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Towards precision medicine in psychiatry: investigating the contribution of cellular aging, pleiotropy and gender differences in psychiatric disorders and pharmacological response

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Ph.D. Student: Claudia Pisanu

Supervisor Alessio Squassina

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To Gianpaolo: the love of my life and my best friend

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Abstract

Severe mental disorders such as bipolar disorder (BD), schizophrenia (SZ) and major depressive disorder (MDD) are characterized by a substantial socio-economic burden. Pharmacological treatment is the mainstay in the acute phase of severe mental disorders as well as in the prevention of recurrences. However, only one third of patients show excellent response to the first pharmacological treatment, while the other two thirds show partial or no response. The identification of reliable tools to stratify patients depending on the probability to respond to a specific treatment would allow to develop improved treatment strategies for these patients. In this regard, precision medicine aims to provide a more tailored treatment by integrating demographic, clinical, lifestyle and biological characteristics. Novel analytical approaches that allow to leverage pleiotropy to improve the yield of existing genome-wide summary statistics might also be of help to identify novel potential drug targets. In this thesis, we focus on the investigation of molecular markers related to cellular aging (telomere length) and inflammation in predisposition to severe mental disorders and response to psychotropic treatments. In addition, we present different studies aimed at identifying genetic loci shared between severe mental disorders and related traits (i.e. risk-taking propensity, telomere length and metabolic phenotypes). In the latter study we also focus on exploring gender differences in genetic determinants shared between mental disorders and metabolic phenotypes, highlighting the relevance of gender in the identification of pleiotropic loci and potential drug targets. Elucidating the shared genetic bases between severe mental disorders and genetically predicted markers of cellular aging, as well as age-related disorders such as metabolic disturbances, might allow us to discover novel drug targets and define subgroups of patients that might benefit of more tailored treatment strategies, moving toward precision medicine in severe mental disorders.

1. Introduction

1.1 Severe mental disorders

According to the World Health Organization (WHO), around 450 million people in the world currently suffer from mental disorders [1]. The global burden of mental illness accounts for 21-32% of years lived with disability, causing a considerable socio-economic impact [2]. Among severe mental disorders, major depressive disorder (MDD) is the most prevalent, affecting more than 250 million people worldwide, but large proportions of the general population are affected by bipolar disorder (BD, 45 million people) and schizophrenia (SZ, 20 million people), which both significantly contribute to the cumulative high prevalence of mental illness worldwide [3]. Differently from somatic disorders, most of severe mental illnesses have their onset in late adolescence and young adulthood, determining substantial impairment over the remaining lifespan [4, 5]. Pharmacological treatment is the mainstay in the acute phase of severe mental disorders as well as in the prevention of recurrences. However, about one third of patients show excellent response to the first pharmacological treatment, while the other two thirds show variable degree of response, from partial to no response [6-8]. An unsatisfying response or an adverse drug reaction represent important obstacles to adherence and can substantially affect the quality of life of patients. Different genetic and environmental factors have been suggested to contribute to the interindividual variability in response to psychopharmacological treatment, but the complex interplay of these factors has yet to be disentangled and fully understood. The relatively low response to psychiatric medications calls for better management of pharmacological interventions, which would significantly benefit from the identification of reliable tools to stratify patients depending on the probability to respond to a specific treatment. In this regard, precision medicine aims to provide a more tailored treatment by integrating demographic, clinical, lifestyle and biological characteristics [9].

1.2 Precision medicine in severe mental disorders

In the last few years, precision medicine has emerged as a novel player in healthcare. [9, 10]. There is consensus that precision medicine is changing the paradigm of clinical care from the traditional evidence-based approach (founded on data gathered in large populations of patients), to an individual-based deep knowledge of clinical and biological characteristics. If identified, these features could then be implemented in the development of specific algorithms that can predict the individual response to treatments [11]. In psychiatry, the transition toward precision medicine is still lagging behind compared to other fields of medicine such as oncology or haematology [12, 13]. While this approach is still in its infancy, successful examples of its application are starting to be provided in the field of neuropsychopharmacology [9]. Among the biological characteristics involved in modulating drug response, an important role is played by genetic and epigenetic factors [14], whose contribution to the efficacy and tolerability of medications is investigated by pharmacogenomics [15] and pharmacoepigenomics [16]. Findings with clinical significance (a concept which is related to the impact and importance of a finding for a patient population) are starting to being applied to dosing recommendations for psychotropic drugs, such as selective serotonin reuptake inhibitors (SSRI) and tricyclic antidepressants (TCAs), based on genetic information. Specifically, information on genotypes of CYP2D6 and/or CYP2C19, two genes encoding enzymes that contribute to the metabolism of several antidepressants, can be used to adjust the dosage or select an alternative treatment based on the recommendations made by the Clinical Pharmacogenetics Implementation Consortium (CPIC) [17, 18]. As regards to drug safety, in the case of carbamazepine, recommendations based on HLA genotypes were formulated on the basis of a large body of evidence supporting an association between specific alleles and the risk of severe adverse drug reactions [19]. These initiatives represent a precious effort to overcome one of the barriers to precision psychiatry, i.e., the difficulty in translating pharmacogenetic results into actionable treatment decisions. While available recommendation for genotyping is generally focused on few specific genes for which the most robust evidence is available, response to

psychotropic drugs represents a complex trait for which the contribution of several genes can be hypothesized. It can be postulated that genes implicated in the development of mental disorders might also play a role in the mechanism of action of psychotropic drugs and/or clinical response. In the last decade, genome-wide association studies (GWAS) have uncovered thousands of genetics variants associated with different complex traits, including susceptibility for psychiatric disorders [20-22]. However, the identification of causal genetic variants and related genes is often challenging. Cross-trait analyses, gene-based analyses, integration of different types of omic data and transcription-wide association studies are only some of the computational approaches that can be used to build on GWAS knowledge, to gain insights on the molecular mechanisms underlying the observed associations. In the case of response to psychotropic drugs, this research is still in its infancy. However, some of these approaches such as cross-trait analyses and polygenic risk score (PRS) have started to be applied to response to lithium. The mood stabilizer lithium represents a cornerstone in the long-term management of BD, due to its efficacy in the treatment of manic episodes, prevention of mood relapses and reduction of the risk of suicide [23, 24]. However, only one third of patients show excellent response to this drug. Excellent responders to lithium have been suggested to represent a subphenotype and seem to share some clinical characteristics, such as family history of BD and of lithium response, absence of rapid cycling and absence of psychotic symptoms [25, 26]. However, low effect sizes and limited predictive value of these characteristics, as well as the necessity of a long time of clinical observation to collect some of this information, do not allow a reliable and prompt identification of lithium responders in the clinical setting. Since lithium response has been suggested to be a heritable trait, a growing body of research investigated the potential predictive value of genetic markers. In the last few years, studies have largely shifted from the assessment of candidate genes to the genome-wide approach, which is however still limited by several challenges related to the necessity to collect large cohorts of patients with a deep clinical characterization. In this sense, international efforts such as the International Consortium on Lithium Genetics (ConLiGen) [27] can provide a crucial contribution towards the identification of

reliable markers of lithium response and the development of precision medicine approaches. Recent studies that leveraged the GWAS dataset from the ConLiGen consortium as well as larger datasets on severe mental disorders from the Psychiatric Genomics Consortium, suggested a high genetic load for SZ [28], or MDD [29] to be associated with poor lithium response. In addition, a PRS combining variants associated with either SZ or MDD was recently shown to be able to improve prediction of lithium response compared to single-disorder PRS (proportion of phenotype variance explained by combined PRS: partial R^2 = 0.91%; schizophrenia-PRS: partial R^2 = 0.82%; depression-PRS partial R^2 = 0.47%) [30]. In the ConLiGen cohort, patients in the highest decile for the combined PRS had 2.5 times higher odds of being poor responders compared with patients in the lowest decile [30]. These approaches are based on pleiotropy, i.e. a condition in which the same gene affects multiple phenotypes simultaneously. In this sense, approaches aimed at increasing knowledge on the genetic and molecular determinants of mental disorders and correlated traits could be of help to improve pharmacological treatment through 1) the identification of novel genetic determinants of mental disorders, that might serve as pharmacological targets, 2) the definition of subgroups of patients sharing a specific genetic background that might play a role in the efficacy or safety of pharmacological treatments.

