


ARTICLE

DOI: 10.1038/s42003-018-0155-y

OPEN

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

Simone de Jong^{1,2}, Mateus Jose Abdalla Diniz^{3,4}, Andiar Saloma^{3,4}, Ary Gadelha³, Marcos L. Santoro⁵, Vanessa K. Ota^{3,5}, Cristiano Noto³, Major Depressive Disorder and Bipolar Disorder Working Groups of the Psychiatric Genomics Consortium[#], Charles Curtis^{1,2}, Stephen J. Newhouse^{2,6,7}, Hamel Patel^{2,6}, Lynsey S. Hall⁸, Paul F. O'Reilly¹, Sintia I. Belangero^{3,5}, Rodrigo A. Bressan³ & Gerome Breen^{1,2} 

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 ($n \sim 260$) 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.

¹MRC Social Genetic and Developmental Psychiatry Centre, Institute of Psychiatry Psychology and Neuroscience, King's College London, London SE5 8AF, UK. ²National 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. ³Department of Psychiatry, Universidade Federal de São Paulo (UNIFESP/EPM), São Paulo 04021-001, Brazil. ⁴Pax Instituto de Psiquiatria, BR153, km 505, Villa Sul V, Aparecida de Goiânia 74911-516, Brazil. ⁵Department of Morphology and Genetics, Universidade Federal de São Paulo (UNIFESP/EPM), São Paulo 04021-001, Brazil. ⁶Department of Biostatistics and Health Informatics, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London SE5 8AF, UK. ⁷Farr Institute of Health Informatics Research, UCL Institute of Health Informatics, University College London, London NW1 2DA, UK. ⁸Division 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 studies¹. 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)^{2,3} has proven to be most powerful in predicting not only SCZ^{1,4} but also other psychiatric disorders^{5–7}. 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 (<https://www.med.unc.edu/pgc/shared-methods>).

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 chance⁸. Results from a recent study by Nordsletten et al.⁹ 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^{9–11}. This includes anticipation, a phenomenon where later generations exhibit more severe symptoms at an earlier age, robustly reported (although not explained) in BPD¹², and recently highlighted in genetic studies of MDD^{13,14}.

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)17 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, $p = 0.035$, $R^2 =$

0.021), and BPD:PRS (Beta = 0.094, SE = 0.030, Z-ratio = 3.123, $p = 0.002$, $R^2 = 0.039$). 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 $p = 0.02$)¹⁵. 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, $p = 0.002$, $R^2 = 0.186$, Fig. 1) and BPD:PRS (Beta = 0.172, SE = 0.066, Z-ratio = 2.613, $p = 0.013$, $R^2 = 0.126$, 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 \pm 21.1), G4 ($n = 53$, AAO = 31.2 yrs \pm 12.3), G5 ($n = 23$, AAO = 19.7 yrs \pm 9.5), and G6 ($n = 4$, AAO = 13 yrs \pm 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, $p = 0.013$, $R^2 = 0.059$). 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, $p = 0.008$, $R^2 = 0.025$). 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.

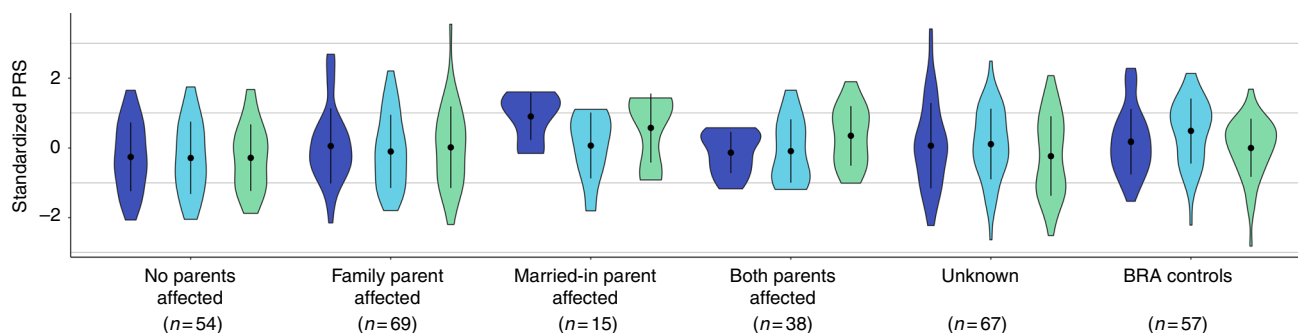


Fig. 1 Violin plots of SCZ:PRS (dark blue plots) MDD:PRS (light blue plots) and BPD:PRS (green plots) for offspring of all spouse pair possibilities. The first category represents PRS in individuals with no affected parents, the next for individuals with an affected family member parent, followed by offspring of an affected married-in individual, and finally offspring of two affected parents. The last two sets of violin plots represent offspring of unknown spouse pairs and the BRA controls. The dot and error bars represent mean \pm standard deviation of standardized PRSs

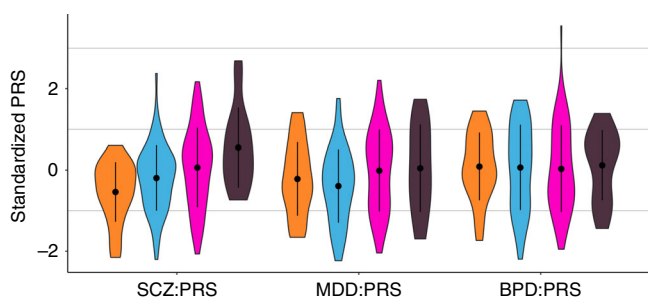


Fig. 2 Violin plots of SCZ:PRS, MDD:PRS and BPD:PRS per generation for family members only, with results for the generations G3 ($n = 25$, orange plots), G4 ($n = 72$, light blue plots), G5 ($n = 80$, pink plots), and G6 ($n = 16$, dark purple plots) (excluding the oldest generation G2 and youngest generation G7 because of $n = 2$ sample size). The dot and error bars represent mean \pm standard deviation of standardized PRSs

Balance of common and rare genetic risk. Transmission disequilibrium test analysis within the chr2p23 linkage region resulted in identification of rs1862975, a SNP originally typed on the Affymetrix linkage array (combined test $p = 0.003$). The homozygous T genotype was detected in 68% affected family members, 57% affected married-ins, 36% unaffected family members and 24% unaffected married-ins. Since this SNP was present only on the Affymetrix array, we identified rs12996218 as a proxy in CEU/TSI populations ($D' = 1.0$, $R^2 = 0.92$) via the LDproxy option in LDlink (Machiela et al.¹⁶, <https://analysisstools.nci.nih.gov/LDlink/>). 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 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 SCZ², 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 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 traits^{9,10}. 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 severity^{20,21} and has been previously associated with genetic risk in MDD^{13,14}. 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	<i>n</i>	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
BP NOS	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	1	0, 1	52	—	1	0
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 ± sd; 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 psychotic episode during their lifetime.

Diagnostic categories are BPI bipolar I, BPII bipolar II, BP NOS 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 our data for teasing apart patterns of assortative mating and anticipation, whereby increased polygenic risk for psychiatric disorders is contributed by affected individuals who married into the family, adding to the already present rare risk variation passed on by the early generations²³.

