann\textsuperscript{41,42,43}, Georg Homuth\textsuperscript{60}, Carsten Horn\textsuperscript{61}, Jouke-Jan Hottenga\textsuperscript{19}, David M. Hougaard\textsuperscript{18,27}, Marcus Ising\textsuperscript{62}, Rick Jansen\textsuperscript{28}, Ian Jones\textsuperscript{8}, Lisa A. Jones\textsuperscript{63}, Eric Jorgenson\textsuperscript{64}, James A. Knowles\textsuperscript{65}, Isaac S. Kohane\textsuperscript{66,67,68}, Julia Kraft\textsuperscript{69}, Warren W. Kretzschmar\textsuperscript{69}, Jesper Krogh\textsuperscript{70}, Zoltán Kutalik\textsuperscript{71,72}, Yihan Li\textsuperscript{70}, Penelope A. Lind\textsuperscript{36}, Donald J. MacIntyre\textsuperscript{20,73}, Dean F. MacKinnon\textsuperscript{55}, Robert M. Maier\textsuperscript{10}, Wolfgang Maier\textsuperscript{74}, Jonathan Marchini\textsuperscript{75}, Hamdi Mbarek\textsuperscript{19}, Patrick McGrath\textsuperscript{76}, Peter McGuffin\textsuperscript{1}, Sarah E. Medland\textsuperscript{36}, Divya Mehta\textsuperscript{10,77}, Christel M. Middeldorp\textsuperscript{19,78,79}, Evelin Mihailov\textsuperscript{80}, Yuri Milaneschi\textsuperscript{28}, Lili Milani\textsuperscript{80}, Francis M. Mondimore\textsuperscript{55}, Grant W. Montgomery\textsuperscript{9}, Sara Mostafavi\textsuperscript{81,82}, Niamh Mullins\textsuperscript{1}, Matthias Nauck\textsuperscript{83,84}, Bernad Nag\textsuperscript{82}, Michel G. Nivard\textsuperscript{19}, Dale R. Nyholt\textsuperscript{85}, Hogni Oskarsson\textsuperscript{86}, Michael J. Owen\textsuperscript{9}, Jodie N. Painter\textsuperscript{37}, Carsten Bøcker Pedersen\textsuperscript{18,21,22}, Marianne Görts Pedersen\textsuperscript{18,21,22}, Roseann E. Peterson\textsuperscript{10,29}, Erik Pettersson\textsuperscript{31}, Wouter J. Peyrot\textsuperscript{28}, Giorgio Pistis\textsuperscript{35}, Danielle Posthuma\textsuperscript{87,88}, Jorge A. Quiroz\textsuperscript{89}, Per Qvist\textsuperscript{14,15,18}, John P. Rice\textsuperscript{90}, Brien P. Riley\textsuperscript{26}, Margarita Rivera\textsuperscript{191}, Saira Saeed Mirza\textsuperscript{43}, Robert Schoevers\textsuperscript{92}, Eva C. Schulte\textsuperscript{93,94}, Ling Shen\textsuperscript{64}, Stanley I. Shyn\textsuperscript{95}, Engilbert Sigurdsson\textsuperscript{96}, Grant C.B. Sinnamon\textsuperscript{97}, Johannes H. Smit\textsuperscript{98}, Daniel J. Smith\textsuperscript{99}, Hreinn Stefansson\textsuperscript{99}, Stacy Steinberg\textsuperscript{99}, Fabian Streit\textsuperscript{53}, Jana Strohmaier\textsuperscript{53}, Katherine E. Tansey\textsuperscript{100},

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Derek Morris, Nicholas J. Schork, Andreas Reif, Jolanta Lissowska, Joanna Hauser, Neonila Szeszenia-Dabrowska, Kevin McGhee, Emma Quinn, Valentina Moskvina, Peter A. Holmans, Anne Farmer, James L. Kennedy, Ole A. Andreassen, Morten Mattingsdal, Michael Gill, Nicholas J. Bass, Hugo Burling, Andrew McQuillin, René Breuer, Christina Hultman, Paul Lichtenstein, Laura M. Hucksins, Marion Leboyer, Mark Lathrop, John Nurnberger, Michael Steffens, Tatiana M. Foroud, Wade H. Berrettini, David W. Craig & Jianxin Shi

Institute for Molecular Bioscience, The University of Queensland, Brisbane, QLD, Australia. Queensland Brain Institute, The University of Queensland, Brisbane, QLD, Australia. Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, MA, USA. Department of Psychiatry and Psychotherapy, Charité - Universitätsmedizin, Berlin, Germany. Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, MA, USA. Center for Integrative Sequencing, Aarhus University, Aarhus, Denmark. Department of Biomedicine, Aarhus University, Aarhus, Denmark. Department of Clinical Neuroscience, Centre for Psychiatry Research, Karolinska Institutet, Stockholm, Sweden. Department of Psychiatry, Psychosomatics and Psychotherapy, Center of Mental Health, University Hospital Würzburg, Würzburg, Germany. PSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Aarhus, Denmark. Department of Health Care Research, Vrije Universiteit Amsterdam, Amsterdam, Netherlands. Division of Psychiatry, University of Edinburgh, Edinburgh, UK. National Centre for Register-Based Research, Aarhus University, Aarhus, Denmark. Centre for Integrated Register-based Research, Aarhus University, Aarhus, Denmark. Discipline of Psychiatry, University of Adelaide, Adelaide, SA, Australia. Department of Translational Research in Psychiatry, Max Planck Institute of Psychiatry, Munich, Germany. Munich Cluster for Systems Neurology (SyNergy), Munich, Germany. Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, USA. Department of Congenital Disorders, Center for Neonatal Screening, Statens Serum Institut, Copenhagen, Denmark. Department of Psychiatry, Vrije Universiteit Medical Center and GGZ inGeest, Amsterdam, Netherlands. Virginia Institute for Psychiatric & Behavioral Genetics, Virginia Commonwealth University, Richmond, VA, USA. Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA. Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. Translational Neuropsychiatry Unit, Department of Clinical Medicine, Aarhus University, Aarhus, Denmark. Human Genetics, Wellcome Trust Sanger Institute, Cambridge, UK. Statistical Genetics and Systems Genetics, European Bioinformatics Institute (EMBL-EBI), Cambridge, UK. Department of Psychiatry, University Hospital of Lausanne, Prilly, Lausanne, Vaud, Switzerland. Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia. Centre for Advanced Imaging, The University of Queensland, Brisbane, QLD, Australia. Center for Genomic and Computational Biology, Duke University, Durham, NC, USA. Division of Medical Genetics, Department of Pediatrics, Duke University, Durham, NC, USA. Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK. Center for Genomic Medicine, University of Bonn, Bonn, Germany. Department of Genomics, Life&Brain Center, University of Bonn, Bonn, Germany. Epidemiology, Erasmus MC, Rotterdam, Zuid-Holland, Netherlands. Psychiatry, Dokuz Eylül University School of Medicine, İzmir, Turkey. Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA. Psychiatric and Neurodevelopmental Genetics Unit (PNGU), Massachusetts General Hospital, Boston, MA, USA. Neuroscience and Mental Health, Cardiff University, Cardiff, UK. Bioinformatics, University of British Columbia, Vancouver, BC, Canada. Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA. Department of Mathematics, Massachusetts Institute of Technology, Cambridge, MA, USA. Department of Psychiatry (UPK), University of Basel, Basel, Switzerland. Human Genomics Research Group, Department of Biomedicine, University of Basel, Basel, Switzerland. Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University-Mannheim, Baden-Württemberg, Germany. Department of Psychiatry, Trinity College Dublin, Dublin, Ireland. Department of Psychiatry & Behavioral Sciences, Johns Hopkins University, Baltimore, MD, USA. Bioinformatics Research Centre, Aarhus University, Aarhus, Denmark. Department of Neurology, Danish Headache Centre, Rigshospitalet, Glostrup, Denmark. Institute of Biological Psychiatry, Mental Health Center SctHans, Mental Health Services Capital Region of Denmark, Copenhagen, Denmark. Brain and Mind Centre, University of Sydney, Sydney, NSW, Australia. Department of Functional Genomics, Interfaculty Institute for Genetics and Functional Genomics, University Medicine and Ernst Moritz Arndt University Greifswald, Greifswald, Mecklenburg-Vorpommern, DE, Germany. Roche Pharmaceutical Research and Early Development, Pharmaceutical Sciences, Roche Innovation Center Basel, F Hoffmann-La Roche Ltd, Basel, Switzerland. Max Planck Institute of Psychiatry, Munich, Germany. Department of Psychological Medicine, University of Worcester, Worcester, UK. Division of Research, Kaiser Permanente Northern California, Oakland, CA, USA. Psychiatry & The Behavioral Sciences, University of Southern California, Los Angeles, CA, USA. Department of Biomedical Informatics, Harvard Medical School, Boston, MA, USA. Department of Medicine, Brigham and Women’s Hospital, Boston, MA, USA. Informatics Program, Boston Children’s Hospital, Boston, MA, USA. Welcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK. Department of Endocrinology at Herlev University Hospital, University of Copenhagen, Copenhagen, Denmark. Institute of Social and Preventive Medicine (IUMSP), University Hospital of Lausanne, Lausanne, Vaud, Switzerland. Swiss Institute of Bioinformatics, Lausanne, Vaud, Switzerland. Mental Health, NHS, Glasgow, UK. Department of Psychiatry and Psychotherapy, University of Bonn, Bonn, Germany. Statistics, University of Oxford, Oxford, UK. Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY, USA. School of Psychology and Counseling, Queensland University of Technology, Brisbane, QLD, Australia. Child and Youth Mental Health Service, Children’s Health Queensland Hospital and Health Service, South Brisbane, QLD, Australia. Child Health Research Centre, University of Queensland, Brisbane, QLD, Australia. Estonian Genome Center, University of Tartu, Tartu, Estonia. Department of Medical Genetics, University of British Columbia, Vancouver, BC, Canada. Department of Statistics, University of British Columbia, Vancouver, BC, Canada. DZHK (German Centre for Cardiovascular Research), Partner Site Greifswald, University Medicine, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, Germany. Institute of Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, Germany. Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, QLD, Australia. Humus Inc, Reykjavik, Iceland. Clinical Genetics, Vrije Universiteit Medisch Centrum, Amsterdam, Netherlands. Complex Trait Genetics, Vrije Universiteit Amsterdam, Amsterdam, Netherlands. Solid Biosciences, Boston, MA, USA. Department of Psychiatry, Washington University in Saint Louis School of Medicine, Saint Louis, MO, USA. Department of Biochemistry and Molecular Biology II, Institute of Neurosciences, Center for Biomedical Research, University of Granada, Granada, Spain. Department of Psychiatry, University of Groningen, University Medical Center Groningen, Groningen, Netherlands. Department of Psychiatry and Psychotherapy, Medical Center of the University of Munich, Campus Innenstadt, Munich, Germany.