1.3 Aims of this thesis

Based on the framework presented in the previous section, aims of this thesis were to investigate the contribution of different genetic and molecular markers in predisposition to mental disorders and response to psychotropic medications. In section 2, we present an original study investigating the interplay between telomere length (TL) and inflammation in patients with BD, SZ, MDD compared with non-psychiatric controls (NPC) [31]. We explored differences in these markers across disorders as well as based on response to psychotropic medications. In Section 3, we present three studies in which we leveraged pleiotropy to identify novel genetic determinants of severe mental disorders and related traits (risk-taking propensity [32], peripheral TL and metabolic traits). In the

third study included in this section we also focused on exploring gender differences in genetic determinants shared between mental disorders and metabolic phenotypes, highlighting the relevance of gender in the identification of pleiotropic loci. In Section 4, we report concluding remarks and future developments of this work.

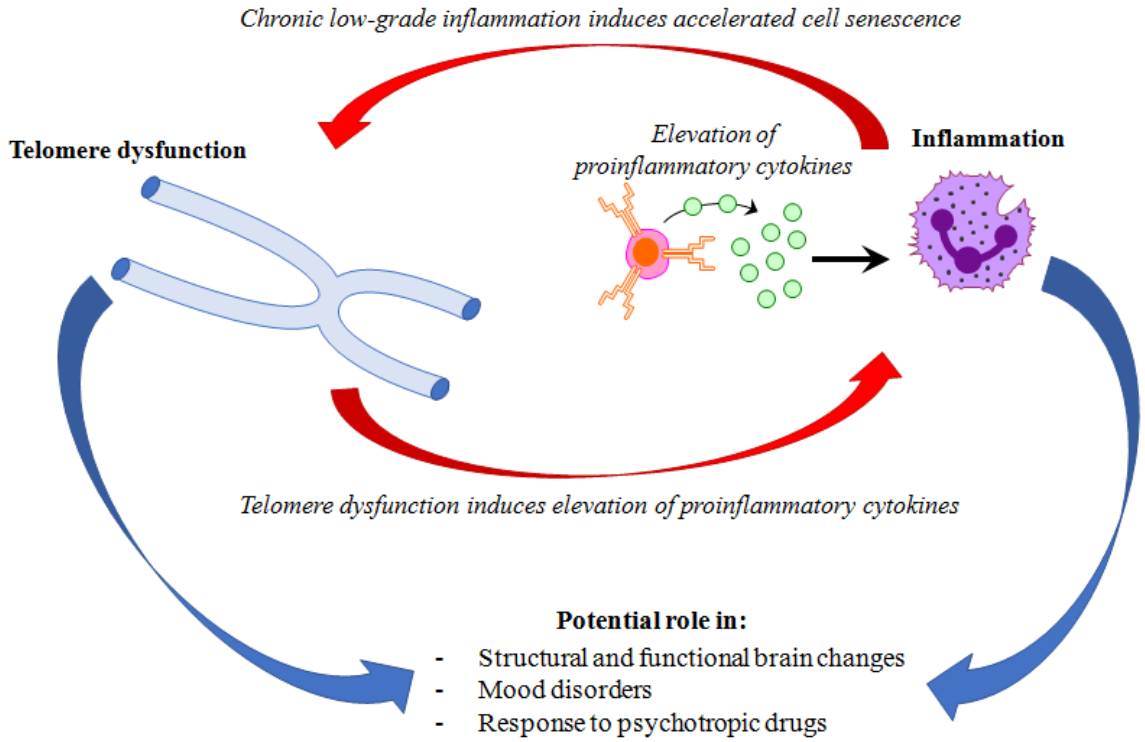
2 Identification of molecular factors associated with efficacy and safety of psychotropic drugs

2.1 Telomere length and inflammatory load in severe mental disorders and in response to psychotropic medications

2.1.1 Telomere length and inflammation

Severe mental disorders are characterized by decreased life expectancy (up to 10-20 years compared to the general population) as well as significant excess mortality [33-36]. Most of these deaths are accounted for by comorbid chronic disorders that are usually associated with aging, such as cardiovascular, respiratory, and infectious diseases, diabetes, and hypertension [37-40]. In particular, age-disorders characterized by an inflammatory component, such as cardiovascular and metabolic disorders, present a higher incidence in patients with mental disorders compared with individuals without mental illness [37, 41, 42]. Based on this evidence, accelerated aging and inflammation have been hypothesized to play a central role in the etiopathogenesis and detrimental course of severe mental disorders (Figure 1.1). Patterns of accelerated epigenetic aging [43, 44] and increased brain age have also been reported in patients with psychiatric disorders compared with non-psychiatric controls [45-49]. In addition, individuals affected by severe psychiatric disorders have shorter TL compared to unaffected individuals [50]. Telomere shortening is a hallmark of cellular aging. In humans, telomeric DNA consists of multiple (TTAGGG)n repeats ending in a single stranded-overhang of the G-rich 3' strand. Together with a number of specific proteins, called shelterins, which directly bind DNA or are associated with chromatin, it contributes to the structure of the chromosome telomeres [51]. This highly conserved complex ensures chromosome stability, preventing chromosome shortening and chromosome end fusion, as well as distinguishing telomeres from double strand breaks, thus avoiding their degradation by the DNA repair machinery. Telomeres physiologically shorten after each cell division in most somatic tissues, whereas early in human development this shortening is counteracted by the enzyme telomerase.

Figure 1.1. Hypothetical interplay between telomere dysfunction and low-grade inflammation in mood disorders.



After birth, telomerase is active predominately in stem cells and germ cells, while in telomerase-negative somatic cells each DNA replication leads to a loss of approximately 100 bp of telomeric sequence. This progressive telomere decline impairs the number of cell generations and causes cell senescence, with either growth arrest or activation of apoptotic processes [52]. A recent study evaluating mortality in more than 64,000 subjects from the general population showed that short telomeres in peripheral blood leukocytes were associated with high mortality [53]. Some studies have also shown that TL correlates with brain age, with shortest telomeres correlating with older age [54-57], and with reduced hippocampal volume in schizophrenia [58]. While data on telomere shortening in mental disorders have not been all concordant, a recent meta-analysis showed a significant overall effect size for telomere shortening across all mental disorders [59].

Telomere attrition is also caused by several biological insults, including inflammatory processes [60]. Interestingly, it has been largely shown that patients affected by severe mental disorders have increased levels of peripheral inflammatory markers, suggesting an involvement of inflammation in

the etiopathogenesis of these disorders [61-63]. This could be enacted through their access into the central nervous system and their impact on neurotransmitters and neural circuits [62, 64-67].

Taken together, these findings suggest a complex interplay of telomere shortening and inflammation in modulating the risk for severe mental disorders. However, the investigation on the potential interaction between the inflammatory processes and telomere shortening in the etiology and progression of these disorders has been scarce. Treatment with mood stabilizers or antidepressants might also play a role in this interplay. Specifically, the duration of long-term lithium treatment has been shown to correlate with longer peripheral TL [68-70], while shorter TL has been associated with worse clinical response to antidepressants [71, 72]. However, overall there is a paucity of data regarding the potential effect of treatment with psychotropic medications (in terms of exposure, duration and clinical response) on TL. In addition, the potential role of comorbid age-related disorders on this interplay has been scarcely investigated.