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 interviews, using the Portuguese version of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)²⁴. Members aged 6–16 were assessed using the Portuguese version of Kiddie-SADS-Present and Lifetime Version (K-SADS-PL)²⁵. In total 308 interviews were completed, and 5 eligible members declined an interview. In the rare event of discrepancies, two independent psychiatrists reviewed them and a final consensus diagnosis was assigned. All affected and unaffected adult family members that have been included in the genetic study have given informed consent. Minors have given assent, followed by consent by their parents in accordance with accepted practice in both the U.K. and Brazil. The project was approved by the Brazilian National Ethics Committee (CONEP). Table 1 contains the demographics of the subjects used in the current analysis (*n* = 243 passed genotype quality control procedures described below). The population control dataset (BRA controls) was collected in Sao Paulo, Brazil, as a control

dataset in a genetic study of first-episode psychosis²⁶. They were volunteers who had no abnormal psychiatric diagnoses (SCID) or family history of psychotic illness. The Research Ethics Committee of Federal University of Sao Paulo (UNIFESP) approved the research protocol, and all participants gave informed consent (CEP No. 0603/10). Demographics for *n* = 57 BRA controls can be found in Table 1.

Genotype data. Following diagnostic interview, interviewers obtained whole blood in EDTA containing monovettes for adults and lesser amounts of saliva given personal preference or age (DNA Genotek Inc., Ontario, Canada). Genomic DNA was isolated from whole blood and saliva at UNIFESP using standard procedures. Whole-genome genotype data was generated using the Illumina Infinium PsychArray-24 (<http://www.illumina.com/products/psycharray.html>) for both the BBF and the BRA control dataset at the in-house BRC BioResource Illumina core lab according to manufacturers protocol. Samples were excluded when average call rate was <98%, missingness >1% with additional check for excess heterozygosity, sex, family relationships and concordance rates with previous genotyping assays. SNPs were excluded when missingness > 1%, MAF < 0.01 or HWE < 0.00001 and if showing Mendelian errors for the BBF dataset in Plink v1.07²⁷ and v1.9²⁸ or Merlin v1.1.2²⁹. The BBF and BRA control datasets were QC'd separately and then merged, applying the same SNP QC thresholds to the merged dataset as well. This quality control procedure resulted in a dataset of 225,235 SNPs for 243 BBF individuals (197 family members and 46 married-in individuals) and 57 BRA controls. Eigensoft v4.2³⁰ was used to check for population differences between the BBF family members, married-in individuals and BRA control sets. The BBF members self-reported mixed Southern European ancestry, confirmed 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 PCs seemingly separating subfamilies (Supplementary Figures 7 and 8). PRS analyses as described below were also performed to include subfamily as a fixed effect, controlling for household effects (Supplementary Table 3). PC1 and PC2 are significantly correlated to the SCZ:PRS (PC1 *r* = −0.131, *p* = 0.023; PC2 *r* = −0.268, *p* = 2.611 × 10^{−6}), PC1 to MDD:PRS (PC1 *r* = −0.251, *p* = 1.114 × 10^{−5}), and PC1 and PC2 to BPD:PRS (PC1 *r* = 0.189, *p* = 9.710 × 10^{−4}; PC2 *r* = −0.123, *p* = 0.033). The principal components were not used in subsequent analyses.

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 software³¹ with the publically available PGC schizophrenia GWAS² as a base dataset (36,989 SCZ cases, 113,075 controls), in addition to MDD (51,865 MDD cases, 112,200 controls, not including 23 and me individuals) and BPD (20,352 BPD cases, 31,358 controls) summary statistics from the latest PGC meta analyses (unpublished data^{18,19}). We performed *p*-value-informed clumping on the genotype data with a cut-off of *r*² = 0.25 within a 200-kb window, excluding the MHC region on chromosome 6 because of its complex linkage disequilibrium structure. Acknowledging the possibility of over-fitting, we selected the PRS thresholds most predictive in discriminating affected from unaffected family members through linear regression in PRSice for SCZ:PRS (*p* < 0.00055, 1218 SNPs), MDD:PRS (*p* <

0.0165, 715 SNPs) and BPD:PRS ($p < 0.00005$, 143 SNPs). PRS showed low to modest correlations (no covariates) amongst each other in our data (SCZ:PRS versus MDD:PRS $r = 0.176$, $p = 0.002$, SCZ:PRS versus BPD:PRS $r = 0.124$, $p = 0.032$, MDD:PRS versus BPD:PRS $r = -0.026$, $p = 0.660$).

Linkage analysis. The main linkage analyses identifying rare genetic risk variation were performed as part of a previous paper on the BBF²³ using the Affymetrix 10K linkage genotyping array. In order to explore the balance between common and rare risk variation, we selected the strongest signal for affected versus unaffected family members on chr2p23 (chr2:30000001-36600000, LOD = 3.83). Following the strategy described by Rioux et al.³², we performed a transmission disequilibrium test on the 25 markers in this linkage region in an attempt to identify “linkage positive” individuals in $n = 300$ family members with one or both types of genotype array data. $N = 155$ individuals overlap with the current study and based on exploration of patterns of PRS in the current study we attempted to answer two questions: (1) with an increase of common risk variation, does rare risk variation become less important over generations, (2) do linkage positive individuals carrying the presumed risk allele show differences in PRS.

Statistical testing. All PRS were standardized mean = 0 and SD = 1. Linear mixed model analyses were selected to be able to model covariates and relatedness within this complicated dataset. The analyses were performed using the Wald conditional F-test³³ in ASReml-R software³⁴ with one of the categories of mood disorders or family status as dependent variable and PRS as the independent variable (Supplementary Methods). Age (except for the generation analysis) and sex were fitted as fixed effects in the models. For 7 individuals in the BBF age at collection was missing and imputed to be the mean age of the relevant generation. To account for relatedness in within-family comparisons, an additive genetic relationship matrix was fitted as a random effect. The relationship matrix was constructed using LDAK software³⁵ with weighted predictors and LD correction parameters suited for pedigree data, resulting in pairwise relatedness estimates and inbreeding coefficients on the diagonal. The variance explained by each PRS was calculated using: $(\text{var}(x \times \beta) / \text{var}(y))$, where x was the standardized PRS, β was the corresponding regression coefficient, and y was the phenotype³⁶. For the analysis of offspring, we defined four spouse pair categories (“both unaffected”, “married-in parent affected”, “family parent affected”, “both affected”). While most spouse pairs contribute 1 or 2 children to the same offspring category (Supplementary Table 1); two “both affected” spouse pairs contribute 7 and 8 children, respectively. To prevent bias in our analysis in the event of more than one child per couple, we calculated the mean PRS for all offspring per spouse pair and entered this in the model as being one representative child for that couple. All p -values reported are uncorrected for multiple testing, since all tests concern overlapping individuals and thus have a complex dependence structure. However, we have performed 42 tests as listed in Supplementary Table 4, and so a conservative Bonferroni threshold for $p < 0.05$ is 0.001.