In this study, we evaluated the interplay between TL and inflammation in three deep-phenotyped samples of patients with severe mental disorders, namely BD, MDD and SZ as well as a sample of non-psychiatric controls (NPC). Aims of this study were to investigate whether there are significant differences across the three disorders in peripheral TL and levels of two inflammatory markers, as well as to specifically explore the role of pharmacological treatments and comorbid age-related disorders in the interplay between telomere shortening and inflammation in these disorders.

2.1.2 Methods

Sample

The cohort included in this study comprised 40 patients with BD, 37 with MDD, and 41 with SZ followed-up and treated at the community mental health center of the Unit of Psychiatry of the Department of Medical Science and Public Health, University of Cagliari and University Hospital Agency of Cagliari, and at the Unit of Clinical Pharmacology, University Hospital Agency, Cagliari, Italy. The recruitment process was based on the inclusion and exclusion criteria described

in Manchia et al., 2020 [73]. Briefly, the diagnosis was made according to DSM-IV criteria and SADS-L (BD patients), and Structured Clinical Interview for DSM IV-TR Axis I Disorders (SCID) (MDD and SZ patients). Exclusion criteria comprised acute infections, chronic autoimmune inflammatory conditions, diagnosis of any eating disorder, post-traumatic stress disorder, substance use disorders, neurological disorders, traumatic brain injury or severe medical conditions (such as cancer, HIV infection). All patients had been followed up longitudinally with periodic assessments of their psychopathological status, which included the use of standard psychometric tools, in certain cases since the illness onset. This accurate clinical depiction of the clinical course was the basis for the definition of treatment resistance (TR) in MDD and SZ patients. Specifically, TR for MDD and SZ patients was defined according to the criteria of Souery et al. [74] and Kane et al. [75], respectively on the basis of the clinical course and assessment of treatment response patterns.

In patients with BD, response to lithium was characterized using the Retrospective Criteria of Long-Term Treatment Response in Research Subjects with Bipolar Disorder scale (or Alda scale), as previously described [26, 76]. The scale quantifies the degree of improvement during lithium treatment with a score from 0 to 10, adjusting for potential confounders. Patients with a total score ≥ 7 are considered as responders [26, 76]. All BD patients enrolled in the study were under mood stabilizing treatment at time of recruitment, with 38 patients being either responders or non-responders to lithium based on the Alda scale. A total of 36 NPC with no personal or familial history of psychiatric disorders in first degree were recruited based on the same exclusion criteria described for patients. NPC were administered the Italian version of the SCID-I/NP 26 to rule out the presence of Axis I psychiatric disorders [77]. For each individual included in the study, information about co-morbid conditions related to aging (specifically cardiovascular diseases, diabetes mellitus type 2, and obesity) were collected. Patients and controls were all from the same geographical area (Sardinia, Italy), Caucasians and of Italian origin.

For all participants, fasting blood was collected in the morning and processed for the different protocols within 1 hour from collection, during which it was stored at controlled temperature (4 °C).

At blood drawn, patients with BD and MDD were in euthymic phases with an interval of at least six months from the last mood episode meeting diagnostic criteria. Similarly, patients with SZ were sampled after at least six months from the last psychotic episode. Clinical and demographic variables collected for the present study are reported in Table 2.1. The research protocol followed the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the University of Cagliari, Italy (approval number: 348/FC/2013 and PG/2018/11693). All participants signed informed written consent after a detailed description of the study procedures.

Quantitative Fluorescence in Situ Hybridization (Q-FISH)

Quantitative Fluorescent *in situ* hybridization (Q-FISH) was adopted to quantify the target repetitive hexameric sequences (TTAGGG) located at the distal end of chromosomes. Telomere peptide nucleic acid fluorescence in situ hybridization (PNA-FISH) and appropriate digital image software were used for capture and quantification of fluorescence signals. Phytohemagglutinin-M (GIBCO, Milan, Italy) stimulated T-lymphocytes chromosomes were obtained from whole blood and short-term cultures set up within 24 hours. Metaphase preparations analyses were carried out as previously described [78]. Metaphase chromosomes were hybridized using a Cy3-labeled (CCCTAA)3 PNA probe (DAKO, Glostrup, Denmark) according to the manufacturer's instructions. Slides with cells from patients from the different subgroups and control cells were randomly distributed in a single experiment. Telomere hybridization signals of 20 complete metaphases per subject, all from a single slide, were randomly selected for microscopic evaluation of FISH signals. Images were captured by a digital image analysis system based on an epifluorescence Olympus BX41 microscope using DAPI and Cy3 filters and charge-coupled device camera (Cohu, San Diego, CA), interfaced with the CytoVysion System software (Applied Imaging). Telomere fluorescence signals were quantified with ImageJ, version 1.43u (National Institutes of Health, http://rsbweb.nih.gov/). The software measures fluorescence intensity of individual telomeres expressed as the product of the telomere area and the average gray value within the selected

telomere. The method provides excellent quantitation as the fluorescence intensity directly correlates to the length of the telomeres and provides a measure of length of individual telomeres. TL was calculated as the mean fluorescence intensity signals for each participant. Two quality control criteria were set for sample exclusion: the number of metaphases in the harvested cultures and processed cells (< 40 available metaphases in the slide), and the appearance of chromosome morphology (fuzzy chromosomes). Ten samples (2 MDD, 2 BD, 5 SZ, and 1 NPC) did not meet the first parameter and were excluded.

Inflammatory markers hsCRP and TNFα

Plasma levels of C-reactive protein (CRP) were measured with high sensitivity (hs) ELISA sandwich kits (Origene: catalog number EA100881). The monoclonal anti-CRP antibody (CRP Mab) was used immobilized on the microtiter wells. Standards (curve range 0.005-0.1 mg/L; 10ul/well in duplicate) and samples (dilutions 1:100, 10 ul/well) were incubated with the second antibody (anti-CRP bound to HRP, 100 ul/well) for 60 minutes at room temperature. Measurements were done by incubating the TMB substrate for 15 minutes at room temperature, stopping the reaction with blocking buffer and measuring optical density at 450 nm in the plate reader (Chameleon: Hidex, Turku, Finland). Plasma tumor necrosis factor alpha (TNFα) was measured by commercial UltraSensitive ELISA kit (Invitrogen Corporation, Carlsbad, CA, USA, catalog number KHC3014). Standards (curve range 0.5-32 pg/mL; 50ul/well in duplicate), samples (50 ul/well) and Hu TNFα biotinylated detection antibody (50 ul/well) were added to the capture antibody coated wells for 2 hours at 37°C. Streptavidin-HRP (30 minutes at room temperature) and TMB substrate (30 minutes at room temperature) were used to reveal the positive labeling. The reaction was stopped with blocking solution and the optical density was measured at 450 nm using a multilabel plate reader (Chameleon: Hidex, Turku, Finland). All samples were run in four assays, each including similar numbers of samples from each subgroup, which were assigned to randomly distributed wells across plates, and across each assay plate. Five samples were assessed in each

assay and used for quality control and to normalize for minor differences in values calculated in the different assay runs. For TNFα assays, all sample values fallen within the range of the standard curve, while in the hsCRP levels equal or higher that 10 mg/L were excluded from the analysis (13 in total), as this threshold is indicative of acute, macro-inflammation [79-81], while our study aimed to focus on signatures of low grade inflammation. Linear regression analysis of standard curves yielded R^2 values between 0.99 and 1. Inter-assays coefficient of variation of TNFα and hsCRP were 7% and 9% respectively.

Statistical analysis

Differences in categorical and quantitative variables among groups were assessed using the Pearson's Chi-Square test and the ANOVA or Kruskal-Wallis tests, respectively. Normality of distribution of TL, hsCRP and TNFα levels was assessed using the Shapiro-Wilk test. Correlation between hsCRP levels and TL was tested with partial correlation, adjusting for age and body mass index (BMI). The association of categorical variables with molecular measures was tested with t-test or Mann-Whitney test. For TL, differences among the diagnostic groups were tested using ANCOVA with TL as dependent variable, diagnosis and gender as factors, and age, and BMI as covariates. Since levels of hsCRP and TNFα were not normally distributed, differences among the diagnostic groups were tested using rank analysis of covariance, with diagnosis and gender as grouping variables. P-values of pairwise comparisons were corrected with Bonferroni. Otherwise, a p-value < 0.05 was considered statistically significant. The analyses were conducted using IBM SPSS Statistics v. 25 (IBM Corporation, Armonk, NY, USA) and Graphpad Prism V. 8 (GraphPad Software, San Diego, CA USA).

2.1.3 Results

Demographic and clinical characteristics of the sample are reported in Table 2.1.

Table 2.1: Demographic and clinical variables in the four diagnostic groups

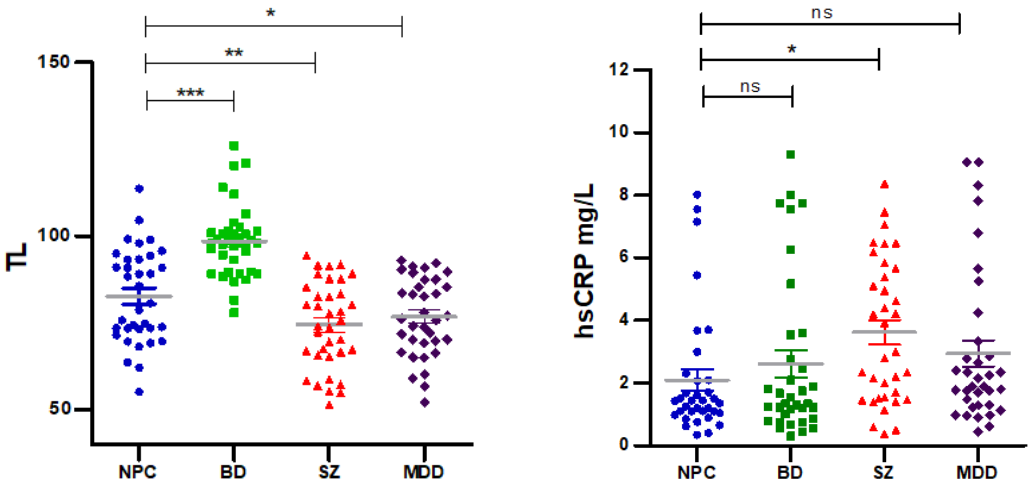
Variables	BD (n=40)	SZ (n=41)	MDD (n=37)	NPC (n=36)	Statistics
Gender (M/F)	17/23	36/5	12/25	21/15	X^2=28.2; p<0.0001
FH (Y/N/U)	19/21	20/20/1	20/13/4	6/30	X^2=15.4; p=0.001
Suicide attempt (Y/N/U)	11/29	8/33	6/30/1	0	X^2=1.4; p=0.484
Smoking (Y/N)	22/18	31/10	18/18/1	13/23	X^2=12.6; p=0.006
Substance use (Y/N/U)	0	16/23/2	1/20/16	0	X^2=7.0; p=0.008
Physical Activity (Y/N/U)	18/22	15/26	13/23/1	25/11	X^2=10.9; p=0.013
Cardio-metabolic disorders (Y/N/U)	14/26	15/26	10/26/1	8/28	X^2=2.4; p=0.498
Cardiovascular disorders (Y/N)	6/34	5/36	6/31	7/29	X^2=0.844; p=0.839
Metabolic disorders (Y/N/U)	13/27	13/28	7/29/1	1/35	X^2=12.5; p=0.006
BMI (mean ± SD)	27.7 ± 6.7	27.2 ± 4.1	25.4 ± 5.1	23 ± 3.5	F=6.5; p=0.0003
Age (mean ± SD)	51.6 ± 10.7	46.9 ± 11.9	51.2 ± 12.9	43.3 ± 10.7	F=4.3; p=0.006
Age of father at birth (mean ± SD)	33.8 ± 5.9	33.4 ± 6.6	33.7 ± 5.4	33.7 ± 5.6	F=0.04; p=0.990
Patients under MS treatment (Y/N)	15/25	11/30	7/30	/	
Patients under AP treatment (Y/N)	19/21	41/0	8/29	/	
Patients under AD treatment (Y/N)	7/33	11/30	29/8	/	
Lithium responders (Y/N/U)	12/26/2	/	/	/	
MD Treatment-resistant (Y/N)	/	/	10/27	/	
SZ Treatment-resistant (Y/N)	/	20/21	/	/	

Abbreviations: AD, antidepressants; AP, antipsychotics; BD, Bipolar Disorder; BMI, Body Mass Index; F, females; FH, family history of any psychiatric disorder; M, males; MDD, Major Depressive Disorder; MS, mood stabilizers; N, no; n, number; NPC, Non psychiatric controls; SD, standard deviation; SZ, Schizophrenia; U, unknown; Y, yes. Smoking was defined as: Y, current or ex-smokers; N, ever smokers. Physical activity was defined as: Y, any physical activity performed at least twice a week; N, no physical activity.

In the model including age, gender and BMI as controlling factors, TL was significantly different among the four groups (model F_6 = 20.13, p = 8.73×10^{-17}, partial eta squared 0.47; effect of diagnosis, F_3 = 31.87; p = 1.08×10^{-15}; partial eta squared = 0.41; Figure 2.1). There was a significant contribution of age to the model (F_1 = 14.81, p = 0.0001, partial eta squared = 0.10), but diagnosis was the most significant variable explaining the largest proportion of variation. Post-hoc analysis

with Bonferroni correction showed that patients with SZ and MDD had significantly shorter TL compared to NPC (SZ versus NPC, p = 0.002; MDD versus NPC, p = 0.039) and to BD (SZ versus BD, p = 1.91×10^{-13}; MDD versus BD, p = 4.22×10^{-12}). Patients with BD had the longest TL compared to all the other groups (Figure 2.1). This finding could be explained by the effect of exposure to mood stabilizers, as suggested by the significant correlation that we observed between duration of treatment with mood stabilizers and TL (partial correlation controlled for age and BMI: correlation coefficient = 0.45; p = 0.001). Indeed, all patients with BD were under mood stabilizing treatment at time of recruitment. The full model was also statistically significant, with diagnosis explaining the largest variance (model $F_{11} = 11.08$, p = 9.42×10^{-14}, partial eta squared = 0.52; effect of diagnosis, $F_3 = 20.568$, p = 9.71×10^{-11}, partial eta squared = 0.35).