Data availability

In order to ensure privacy of the family members and to comply with Brazilian regulations, restrictions apply on availability of the data as determined by the Brazilian National Ethics Committee (CONEP). Data are available upon reasonable request from the corresponding author, pending approval by the BBF ethics committee (CONEP).

Received: 6 February 2018 Accepted: 6 August 2018

Published online: 08 October 2018

References

- Purcell, S. M. et al. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature* **460**, 748–752 (2009).
- Ripke, S. et al. Biological insights from 108 schizophrenia-associated genetic loci. *Nature* **511**, 421–427 (2014).
- Sullivan, P. F. The psychiatric GWAS consortium: big science comes to psychiatry. *Neuron* **68**, 182–186 (2010).
- Ahn, K., An, S. S., Shugart, Y. Y. & Rapoport, J. L. Common polygenic variation and risk for childhood-onset schizophrenia. *Mol. Psychiatry* **21**, 94–96 (2016).
- Lichtenstein, P. et al. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. *Lancet* **373**, 234–239 (2009).
- Lee, S. H. et al. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat. Genet.* **45**, 984–994 (2013).
- Cross-Disorder Group of the Psychiatric Genomics Consortium. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *Lancet* **381**, 1371–1379 (2013).
- Merikangas, K. R. & Spiker, D. G. Assortative mating among in-patients with primary affective disorder. *Psychol. Med.* **12**, 753–764 (1982).
- Nordsletten, A. E. et al. Patterns of nonrandom mating within and across 11 major psychiatric disorders. *JAMA Psychiatry* **73**, 354–361 (2016).
- Plomin, R., Krapohl, E. & O’Reilly, P. F. Assortative mating—a missing piece in the jigsaw of psychiatric genetics. *JAMA Psychiatry* **73**, 323–324 (2016).
- Robinson, M. R. et al. Genetic evidence of assortative mating in humans. *Nat. Hum. Behav.* **1**, 16 (2017).
- O’Donovan, M., Jones, I. & Craddock, N. Anticipation and repeat expansion in bipolar disorder. *Am. J. Med. Genet. C* **123C**, 10–17 (2003).
- Power, R. A. et al. Genome-wide association for major depression through age at onset stratification. *Biol. Psychiatry* <https://doi.org/10.1016/j.biopsych.2016.05.010> (2016).
- Power, R. A. et al. Dissecting the genetic heterogeneity of depression through age at onset. *Am. J. Med. Genet. B* **159B**, 859–868 (2012).
- Silva, M. T., Galvao, T. F., Martins, S. S. & Pereira, M. G. Prevalence of depression morbidity among Brazilian adults: a systematic review and meta-analysis. *Rev. Bras. Psiquiatr.* **36**, 262–270 (2014).
- Machiela, M. J. & Chanock, S. J. LDlink: a web-based application for exploring population-specific haplotype structure and linking correlated alleles of possible functional variants. *Bioinformatics* **31**, 3555–3557 (2015).
- Boies, S., Mérette, C., Paccalet, T., Maziade, M. & Bureau, A. Polygenic risk scores distinguish patients from non-affected adult relatives and from normal controls in schizophrenia and bipolar disorder multi-affected kindreds. *Am. J. Med. Genet. B* <https://doi.org/10.1002/ajmg.b.32614> (2017).
- Wray, N. R. et al. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nat. Genet.* **50**, 668–681 (2018).
- Stahl, E. et al. Genomewide association study identifies 30 loci associated with bipolar disorder. *bioRxiv* 173062. <https://doi.org/10.1101/173062> (2017).
- Schulze, T. G. et al. Further evidence for age of onset being an indicator for severity in bipolar disorder. *J. Affect. Disord.* **68**, 343–345 (2002).
- Schürhoff, F. et al. Early and late onset bipolar disorders: two different forms of manic-depressive illness? *J. Affect. Disord.* **58**, 215–221 (2000).
- Alda, M. et al. Anticipation in bipolar affective disorder: is age at onset a valid criterion? *Am. J. Med. Genet.* **96**, 804–807 (2000).
- Diniz, M. J. A. et al. Whole genome linkage analysis in a large Brazilian multigenerational family reveals distinct linkage signals for bipolar disorder and depression. *bioRxiv* 106260 (2017).
- Del-Ben, C. M., Rodrigues, C. R. & Zuardi, A. W. Reliability of the Portuguese version of the structured clinical interview for DSM-III-R (SCID) in a Brazilian sample of psychiatric outpatients. *Braz. J. Med. Biol. Res.* **29**, 1675–1682 (1996).
- Brasil, H. H. A. & Bordin, I. A. Convergent validity of K-SADS-PL by comparison with CBCL in a Portuguese speaking outpatient population. *BMC Psychiatry* **10**, 83 (2010).
- Noto, C. et al. Effects of depression on the cytokine profile in drug naïve first-episode psychosis. *Schizophr. Res.* **164**, 53–58 (2015).
- Purcell, S. et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am. J. Hum. Genet.* **81**, 559–575 (2007).
- Chang, C. C. et al. Second-generation PLINK: rising to the challenge of larger and richer datasets. *Gigascience* **4**, 7 (2015).
- Abecasis, G. R., Cherny, S. S., Cookson, W. O. & Cardon, L. R. Merlin—rapid analysis of dense genetic maps using sparse gene flow trees. *Nat. Genet.* **30**, 97–101 (2002).
- Patterson, N., Price, A. L. & Reich, D. Population structure and eigenanalysis. *PLoS Genet.* **2**, e190 (2006).
- Euesden, J., Lewis, C. M. & O’Reilly, P. F. PRSice: Polygenic Risk Score software. *Bioinformatics* <https://doi.org/10.1093/bioinformatics/btu848> (2014).
- Rioux, J. D. et al. Genetic variation in the 5q31 cytokine gene cluster confers susceptibility to Crohn disease. *Nat. Genet.* **29**, 223–228 (2001).
- Kenward, M. G. & Roger, J. H. Small sample inference for fixed effects from restricted maximum likelihood. *Biometrics* **53**, 983–997 (1997).
- Butler, D. G., Cullis, B. R., Gilmour, A. R. & Gogel, B. J. ASReml-R reference manual 3. Technical Report, Department of Primary Industries Queensland (2002).
- Speed, D., Hemani, G., Johnson, M. R. & Balding, D. J. Improved heritability estimation from genome-wide SNPs. *Am. J. Hum. Genet.* **91**, 1011–1021 (2012).
- Nakagawa, S. & Schielzeth, H. A general and simple method for obtaining R² from generalized linear mixed-effects models. *Methods Ecol. Evol.* **4**, 133–142 (2013).

Acknowledgements

We would like to thank the family members for their enthusiastic participation. We thank our ethics consultant Prof. Barbara Prainsack for insightful discussions. This paper represents independent research part-funded by FAPESP (2014/50830-2; 2010/08968-6), the Marie Curie International Research Staff Exchange (FP7-PEOPLE-2011-IRSES/295192), and the National Institute for Health Research (NIHR) Biomedical Research

Centre at South London and Maudsley NHS Foundation Trust and King's College London. SDJ is funded by the European Union's Horizon 2020 research and innovation programme under Marie Skłodowska-Curie grant IF 658195. S.J.N. is also supported by the National Institute for Health Research (NIHR) University College London Hospitals Biomedical Research Centre, and by awards establishing the Farr Institute of Health Informatics Research at UCLPartners, from the Medical Research Council, Arthritis Research UK, British Heart Foundation, Cancer Research UK, Chief Scientist Office, Economic and Social Research Council, Engineering and Physical Sciences Research Council, National Institute for Health Research, National Institute for Social Care and Health Research, and Wellcome Trust (grant MR/K006584/1). The views expressed are those of the authors and not necessarily those of the EU, the NHS, the NIHR or the Department of Health.