Figure 2.1. Difference in telomere length (TL) and high sensitivity C-reactive protein (hsCRP) levels among the four diagnostic groups



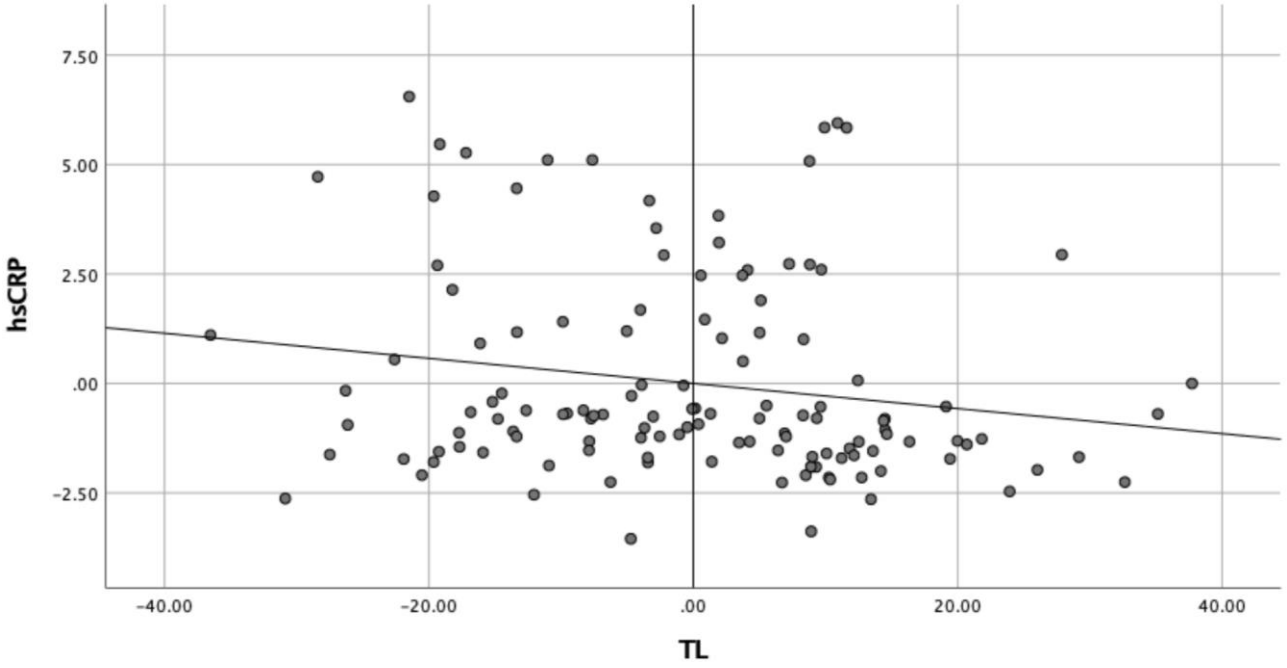
The left panel shows the difference in TL among the four diagnostic groups (effect of diagnosis $F_3 = 31.87$, p = 1.08×10^{-15}), while the right panel the difference in hsCRP levels among the four diagnostic groups (effect of diagnosis $F_3 = 4.680$, p =0.004). Graphs were obtained using the raw values (unadjusted), while the statistical significance for TL and hsCRP is based on post-hoc analysis with Bonferroni correction of the univariate models controlling of age, gender and BMI as covariates. * p<0.05; ** p<0.005; *** p<0.0005; ns, not significant. Bars represent mean and standard errors on the mean. Abbreviations: BD, bipolar disorder; MDD, major depressive disorder; NPC, non-psychiatric controls; SZ, schizophrenia

The rank analysis of covariance with age, gender and BMI as controlling variables showed that hsCRP levels were higher in patients with severe mental disorders (model $F_4 = 4.18$; p = 0.004, partial eta squared = 0.11), with diagnosis being the most significant independent variable (F_3 =

4.68; p = 0.004; partial eta squared = 0.10; contribution of gender, F_1 = 5.42, p = 0.021, partial eta squared = 0.039, Figure 2.1).

The highest hsCRP levels were observed in patients with SZ (post-hoc analysis: SZ versus NPC, adjusted p = 0.027), with a mean value of 3.62 mg/L (standard deviation ± 2.28; mean value in NPC = 2.09, standard deviation ± 1.99), suggesting the presence of low grade peripheral inflammation, which is generally defined by hsCRP level ≥ 3.0 mg/L [82-85]. Moreover, hsCRP levels were inversely correlated with TL when controlling for age and BMI (partial correlation coefficient = -0.18; p = 0.042, Figure 2.2). While modest, this finding suggests a potential interplay between shorter TL and low-grade inflammation, which appeared to be stronger in SZ.

Figure 2.2. Correlation between hsCRP and TL

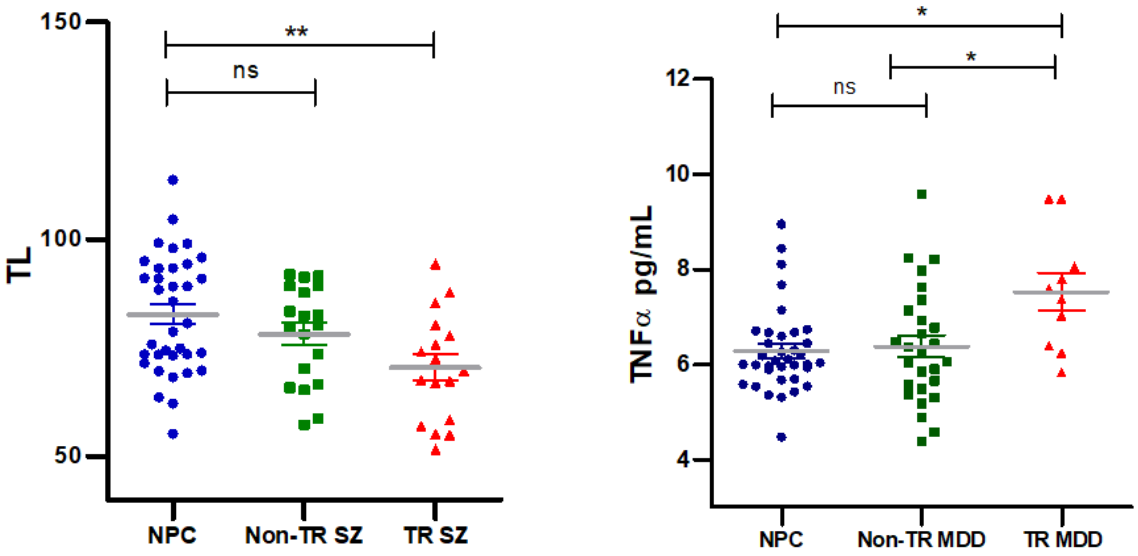


Partial correlation between hsCRP levels and TL in the whole sample controlled for BMI and age. Correlation coefficient = -0.180, p = 0.042. Abbreviations: hsCRP, high sensitivity C-reactive protein; TL, telomere length

We found no significant differences in TNFα levels among the four diagnostic groups in the simplified model. We also tested possible differences in molecular measures according to response to antipsychotics in SZ and antidepressants in MDD, characterized as TR or non-TR, and to lithium response in BD, characterized as responders or non-responders. In SZ, TL was significantly different among groups (model F_5 = 4.58, p = 0.001, partial eta squared = 0.26; effect of diagnosis,

F_2 = 6.93, p = 0.002, partial eta squared = 0.18), with shorter TL in TR-SZ compared to NPC (adjusted p = 0.001), but not in non-TR compared to NPC (adjusted p = 0.13; Figure 2.3), suggesting that TR SZ might be characterized by more severe molecular impairments. Age (F = 7.63, p = 0.007, partial eta squared = 0.105) and gender (F = 5.01, p = 0.029, partial eta squared = 0.072) also significantly contributed to the model, but diagnosis was the most significant factor explaining the largest proportion of variation. There was no difference in hsCRP or TNFα levels between TR and non-TR patients.

Figure 2.3. Difference in TL or TNFα levels among patients with treatment-resistant schizophrenia or depression, patients with non-treatment resistant schizophrenia or depression and controls



The left panel shows the difference in TL among non-psychiatric controls (NPC), patients with treatment-resistant schizophrenia (TR), and patients with non-treatment resistant schizophrenia (non-TR) (effect of diagnosis F_2 = 6.93; p = 0.002). The right panel shows the difference in levels of tumor necrosis factor alpha (TNFα) among non-psychiatric controls (NPC), patients with treatment-resistant major depressive disorder (TR), and patients with non-treatment resistant major depressive disorder (non-TR) (effect of diagnosis F_2 = 4,00; p = 0.023). Graphs were obtained using the raw values (unadjusted), while the statistical significance for TL, hsCRP and TNFα is based on post-hoc analysis with Bonferroni correction of the univariate models, with age, gender and BMI as covariates.
**p<0.005; *p<0.05; ns, not significant. Bars represent mean and standard error of the mean

In MDD, there was no significant difference in TR, non-TR or NPC in terms of TL or hsCRP. However, the rank analysis of covariance with age, gender and BMI as controlling variables showed significant differences in TNFα among TR MDD, non-TR MDD, and NPC (model F_3 = 2.72, p = 0.05, partial eta squared = 0.11; effect of diagnosis, F_2 = 3.998, p = 0.023, partial eta squared =

0.11). Post-hoc comparison showed that patients with TR MDD had higher levels of TNFα compared to both non-TR (adjusted p = 0.039) and NPC (adjusted p = 0.028), while non-TR and NPC had similar levels (adjusted p = 1; Figure 2.3), suggesting that treatment resistance might be associated with increased inflammation compared to non-TR. As regards to lithium response, we found no difference for any of the molecular measures tested between BD patients responders or non-responders (data not shown).

2.1.4 Discussion

We compared TL and levels of circulating inflammatory markers among groups of patients with different severe mental disorders (BD, MDD and SZ) and NPC, and investigated the role of treatment with psychotropic medications and comorbid cardio-metabolic disorders in the potential interplay between telomere shortening, inflammation and psychiatric disorders. Patients with SZ and MDD had shorter TL compared to NPC, while BD patients presented the longest telomeres of all groups. Shorter TL has been extensively reported in psychiatric disorders though negative or opposite findings have also been published [86]. Concerning SZ, a recent study by Russo and colleagues (2018) supported the hypothesis of telomere attrition in SZ, showing that a diagnosis of SZ was the most significant variable contributing to shorter leukocyte telomere length (LTL), with a higher weight than gender, age, cigarette smoking or alcohol drinking [87]. Moreover, in this study the authors performed a meta-analysis showing decreased LTL in SZ compared to controls. In our study we also showed that only patients with TR-SZ and not the non-TR group had significantly shorter telomeres compared to NPC. Shorter telomeres in patients with SZ with poor response to antipsychotics have been previously reported by other studies [88-91]. However, to our knowledge, this is the first study exploring TL in TR versus non-TR patients. We can hypothesize that short telomeres could be a trait marker of poor response to antipsychotics and possibly TR-SZ. Another finding of our study was that patients with SZ had higher plasma levels of hsCRP compared to controls and to the other groups of patients with psychiatric disorders, suggesting a state of low-

grade systemic inflammation and a putative interaction between inflammatory processes and telomere shortening. This interpretation is supported by our finding of an inverse correlation between TL and hsCRP levels, which was not influenced by age, BMI, or cardio-metabolic disorders. Although inflammation and telomere shortening have been largely studied as independent phenomena in ageing and disease association, their possible interdependent nature has been hypothesized, and a detrimental effect of inflammation on telomere dynamics has been suggested [60]. One of the most valuable findings from longitudinal studies in psychiatric disorders was published by Osler and coworkers [92], who explored the interplay between stressful life events, clinical features (including the characterization of depressive symptoms) and measures of inflammation and biological stress in a large cohort of Danish men. Results showed that early stressful events were associated with shorter TL in middle-aged men, and that the largest proportion of this association was mediated through depressive mood and CRP. Nevertheless, the number of longitudinal studies exploring TL and inflammation in psychiatric disorders remains limited and more efforts are needed to better elucidate the role of disturbances in these molecular dynamics in mental disorders.

While we did not show a significant difference in hsCRP levels between MDD and NPC, we showed significantly higher plasma levels of TNFα in TR-MDD when compared to both non-TR MDD and NPC, while levels in non-TR were similar to NPC. This finding suggests that TR-MDD patients might be characterized by increased inflammation, an hypothesis that has been investigated and supported by previous investigations [93-95]. Treatment with antidepressants fails in about 30% of patients, and data suggest that those patients with high inflammation are more prone to be resistant [96, 97]. A role of TNFα in MDD is also supported by the evidence that TNFα inhibitors show antidepressant effects in patients with TR-MDD with higher baseline levels of inflammatory markers [98], that lower baseline levels of TNFα (pretreatment) correlates with better response to electroconvulsive therapy (ECT) in TR-MDD [99], and that ECT reduces plasma levels of TNFα [100, 101]. The importance of modulating levels of TNFα in MDD has been also supported by a

recent meta-analysis including 22 studies and 827 patients, which showed that treatment with SSRIs significantly reduces circulating levels of a number of inflammatory markers, including TNFα [102], suggesting that part of the therapeutic effects of SSRIs could be attributable to their anti-inflammatory properties.

In our study, MDD patients had shorter telomeres compared to NPC, while there was no significant difference between TR-MDD, TR MDD, and NPC. Shorter TL in MDD has been reported in several studies suggesting that telomere attrition could be a marker of MDD [50, 103]. A recent meta-analysis including 38 studies and a total of 34,347 cases, showed that MDD was significantly associated with shorter TL [104]. Recently, we showed that patients with MDD had shorter LTL compared to controls in an independent sample of 54 MDD patients and 47 NPC [105]. Similar to the present study, our previous work did not show a significant difference in TL between TR and non-TR MDD. Only a small number of investigations explored the correlation between TL and response to antidepressants in patients. Hough and coworkers (2016) showed that LTL before treatment with SSRIs was shorter in patients with MDD non-responders to treatment than in responders. Moreover, the authors observed less improvement in negative affect in patients with shorter pre-treatment LTL. Another study published by Wolkowitz et al. [71] showed that MDD patients with lower pretreatment activity of telomerase and greater increase in telomerase activity during antidepressant treatment had better response to antidepressants. Nevertheless, the number of studies exploring the correlation between TL and response to antidepressants remains too scarce to draw definite conclusions and require further investigation.

In our study, patients with BD had the longest TL of the tested groups. This finding appears in contrast with the hypothesis of telomere attrition in mental disorders, but previous authors reported similar results in BD [69, 106]. This discrepancy between BD and the other groups of psychiatric disorders could be determined by several factors, but our findings suggest that a great role could be played by exposure to mood stabilizing treatments. In fact, TL was significantly positively correlated with duration of treatment with mood stabilizers, and all BD patients included in the

study were under treatment with these medications at time of recruitment. A correlation between TL and duration of treatment with lithium, the mood stabilizer of first choice in BD, have been shown by previous works [68-70, 107]. While in the present study we were not able to compare patients with BD exposed versus non-exposed to mood stabilizers, our hypothesis is corroborated by our previous study [108] showing that patients with BD exposed to lithium had longer LTL compared to patients never exposed and to healthy controls, thus suggesting that lithium, and possibly other mood stabilizers, might counteract telomere attrition in psychiatric disorders. Overall, our findings suggest that severe mental disorders present altered TL and peripheral levels of inflammatory markers compared to non-psychiatric controls.

These results need to be interpreted in light of the strengths and limitations of our study. TL was measured using Q-FISH, which compared to other more utilized methods, such as qPCR, provides a more sensitive and accurate tool, especially if performed on metaphases chromosomes rather than on interphase nuclei: the measurements made on individual chromosome provide indeed an accurate estimation of fluorescence, allowing precise signal count. On the other hand, being more time consuming and less cost-effective, the choice to use Q-FISH contributed to limiting the sample size included in the present study. One of the major strengths of our study is the deep phenotypic characterization of the subjects included, which allowed a deeper exploration on the role of a number of potentially relevant features which have been often overlooked in previous investigations, including but not limited to history of pharmacological treatments, cigarette smoking, substance abuse, physical activity, suicidal behavior, family history for psychiatric disorders, and age of father at birth. On the other hand, the main limitation of our study resides is in its cross-sectional nature and the lack of patients naïve to treatment with psychotropic medications.