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.

Reprints and permission information is available online at <http://npg.nature.com/reprintsandpermissions/>

Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/>.

© The Author(s) 2018

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

Naomi R. Wray^{9,10}, Stephan Ripke^{11,12,13}, Manuel Mattheisen^{14,15,16,17,18}, Maciej Trzaskowski⁹, Enda M. Byrne⁹, Abdel Abdellaoui¹⁹, Mark J. Adams²⁰, Esben Agerbo^{18,21,22}, Tracy M. Air²³, Till F.M. Andlauer^{24,25}, Silviu-Alin Bacanu²⁶, Marie Bækvad-Hansen^{18,27}, Aartjan T.F. Beekman²⁸, Tim B. Bigdeli^{26,29}, Elisabeth B. Binder^{24,30}, Douglas H.R. Blackwood²⁰, Julien Bryois³¹, Henriette N. Buttenschøn^{14,18,32}, Jonas Bybjerg-Grauholm²⁷, Na Cai^{33,34}, Enrique Castelao³⁵, Jane Hvarregaard Christensen^{14,15,18}, Toni-Kim Clarke²⁰, Jonathan R.I. Coleman¹, Lucía Colodro-Conde³⁶, Baptiste Couvy-Duchesne^{10,37}, Nick Craddock⁸, Gregory E. Crawford^{38,39}, Gail Davies⁴⁰, Ian J. Deary⁴⁰, Franziska Degenhardt^{41,42}, Eske M. Derks³⁶, Nese Direk^{43,44}, Conor V. Dolan¹⁹, Erin C. Dunn^{45,46,47}, Thalia C. Eley¹, Valentina Escott-Price⁴⁷, Farnush Farhadi Hassan Kiadeh⁴⁸, Hilary K. Finucane^{49,50}, Andreas J. Forstner^{41,42,51,52}, Josef Frank⁵³, Héléna A. Gaspar¹, Michael Gill⁵⁴, Fernando S. Goes⁵⁵, Scott D. Gordon³⁶, Jakob Grove^{14,15,18,56}, Christine Sørholm Hansen^{18,27}, Thomas F. Hansen^{18,57,58}, Stefan Herms^{41,42,43}, Ian B. Hickie⁵⁹, Per Hoffmann^{41,42,43}, Georg Homuth⁶⁰, Carsten Horn⁶¹, Jouke-Jan Hottenga¹⁹, David M. Hougaard^{18,27}, Marcus Ising⁶², Rick Jansen²⁸, Ian Jones⁸, Lisa A Jones⁶³, Eric Jorgenson⁶⁴, James A. Knowles⁶⁵, Isaac S. Kohane^{66,67,68}, Julia Kraft¹², Warren W. Kretschmar⁶⁹, Jesper Krogh⁷⁰, Zoltán Kutalik^{71,72}, Yihan Li⁷⁰, Penelope A. Lind³⁶, Donald J. MacIntyre^{20,73}, Dean F. MacKinnon⁵⁵, Robert M. Maier¹⁰, Wolfgang Maier⁷⁴, Jonathan Marchini⁷⁵, Hamdi Mbarek¹⁹, Patrick McGrath⁷⁶, Peter McGuffin¹, Sarah E. Medland³⁶, Divya Mehta^{10,77}, Christel M. Middeldorp^{19,78,79}, Evelin Mihailov⁸⁰, Yuri Milaneschi²⁸, Lili Milani⁸⁰, Francis M. Mondimore⁵⁵, Grant W. Montgomery⁹, Sara Mostafavi^{81,82}, Niamh Mullins¹, Matthias Nauck^{83,84}, Bernard Ng⁸², Michel G. Nivard¹⁹, Dale R. Nyholt⁸⁵, Hogni Oskarsson⁸⁶, Michael J. Owen⁸, Jodie N. Painter³⁷, Carsten Bøcker Pedersen^{18,21,22}, Marianne Giørtz Pedersen^{18,21,22}, Roseann E. Peterson^{26,29}, Erik Pettersson³¹, Wouter J. Peyrot²⁸, Giorgio Pistis³⁵, Danielle Posthuma^{87,88}, Jorge A. Quiroz⁸⁹, Per Qvist^{14,15,18}, John P. Rice⁹⁰, Brien P. Riley²⁶, Margarita Rivera^{1,91}, Saira Saeed Mirza⁴³, Robert Schoevers⁹², Eva C. Schulte^{93,94}, Ling Shen⁶⁴, Stanley I. Shyn⁹⁵, Engilbert Sigurdsson⁹⁶, Grant C.B. Sinnamon⁹⁷, Johannes H. Smit²⁸, Daniel J. Smith⁹⁸, Hreinn Stefansson⁹⁹, Stacy Steinberg⁹⁹, Fabian Streit⁵³, Jana Strohmaier⁵³, Katherine E. Tansey¹⁰⁰,