Future studies with a longitudinal prospective design are needed to clearly elucidate the role of telomeres, inflammation and aging in severe mental disorders.

3 Characterizing the genetic overlap between severe mental disorders and related traits

3.1 Pleiotropy and available methods to investigate loci shared between two traits

In the last few years, the improved statistical power of GWAS has allowed to discover thousands of genetic variants associated with different complex traits, including mental disorders. However, a large part of the genetic architecture underlying these disorders is still undetected. In fact, while recent GWAS usually involve hundreds of thousands of participants, the sample size needed for a GWAS to be able to detect all common genetic variants affecting a phenotype can be different based on the number of causal variants involved and their effect sizes [109]. Besides improving GWAS sample size, a complementary approach to further study the genetic bases of complex traits relies on the application of statistical tools that improve results obtained by existing GWAS. Genome-wide genetic correlations (rg) evaluated with linkage-disequilibrium score regression (LDSC) have pointed to widespread shared genetic factors across multiple mental disorders and related traits. This method allows to estimate heritability and genetic correlation from GWAS summary statistics and to study genetic correlation globally, considering the average of the shared signals across the genome, including the contribution of single nucleotide polymorphisms (SNP) that do not reach genome-wide significance [110], considering possible sample overlap and population stratification. Genetic correlation is computed by normalizing genetic covariance by SNP heritabilities as in the equation:

$$r_g = \frac{\varrho_s}{\sqrt{h_1^2 h_2^2}}$$

where ϱ_s indicates the genetic covariance and h_i^2 indicates the SNP heritability from study *i*.

However, this approach may underestimate some of the shared genetic signals between mental disorders and related traits, as it does not allow to identify mixtures of concordant and discordant direction of effects. Using novel statistical genetics tools, it is possible to identify the shared genetic underpinnings of mental disorders and related traits even when mixed direction of effects across

loci are present. In addition, novel methods allow to identify specific genetic loci involved in both disorders, in order to evaluate their potential functional relevance and try to identify potentially implicated genes. All these approaches rely on pleiotropy, i.e. the association of a genetic variant with multiple traits. The identification of shared genetic signals between different traits or disorders can inform diagnostic classification systems, provide biological insights and be of help to develop improved treatment strategies [111].

Recently, the conditional false discovery rate (condFDR)/conjunctional false discovery rate (conjFDR) method has been developed [112, 113]. This method, implemented in the pleioFDR software, allows to re-adjust the GWAS statistics in a primary phenotype by leveraging pleiotropic enrichment with a GWAS in a secondary phenotype. The condFDR method represents a Bayesian extension of FDR that allows to incorporate prior information on each SNP to improve power. We define the conditional FDR as the posterior probability that a given SNP is null for the first trait given that the p-values for both traits are as small or smaller as the observed p-values. For each p-value in the primary phenotype, condFDR estimates are obtained by calculating the stratified empirical cumulative distribution function of the p-values [111]. Formally:

$$FDR\ (p_1|p_2) = \pi_0\ (p_2)p_1\ /\ F(p_1|p_2)$$

where p_1 is the p-value for the first trait, p_2 is the p-value for the second trait, $F(p_1|p_2)$ is the conditional cdf and $\pi_0(p_2)$ the conditional proportion of null SNPs for the first trait given that p-values for the second trait are as small as p_2 or smaller.

The strata are obtained by the enrichment of SNP associations depending on increased p-values in a secondary phenotype [111]. In the presence of pleiotropy, stratification of test statistics in a primary phenotype based on the association with a second trait will result in a reduction in the FDR at a given nominal p-value relative to the FDR computed from the unstratified distribution of the primary phenotype p-values [111]. Conjunctional FDR represents an extension of the conditional FDR, defined as the maximum of the two conditional FDR statistics for a specific SNP.

The condFDR/conjFDR method has recently been applied to the study of several pairs of traits, including mental disorders and related traits (for a recent review see [109]). In the following section, we present results from three studies in which we applied this method to discover novel loci associated with mental disorders as well as to investigate shared genetic bases between mental disorders and related traits such as risk-taking propensity (Section 3.2), LTL (Section 3.3) and metabolic traits (Section 3.4).

3.2 Genetic loci shared between bipolar disorder and risk-taking propensity

3.2.1 Bipolar disorder and risk-taking propensity

Besides mood episodes of mania and depression, which represent primary features of this disorder, a subset of patients with BD might also present deficits across multiple domains of cognitive function [114-117]. These impairments are not exclusively observed in patients with BD but also in other mental disorders such as e.g. SZ [118] and attention-deficit hyperactivity disorder (ADHD) [119, 120], with the latter being specifically characterized by symptoms in the inattentive or hyperactive and impulsive domains [121].

Among deficits in executive function, patients with BD may exhibit abnormalities in impulsivity, sub-optimal decision-making and increased propensity for risk-taking behaviors. Risk-taking behaviors can be described as activities with high potential for negative consequences and may be linked to abnormal processing of reward-predicting stimuli [122-125]. Excessive involvement in activities with high potential for negative consequences is one of the 7 symptoms included in the DSV-IV or DSM-V diagnostic criteria for a manic episode (at least 3 symptoms must be present during a period characterized by persistently elevated, expansive, or irritable mood and increased energy) [126, 127]. However, in patients with BD increased risk-taking propensity can also be present during remission and may contribute to poor clinical outcome, being linked to increased prevalence of substance abuse and suicide [128, 129]. Risk-taking propensity in BD is still understudied, as can be inferred from a recent meta-analysis which included only six studies [130].

In this meta-analysis, a non-significant trend for impairment in risk-behavior was observed when considering all studies in a sample with high heterogeneity ($p = 0.06$; $I^2 = 81.3\%$), while significant impairment was observed in a more homogenous subgroup of BD type I and euthymic patients with no heterogeneity ($I^2 = 0\%$, standardized mean difference = 0.92; $p < 0.0001$).

The neurobiological determinants of impairments in decision-making and, specifically of increased risk-taking propensity, are still largely unknown. A recent study suggested risk-taking to be negatively associated with white matter integrity in the right cingulum in both patients with BD and controls, while white matter alterations in the left inferior frontooccipital fasciculus were specifically implicated in risk-taking behavior in patients with BD [131]. In addition, risk-taking propensity has been associated with alterations in reward salience in the frontostriatal pathway in patients with BD [132], reduced gray matter volume in the amygdala and hippocampus in humans [133] and increased hippocampal glutamate and monoamine levels in preclinical studies and in humans [134-136]. The mood stabilizer lithium, which represents the gold-standard in the maintenance of BD, being able to reduce recurrences and suicide risk [114, 137], has been suggested to be able to reduce risk-taking behaviors in preclinical models of mania [138, 139], although the underlying molecular mechanisms are not known.

Specific subgroups of patients with BD might show increased predisposition to risk-taking propensity. Indeed, a recent study including 54 euthymic BD type 1 patients who underwent cognitive testing and resting state neuroimaging identified three main clusters using hierarchical cluster-analysis on executive function scores [140]. One of these clusters was characterized by increased risk-taking propensity during the Cambridge Gambling Task [140]. Increased risk-taking predisposition in a subset of patients with BD might be at least partly explained by shared genetic determinants, as also supported by the observation of poorer adjustment in risk-taking behavior measured with the Balloon Analogue Risk Task (BART) in both patients with BD and their first-degree relatives compared to healthy controls [141]. BD has a strong genetic component which has recently started to be elucidated by GWAS that identified multiple SNPs associated with this

disorder [142, 143]. Similarly, a recent GWAS identified several genetic variants associated with risk-taking [144] and also showed this trait to be positively genetically correlated with BD (r_g = 0.21), SZ (r_g = 0.17) and ADHD (r_g = 0.25), using LDSC [144]. However, the specific casual genes and biological mechanisms, as well as the potential shared genetic factors between BD and risk-taking propensity, have not been investigated. It is well known that several genetic variants exhibit allelic pleiotropy, i.e. are associated with more than one phenotype [111]. For instance, BD has been shown to share part of its genetic architecture with other mental disorders [145-147]. The identification of shared genetic variants can improve our understanding of the biological underpinnings of two phenotypes as well as lay the basis to develop improved treatment strategies [111]. Recently, the condFDR/conjFDR method allowed to identify novel loci associated with BD leveraging pleiotropic association with SZ [112], ADHD [148] and intelligence [109]. However, this approach has never been applied to leverage pleiotropic association between BD and risk-taking propensity.