Henning Teismann¹⁰¹, Alexander Teumer¹⁰², Wesley Thompson^{18,58,103,104}, Pippa A. Thomson¹⁰⁵, Thorgeir E. Thorgeirsson¹⁰⁰, Matthew Traylor¹⁰⁶, Jens Treutlein⁵³, Vassily Trubetskoy¹², André G. Uitterlinden¹⁰⁷, Daniel Umbricht¹⁰⁸, Sandra Van der Auwera¹⁰⁹, Albert M. van Hemert¹¹⁰, Alexander Viktorin³¹, Peter M. Visscher^{9,10}, Yunpeng Wang^{18,58,104}, Bradley T. Webb²⁹, Shantel Marie Weinsheimer^{18,58}, Jürgen Wellmann¹⁰¹, Gonneke Willemsen¹⁹, Stephanie H. Witt⁵³, Yang Wu⁹, Hualin S. Xi¹¹¹, Jian Yang¹⁰, Futao Zhang⁹, Volker Arolt¹¹², Bernhard T. Baune²³, Klaus Berger¹⁰², Dorret I. Boomsma¹⁹, Sven Cichon^{41,52,112,113}, Udo Dannlowski¹¹⁴, E.J.C. de Geus^{19,115}, J. Raymond DePaulo⁵⁵, Enrico Domenici¹¹⁶, Katharina Domschke¹¹⁷, Tõnu Esko^{11,80}, Hans J. Grabe¹⁰⁹, Steven P. Hamilton¹¹⁸, Caroline Hayward¹¹⁹, Andrew C. Heath⁹¹, Kenneth S. Kendler²⁶, Stefan Kloiber^{61,120,121}, Glyn Lewis¹²², Qingqin S. Li¹²³, Susanne Lucae⁶², Pamela A.F. Madden⁹¹, Patrik K. Magnusson³¹, Nicholas G. Martin³⁶, Andrew M. McIntosh^{20,40,105}, Andres Metspalu^{80,124}, Ole Mors^{18,125}, Preben Bo Mortensen^{14,18,21,22}, Bertram Müller-Myhsok^{24,25,126}, Merete Nordentoft^{18,127}, Markus M. Nöthen^{41,42}, Michael C. O'Donovan⁸, Sara A. Paciga¹²⁸, Nancy L. Pedersen³¹, Brenda W.J.H. Penninx²⁸, Roy H. Perlis^{45,129}, David J. Porteous¹⁰⁵, James B. Potash¹³⁰, Martin Preisig³⁵, Marcella Rietschel⁵³, Catherine Schaefer⁶⁴, Thomas G. Schulze^{53,55,94,131,132}, Jordan W. Smoller^{11,45,46}, Kari Stefansson^{100,133}, Henning Tiemeier^{43,134,135}, Rudolf Uher¹³⁶, Henry Völzke¹⁰², Myrna M. Weissman^{76,137}, Thomas Werge^{18,58,138}, Cathryn M. Lewis^{1,139}, Douglas F. Levinson¹⁴⁰, Anders D. Børglum^{14,15,18}, Patrick F. Sullivan^{31,141,142}, Sandra Meier⁵³, John Strauss^{120,121}, Wei Xu^{143,144}, John B. Vincent¹²¹, Keith Matthews¹⁴⁵, Manuel Ferreira¹⁴⁶, Colm O'Dushlaine¹¹, Shaun Purcell^{147,148}, Soumya Raychaudhuri⁶⁶, Douglas M. Ruderfer¹⁴⁹, Pamela Sklar^{147,150}, Laura J. Scott¹⁵¹, Matthew Flickinger¹⁵¹, Margit Burmeister¹⁵², Jun Li¹⁵¹, Weihua Guan¹⁵³, Devin Absher¹⁵⁴, Robert C. Thompson¹⁵¹, Fan Guo Meng¹⁵¹, Alan F. Schatzberg¹⁴⁰, William E. Bunney¹⁵⁵, Jack D. Barchas¹⁵⁶, Stanley J. Watson¹⁵⁷, Richard M. Myers¹⁵⁴, Huda Akil¹⁵², Michael Boehnke¹⁵¹, Kimberly Chambert¹¹, Jennifer Moran¹¹, Edward Scolnick¹¹, Srdjan Djurovic^{158,159}, Ingrid Melle¹⁶⁰, Gunnar Morken^{161,162}, Aiden Corvin⁵⁴, Adebayo Anjorin¹⁶³, Radhika Kandaswamy¹, Jacob Lawrence¹⁶⁴, Alan W. McLean^{20,105}, Benjamin S. Pickard^{20,105}, Sarah E. Bergen³¹, Vishwajit Nimgaonkar¹⁶⁵, Mikael Landén^{31,166}, Martin Schalling¹⁶⁷, Urban Osby¹⁶⁷, Lena Backlund¹⁶, Louise Frisé¹⁶⁷, Niklas Langstrom¹⁶⁶, Eli Stahl^{11,147,150}, Amanda Dobbyn^{147,150}, Stéphane Jamain^{168,169,170}, Bruno Etain^{168,169,170}, Frank Bellivier^{168,169,170}, Markus Leber¹⁷¹, Anna Maaser^{41,42}, Sascha B. Fischer^{112,172}, Céline S. Reinbold^{112,172}, Sarah Kittel-Schneider⁵¹, Janice M. Fullerton^{173,174}, Lilijana Oruč^{173,174}, José G. Para¹⁷⁵, Fermin Mayoral¹⁷⁵, Fabio Rivas¹⁷⁵, Piotr M. Czerski¹⁷⁶, Jutta Kammerer-Ciernioch¹⁷⁷, Helmut Vedder¹⁷⁷, Margitta Borrmann-Hassenbach¹⁷⁸, Andrea Pfennig¹⁷⁹, Paul Brennan¹⁸⁰, James D. McKay¹⁸⁰, Manolis Kogevinas¹⁸¹, Markus Schwarz¹⁷⁷, Peter R. Schofield^{173,174}, Thomas W. Mühleisen^{113,172}, Johannes Schumacher⁴¹, Michael Bauer¹⁷⁹, Adam Wright¹⁸², Philip B. Mitchell¹⁸², Martin Hautzinger¹⁸³, John R. Kelsoe¹⁰³, Tiffany A. Greenwood¹⁰³, Caroline M. Nievergelt¹⁰³, Paul D. Shilling¹⁰³, Erin N. Smith¹⁸⁴, Cinnamon S. Bloss¹⁸⁴, Howard J. Edenberg^{185,186}, Daniel L. Koller¹⁸⁶, Elliot S. Gershon^{187,188}, Chunyu Liu^{187,188}, Judith A. Badner^{187,188}, William A. Scheftner¹⁸⁹, William B. Lawson¹⁹⁰, Evaristus A. Nwulia¹⁹⁰, Maria Hipolito¹⁹⁰, William Coryell¹³⁰, John Rice¹⁹¹, William Byerley¹⁹², Francis J. McMahon¹³², Falk W. Lohoff¹⁹³, Peter P. Zandi¹⁹⁴, Pamela B. Mahon¹⁹⁴, Melvin G. McInnis¹⁵⁷, Sebastian Zöllner¹⁵⁷, Peng Zhang¹⁵⁷, Szabolcs Szelinger¹⁹⁵, David St. Clair¹⁹⁶, Sian Caesar¹⁹⁷, Katherine Gordon-Smith¹⁹⁷, Christine Fraser⁸, Elaine K. Green⁸, Detelina Grozeva⁸, Marian L. Hamshere⁸, George Kirov⁸, Ivan Nikolov⁸, David A. Collier¹, Amanda Elkin¹, Richard Williamson¹, Allan H. Young¹⁹⁸, I. Nicol Ferrier¹⁹⁹, Vihra Milanova²⁰⁰, Martin Alda¹³⁶, Pablo Cervantes²⁰¹, Cristiana Cruceanu^{24,201}, Guy A. Rouleau^{202,203}, Gustavo Turecki²⁰¹, Sara Paciga¹²⁸, Ashley R. Winslow²⁰⁴, Maria Grigoriou-Serbanescu²⁰⁵, Roel Ophoff^{206,207,208}, Rolf Adolfsson²⁰⁹, Annelie Nordin Adolfsson²⁰⁹, Jurgen Del-Favero²¹⁰, Carlos Pato²¹¹, Joanna M. Biernacka²¹², Mark A. Frye²¹³,

Derek Morris^{54,214}, Nicholas J. Schork^{184,215}, Andreas Reif^{41,42,51,112,172}, Jolanta Lissowska²¹⁶, Joanna Hauser¹⁷⁶, Neonila Szeszenia-Dabrowska²¹⁷, Kevin McGhee^{20,105}, Emma Quinn²¹⁸, Valentina Moskvina⁸, Peter A. Holmans²¹⁹, Anne Farmer⁸, James L. Kennedy^{120,121,220,221}, Ole A. Andreassen^{159,160}, Morten Mattingsdal²²², Michael Gill⁵⁴, Nicholas J. Bass¹²², Hugh Gurling¹²², Andrew McQuillin¹²², René Breuer⁵³, Christina Hultman³¹, Paul Lichtenstein³¹, Laura M. Huckins^{147,150}, Marion Leboyer^{168,169,170}, Mark Lathrop²²³, John Nurnberger¹⁸⁶, Michael Steffens²²⁴, Tatiana M. Foroud¹⁸⁶, Wade H. Berrettini¹⁹³, David W. Craig²¹⁵ & Jianxin Shi²²⁵

⁹Institute for Molecular Bioscience, The University of Queensland, Brisbane, QLD, Australia. ¹⁰Queensland Brain Institute, The University of Queensland, Brisbane, QLD, Australia. ¹¹Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, MA, USA. ¹²Department of Psychiatry and Psychotherapy, Charité - Universitätsmedizin, Berlin, Germany. ¹³Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, MA, USA. ¹⁴SEQ, Center for Integrative Sequencing, Aarhus University, Aarhus, Denmark. ¹⁵Department of Biomedicine, Aarhus University, Aarhus, Denmark. ¹⁶Department of Clinical Neuroscience, Centre for Psychiatry Research, Karolinska Institutet, Stockholm, Sweden. ¹⁷Department of Psychiatry, Psychosomatics and Psychotherapy, Center of Mental Health, University Hospital Würzburg, Würzburg, Germany. ¹⁸PSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Aarhus, Denmark. ¹⁹Department of Biological Psychology & EMGO+ Institute for Health and Care Research, Vrije Universiteit Amsterdam, Amsterdam, Netherlands. ²⁰Division of Psychiatry, University of Edinburgh, Edinburgh, UK. ²¹National Centre for Register-Based Research, Aarhus University, Aarhus, Denmark. ²²Centre for Integrated Register-based Research, Aarhus University, Aarhus, Denmark. ²³Discipline of Psychiatry, University of Adelaide, Adelaide, SA, Australia. ²⁴Department of Translational Research in Psychiatry, Max Planck Institute of Psychiatry, Munich, Germany. ²⁵Munich Cluster for Systems Neurology (SyNergy), Munich, Germany. ²⁶Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, USA. ²⁷Department for Congenital Disorders, Center for Neonatal Screening, Statens Serum Institut, Copenhagen, Denmark. ²⁸Department of Psychiatry, Vrije Universiteit Medical Center and GGZ inGeest, Amsterdam, Netherlands. ²⁹Virginia Institute for Psychiatric & Behavioral Genetics, Virginia Commonwealth University, Richmond, VA, USA. ³⁰Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA. ³¹Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. ³²Translational Neuropsychiatry Unit, Department of Clinical Medicine, Aarhus University, Aarhus, Denmark. ³³Human Genetics, Wellcome Trust Sanger Institute, Cambridge, UK. ³⁴Statistical Genomics and Systems Genetics, European Bioinformatics Institute (EMBL-EBI), Cambridge, UK. ³⁵Department of Psychiatry, University Hospital of Lausanne, Prilly, Lausanne, Vaud, Switzerland. ³⁶Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia. ³⁷Centre for Advanced Imaging, The University of Queensland, Brisbane, QLD, Australia. ³⁸Center for Genomic and Computational Biology, Duke University, Durham, NC, USA. ³⁹Division of Medical Genetics, Department of Pediatrics, Duke University, Durham, NC, USA. ⁴⁰Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK. ⁴¹Institute of Human Genetics, University of Bonn, Bonn, Germany. ⁴²Department of Genomics, Life&Brain Center, University of Bonn, Bonn, Germany. ⁴³Epidemiology, Erasmus MC, Rotterdam, Zuid-Holland, Netherlands. ⁴⁴Psychiatry, Dokuz Eylul University School of Medicine, Izmir, Turkey. ⁴⁵Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA. ⁴⁶Psychiatric and Neurodevelopmental Genetics Unit (PNGU), Massachusetts General Hospital, Boston, MA, USA. ⁴⁷Neuroscience and Mental Health, Cardiff University, Cardiff, UK. ⁴⁸Bioinformatics, University of British Columbia, Vancouver, BC, Canada. ⁴⁹Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA. ⁵⁰Department of Mathematics, Massachusetts Institute of Technology, Cambridge, MA, USA. ⁵¹Department of Psychiatry (UPK), University of Basel, Basel, Switzerland. ⁵²Human Genomics Research Group, Department of Biomedicine, University of Basel, Basel, Switzerland. ⁵³Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University-Mannheim, Baden-Württemberg, Germany. ⁵⁴Department of Psychiatry, Trinity College Dublin, Dublin, Ireland. ⁵⁵Department of Psychiatry & Behavioral Sciences, Johns Hopkins University, Baltimore, MD, USA. ⁵⁶Bioinformatics Research Centre, Aarhus University, Aarhus, Denmark. ⁵⁷Department of Neurology, Danish Headache Centre, Rigshospitalet, Glostrup, Denmark. ⁵⁸Institute of Biological Psychiatry, Mental Health Center SctHans, Mental Health Services Capital Region of Denmark, Copenhagen, Denmark. ⁵⁹Brain and Mind Centre, University of Sydney, Sydney, NSW, Australia. ⁶⁰Department of Functional Genomics, Interfaculty Institute for Genetics and Functional Genomics, University Medicine and Ernst Moritz Arndt University Greifswald, Greifswald, Mecklenburg-Vorpommern, DE, Germany. ⁶¹Roche Pharmaceutical Research and Early Development, Pharmaceutical Sciences, Roche Innovation Center Basel, F Hoffmann-La Roche Ltd, Basel, Switzerland. ⁶²Max Planck Institute of Psychiatry, Munich, Germany. ⁶³Department of Psychological Medicine, University of Worcester, Worcester, UK. ⁶⁴Division of Research, Kaiser Permanente Northern California, Oakland, CA, USA. ⁶⁵Psychiatry & The Behavioral Sciences, University of Southern California, Los Angeles, CA, USA. ⁶⁶Department of Biomedical Informatics, Harvard Medical School, Boston, MA, USA. ⁶⁷Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA. ⁶⁸Informatics Program, Boston Children's Hospital, Boston, MA, USA. ⁶⁹Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK. ⁷⁰Department of Endocrinology at Herlev University Hospital, University of Copenhagen, Copenhagen, Denmark. ⁷¹Institute of Social and Preventive Medicine (IUMSP), University Hospital of Lausanne, Lausanne, Vaud, Switzerland. ⁷²Swiss Institute of Bioinformatics, Lausanne, Vaud, Switzerland. ⁷³Mental Health, NHS, Glasgow, UK. ⁷⁴Department of Psychiatry and Psychotherapy, University of Bonn, Bonn, Germany. ⁷⁵Statistics, University of Oxford, Oxford, UK. ⁷⁶Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY, USA. ⁷⁷School of Psychology and Counseling, Queensland University of Technology, Brisbane, QLD, Australia. ⁷⁸Child and Youth Mental Health Service, Children's Health Queensland Hospital and Health Service, South Brisbane, QLD, Australia. ⁷⁹Child Health Research Centre, University of Queensland, Brisbane, QLD, Australia. ⁸⁰Estonian Genome Center, University of Tartu, Tartu, Estonia. ⁸¹Department of Medical Genetics, University of British Columbia, Vancouver, BC, Canada. ⁸²Department of Statistics, University of British Columbia, Vancouver, BC, Canada. ⁸³DZHK (German Centre for Cardiovascular Research), Partner Site Greifswald, University Medicine, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, Germany. ⁸⁴Institute of Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, Germany. ⁸⁵Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, QLD, Australia. ⁸⁶Humus Inc, Reykjavik, Iceland. ⁸⁷Clinical Genetics, Vrije Universiteit Medical Center, Amsterdam, Netherlands. ⁸⁸Complex Trait Genetics, Vrije Universiteit Amsterdam, Amsterdam, Netherlands. ⁸⁹Solid Biosciences, Boston, MA, USA. ⁹⁰Department of Psychiatry, Washington University in Saint Louis School of Medicine, Saint Louis, MO, USA. ⁹¹Department of Biochemistry and Molecular Biology II, Institute of Neurosciences, Center for Biomedical Research, University of Granada, Granada, Spain. ⁹²Department of Psychiatry, University of Groningen, University Medical Center Groningen, Groningen, Netherlands. ⁹³Department of Psychiatry and Psychotherapy, Medical Center of the University of Munich, Campus Innenstadt, Munich,

Germany. ⁹⁴Institute of Psychiatric Phenomics and Genomics (IPPG), Medical Center of the University of Munich, Campus Innenstadt, Munich, Germany. ⁹⁵Behavioral Health Services, Kaiser Permanente Washington, Seattle, WA, USA. ⁹⁶Department of Psychiatry, Faculty of Medicine, University of Iceland, Reykjavik, Iceland. ⁹⁷School of Medicine and Dentistry, James Cook University, Townsville, QLD, Australia. ⁹⁸Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK. ⁹⁹deCODE Genetics/Amgen, Reykjavik, Iceland. ¹⁰⁰College of Biomedical and Life Sciences, Cardiff University, Cardiff, UK. ¹⁰¹Institute of Epidemiology and Social Medicine, University of Münster, Münster, Nordrhein-Westfalen, Germany. ¹⁰²Institute for Community Medicine, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, Germany. ¹⁰³Department of Psychiatry, University of California, San Diego, San Diego, CA, USA. ¹⁰⁴KG Jebsen Centre for Psychosis Research, Norway Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway. ¹⁰⁵Medical Genetics Section, CGEM, IGMM, University of Edinburgh, Edinburgh, UK. ¹⁰⁶Clinical Neurosciences, University of Cambridge, Cambridge, UK. ¹⁰⁷Internal Medicine, Erasmus MC, Rotterdam, Zuid-Holland, Netherlands. ¹⁰⁸Roche Pharmaceutical Research and Early Development, Neuroscience, Ophthalmology and Rare Diseases Discovery & Translational Medicine Area, Roche Innovation Center Basel, F Hoffmann-La Roche Ltd, Basel, Switzerland. ¹⁰⁹Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, Germany. ¹¹⁰Department of Psychiatry, Leiden University Medical Center, Leiden, Netherlands. ¹¹¹Computational Sciences Center of Emphasis, Pfizer Global Research and Development, Cambridge, MA, USA. ¹¹²Institute of Medical Genetics and Pathology, University Hospital Basel, University of Basel, Basel, Switzerland. ¹¹³Institute of Neuroscience and Medicine (INM-1), Research Center Juelich, Juelich, Germany. ¹¹⁴Department of Psychiatry, University of Münster, Münster, Nordrhein-Westfalen, Germany. ¹¹⁵Amsterdam Public Health Institute, Vrije Universiteit Medical Center, Amsterdam, Netherlands. ¹¹⁶Centre for Integrative Biology, Università degli Studi di Trento, Trento, Trentino-Alto Adige, Italy. ¹¹⁷Department of Psychiatry and Psychotherapy, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany. ¹¹⁸Psychiatry, Kaiser Permanente Northern California, San Francisco, CA, USA. ¹¹⁹Medical Research Council Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK. ¹²⁰Department of Psychiatry, University of Toronto, Toronto, ON, Canada. ¹²¹Centre for Addiction and Mental Health, Toronto, ON, Canada. ¹²²Division of Psychiatry, University College London, London, UK. ¹²³Neuroscience Therapeutic Area, Janssen Research and Development, LLC, Titusville, NJ, USA. ¹²⁴Institute of Molecular and Cell Biology, University of Tartu, Tartu, Estonia. ¹²⁵Psychosis Research Unit, Aarhus University Hospital, Risskov, Aarhus, Denmark. ¹²⁶University of Liverpool, Liverpool, UK. ¹²⁷Mental Health Center Copenhagen, Copenhagen University Hospital, Copenhagen, Denmark. ¹²⁸Human Genetics and Computational Biomedicine, Pfizer Global Research and Development, Groton, CT, USA. ¹²⁹Psychiatry, Harvard Medical School, Boston, MA, USA. ¹³⁰Psychiatry, University of Iowa, Iowa City, IA, USA. ¹³¹Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Goettingen, Niedersachsen, Germany. ¹³²Human Genetics Branch, NIMH Division of Intramural Research Programs, Bethesda, MD, USA. ¹³³Faculty of Medicine, University of Iceland, Reykjavik, Iceland. ¹³⁴Child and Adolescent Psychiatry, Erasmus MC, Rotterdam, Zuid-Holland, Netherlands. ¹³⁵Psychiatry, Erasmus MC, Rotterdam, Zuid-Holland, Netherlands. ¹³⁶Department of Psychiatry, Dalhousie University, Halifax, NS, Canada. ¹³⁷Division of Epidemiology, New York State Psychiatric Institute, New York, NY, USA. ¹³⁸Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark. ¹³⁹Department of Medical & Molecular Genetics, King's College London, London, UK. ¹⁴⁰Psychiatry & Behavioral Sciences, Stanford University, Stanford, Ca, USA. ¹⁴¹Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. ¹⁴²Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. ¹⁴³Department of Biostatistics, Princess Margaret Cancer Centre, Toronto, ON, Canada. ¹⁴⁴Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada. ¹⁴⁵Centre for Immunity, Infection and Evolution, University of Edinburgh, Edinburgh, UK. ¹⁴⁶Alvord Brain Tumor Center and Neurological Surgery Clinic, University of Washington Medical Center, Seattle, WA, USA. ¹⁴⁷Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA. ¹⁴⁸Department of Psychiatry, Brigham and Women's Hospital, Boston, MA, USA. ¹⁴⁹Department of Medicine, Psychiatry, Biomedical Informatics, Vanderbilt University Medical Center, Nashville, TN, USA. ¹⁵⁰Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA. ¹⁵¹Center for Statistical Genetics and Department of Biostatistics, University of Michigan, Ann Arbor, MI, USA. ¹⁵²Molecular & Behavioral Neuroscience Institute and Department of Computational Medicine & Bioinformatics, University of Michigan, Ann Arbor, MI, USA. ¹⁵³Biostatistics, University of Minnesota System, Minneapolis, MN, USA. ¹⁵⁴HudsonAlpha Institute for Biotechnology, Huntsville, AL, USA. ¹⁵⁵Department of Psychiatry and Human Behavior, University of California, Irvine, Irvine, CA, USA. ¹⁵⁶Department of Psychiatry, Weill Cornell Medical College, New York, NY, USA. ¹⁵⁷Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA. ¹⁵⁸Department of Medical Genetics, Oslo University Hospital, Oslo, Norway. ¹⁵⁹Department of Clinical Science, NORMENT, KG Jebsen Centre for Psychosis Research, University of Bergen, Bergen, Norway. ¹⁶⁰Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway. ¹⁶¹Department of Neuroscience, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Trondheim, Norway. ¹⁶²Department of Psychiatry, St. Olav's University Hospital, Trondheim, Norway. ¹⁶³Department of Psychiatry, Berkshire Healthcare NHS Foundation Trust, Bracknell, UK. ¹⁶⁴Psychiatry, North East London NHS Foundation Trust, Ilford, UK. ¹⁶⁵Psychiatry and Human Genetics, University of Pittsburgh, Pittsburgh, PA, USA. ¹⁶⁶Institute of Neuroscience and Physiology, University of Gothenburg, Gothenburg, Sweden. ¹⁶⁷Department of Molecular Medicine and Surgery, Karolinska Institutet and Center for Molecular Medicine, Karolinska University Hospital, Stockholm, Sweden. ¹⁶⁸Psychiatrie Translacionnelle, Inserm U955, Créteil, France. ¹⁶⁹Faculté de Médecine, Université Paris Est, Créteil, France. ¹⁷⁰Département de Psychiatrie, Hôpital H. Mondor-A. Chenevier, Assistance Publique-Hôpitaux de Paris (AP-HP), Créteil, France. ¹⁷¹Clinic for Psychiatry and Psychotherapy, University Hospital Cologne, Cologne, Germany. ¹⁷²Department of Biomedicine, University of Basel, Basel, Switzerland. ¹⁷³Neuroscience Research Australia, Sydney, NSW, Australia. ¹⁷⁴School of Medical Sciences, University of New South Wales, Sydney, NSW, Australia. ¹⁷⁵Mental Health Department, University Regional Hospital, Biomedicine Institute (IBIMA), Málaga, Spain. ¹⁷⁶Laboratory of Psychiatric Genetics, Department of Psychiatry, Poznan University of Medical Sciences, Poznan, Poland. ¹⁷⁷Psychiatric Center Nordbaden, Wiesloch, Germany. ¹⁷⁸Kliniken des Bezirks Oberbayern, Munich, Germany. ¹⁷⁹Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany. ¹⁸⁰Genetic Epidemiology Group, International Agency for Research on Cancer (IARC), Lyon, France. ¹⁸¹Center for Research in Environmental Epidemiology (CREAL), Barcelona, Spain. ¹⁸²School of Psychiatry, University of New South Wales and Black Dog Institute, Sydney, NSW, Australia. ¹⁸³Department of Clinical and Developmental Psychology, Institute of Psychology, University of Tübingen, Tübingen, Germany. ¹⁸⁴The Scripps Translational Science Institute and Scripps Health, La Jolla, CA, USA. ¹⁸⁵Department of Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, IN, USA. ¹⁸⁶Department of Psychiatry, Indiana University School of Medicine, Indianapolis, IN, USA. ¹⁸⁷Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, IL, USA. ¹⁸⁸Department of Human Genetics, University of Chicago, Chicago, IL, USA. ¹⁸⁹Rush University Medical Center, Chicago, IL, USA. ¹⁹⁰Department of Psychiatry and Behavioral Sciences, Howard University College of Medicine, Washington, DC, USA. ¹⁹¹Washington University School of Medicine, St. Louis, MO, USA. ¹⁹²Department of Psychiatry, University of California San Francisco School of Medicine, San Francisco, CA, USA. ¹⁹³Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, USA. ¹⁹⁴Department of Mental Health, Johns Hopkins University and Hospital, Baltimore, MD, USA. ¹⁹⁵Neurogenomics, TGen, Phoenix, AZ, USA. ¹⁹⁶Institute of Medical Sciences, Foresterhill, University of Aberdeen, Aberdeen, UK. ¹⁹⁷Department of Psychiatry, School of Clinical and Experimental Medicine, Birmingham University, Birmingham, UK. ¹⁹⁸Division of Neuroscience, Ninewells Hospital & Medical School, University of Dundee, Dundee, UK. ¹⁹⁹University of British Columbia (UBC) Institute of Mental Health, Vancouver, BC, Canada.

²⁰⁰Medical University - Sofia, Sofia, Bulgaria. ²⁰¹Department of Psychiatry, Mood Disorders Program, McGill University Health Center, Montreal, QC, Canada. ²⁰²Department of Neurology and Neurosurgery, Faculty of Medicine, McGill University, Montreal, QC, Canada. ²⁰³Montreal Neurological Institute and Hospital, Montreal, QC, Canada. ²⁰⁴Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA, USA. ²⁰⁵Biometric Psychiatric Genetics Research Unit, Alexandru Obregia Clinical Psychiatric Hospital, Bucharest, Romania. ²⁰⁶Psychiatry, UMC Utrecht Hersencentrum Rudolf Magnus, Utrecht, Netherlands. ²⁰⁷Human Genetics, University of California, Los Angeles, Los Angeles, CA, USA. ²⁰⁸Center for Neurobehavioral Genetics, University of California, Los Angeles, Los Angeles, CA, USA. ²⁰⁹Department of Clinical Sciences, Psychiatry, Umeå University Medical Faculty, Umeå, Sweden. ²¹⁰Applied Molecular Genomics Unit, VIB Department of Molecular Genetics, University of Antwerp, Antwerp, Belgium. ²¹¹Institute for Genomic Health, SUNY Downstate Medical Center College of Medicine, Brooklyn, NY, USA. ²¹²Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA. ²¹³Department of Psychiatry & Psychology, Mayo Clinic, Rochester, MN, USA. ²¹⁴Discipline of Biochemistry, Neuroimaging and Cognitive Genomics (NICOG) Centre, National University of Ireland, Galway, Galway, Ireland. ²¹⁵Department of Translational Genomics, University of Southern California, Los Angeles, CA, USA. ²¹⁶Cancer Epidemiology and Prevention, M. Sklodowska-Curie Cancer Center and Institute of Oncology, Warsaw, Poland. ²¹⁷Institute of Occupational Medicine, Lodz, Poland. ²¹⁸New South Wales Ministry of Health, Sydney, NSW, Australia. ²¹⁹Bioinformatics and Biostatistics Unit, College of Medicine, Cardiff University, Cardiff, UK. ²²⁰Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, ON, Canada. ²²¹Institute of Medical Sciences, University of Toronto, Toronto, ON, Canada. ²²²Department of Natural Sciences, Centre for Coastal Research, University of Agder, Kristiansand, Norway. ²²³McGill University and Genome Quebec Innovation Centre, Montreal, QC, Canada. ²²⁴Research Division, Federal Institute for Drugs and Medical Devices (BfArM), Bonn, Germany. ²²⁵Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD 20892, USA