Aims of our study were to 1) identify genetic variants and genes that influence both susceptibility to BD and risk-taking propensity, 2) investigate whether genetic data on risk-taking propensity may improve discovery of loci associated with BD, and 3) evaluate the potential functional role, functional enrichment and suitability as drug targets of genetic loci associated with these two traits. In addition, we explored which of the identified genetic loci might be specifically shared between risk-taking and BD and which represent instead cross-disorders markers, being also shared between risk-taking propensity and either SZ or ADHD. These two disorders were selected based on previous reports of positive genetic correlation with risk-taking propensity [144] as well as studies supporting their association with executive function disturbances [118-120].

3.2.2 Methods

GWAS samples

GWAS summary statistics for BD were obtained from the Psychiatric Genomics Consortium (PGC) BD group (freeze 3) [149]. The BD sample included 41,917 cases from 57 cohorts collected in Europe, North America and Australia and 371,549 controls of European origin [149]. GWAS summary statistics on risk-taking propensity were obtained from the Social Science Genetic Association Consortium [144]. The sample included 466,571 participants from UK Biobank and replication cohorts. General risk tolerance was coded as a categorical variable based on the answer to the question: "Would you describe yourself as someone who takes risks?". After exclusion of variants ambiguous (A/T and C/G) or located in regions characterized by strong linkage disequilibrium (LD) such as the Major Histocompatibility Complex (MHC) region (chr6:25119106-33854733), chromosome 8p23.1 (chr8:7200000–12500000) and the *MAPT* gene (chr17:40000000–47000000), 6,346,208 variants common to the two datasets were retained.

In order to verify whether observed associations between BD and risk-taking propensity were specific for BD or common to other mental disorders, we also conducted cross-trait analyses using large publicly available datasets on SZ (dataset from the PGC, freeze 2, including data 35,476 patients with SZ or schizoaffective disorder and 46,839 controls [150]) and ADHD (PGC dataset including data for 19,099 cases and 34,194 controls of European ancestry from 10 cohorts [151]). After exclusion of ambiguous variants and variants located in regions characterized by strong LD, analyses were conducted on 8,176,252 and 5,448,916 variants common between risk-taking and SZ or ADHD, respectively. For all GWAS datasets, quality control procedures, including adjustment for population stratification, were performed by the original studies [144, 150-152].

Conditional and conjunctional false discovery rate analysis

To identify shared loci between LTL and psychiatric traits, we used the condFDR/conjFDR method implemented in pleioFDR [112, 113], which allows to re-adjust the GWAS statistics in a primary

phenotype (e.g. BD) by leveraging pleiotropic enrichment with a GWAS in a secondary phenotype (e.g. risk-taking propensity). For each p-value in the primary phenotype, condFDR estimates are obtained by calculating the stratified empirical cumulative distribution function of the p-values [111]. The strata are obtained by the enrichment of SNP associations depending on increased p-vlues in a secondary phenotype [111]. We first constructed conditional QQ plots, which extend the standard QQ plots to visualize the cross-trait polygenic enrichment. The plot is constructed by creating subsets of SNPs based on the level of association with the secondary phenotype (using three thresholds $p \leq 0.10$, $p \leq 0.01$ and $p \leq 0.001$). Under the null hypothesis, nominal p-values follow the straight line, while under cross-trait polygenic enrichment they show leftward deflections as levels of SNP association with the secondary phenotype increase. We also constructed fold enrichment plots, in which the fold enrichment is calculated as the ratio between the –log10(p) cumulative distribution for a given stratum and the cumulative distribution for all SNPs. The conjFDR method is an extension of condFDR aimed at discovering SNPs associated with two phenotypes simultaneously. After inverting the roles of the primary and secondary phenotypes, the conjFDR is defined as the maximum of the two condFDR values. Thresholds for significant condFDR and conjFDR associations were set at 0.05 and 0.01 as in previous studies [111, 153-155]. We checked for correlation of *Z* scores among intergenic SNPs using the function implemented in pleioFDR and controlled results for sample overlap using the function implemented in pleioFDR consisting in decorrelation of vectors of *Z* scores based on the Mahalanobis Transformation [113].

Definition of genetic loci and functional enrichment

Independent significant genetic loci were defined according to the FUMA protocol [156]. Lead SNPs were defined by double clumping (a clumping of SNPs significant and independent at $r^2 < 0.6$, and a secondary clumping of these SNPs at $r^2 < 0.1$). Loci separated by a distance lower than 250 kb were merged. 1000 genome phase 3 was used as a reference panel to compute LD in FUMA. The direction of allelic effects for significant variants was evaluated by comparing betas reported in

the original GWAS. Positional and functional annotation of lead SNPs was performed using different tools. Nearest gene and functional category as well as the combined Annotation Dependent Depletion (CADD) score [157], which predicts how deleterious a variant is on protein structure/function by contrasting variants that survived natural selection with simulated mutations, were computed in FUMA. RegulomeDB rank (from 1 to 7, with 1 being associated with highest evidence of functional effects) was calculated using RegulomeDB [158] based on known and predicted regulatory elements including regions of DNase hypersensitivity, binding sites of transcription factors and promoter regions. We searched whether SNPs acted as expression quantitative trait loci (eQTL) based on genotyping and gene expression data (obtained from a range of 114 - 209 samples) from Genotype-Tissue Expression (GTEx) v.8 in brain regions. In the GTEx project, gene expression was measured with Illumina TrueSeq RNA sequencing or Affymetrix Human Gene 1.1 ST Expression Array, while genotyping data were obtained with whole genome sequencing, whole exome sequencing, Illumina OMNI 5M, 2.5M or Exome SNP arrays [159]. We reported cis eQTLs in a +/- 1Mb cis window around the transcription start site (TSS) and significant based on FDR. We tested the functional enrichment for GO terms and Panther pathways using WebGestalt [160] with default options, adjusting results based on FDR. In addition, we investigated whether proteins encoded by the identified genes showed significant protein-protein interaction (PPI) enrichment using STRING. A significant PPI indicates that the identified proteins have more interactions among themselves than would be expected for a random set of proteins of the same size and degree distribution drawn from the genome. Genes in which significantly associated variants were located or nearest genes were searched in the Drug Gene Interaction Database (DGIdb) [161] to assess whether they are known targets of existing drugs (drug-gene interactions) or ‘potentially druggable’ based on their involvement in selected pathways, molecular functions or gene families (druggable genome). According to this definition, the genes included in the druggable genome have some properties that make them suitable for drug targeting, even in absence of a drug currently targeting them [161]. The DGIdb database classifies genes in categories based on information

retrieved from different drug target repositories (DrugBank, PharmGKB, Chembl, Drug Target Commons, Therapeutic Target Database and others). Functional enrichment for drug targets classified based on clinical indication according to Anatomical Therapeutic Chemical Classification System (ATC) or International Classification of Diseases 10 (ICD10) diagnostic codes was conducted using genome for REPositioning drugs (GREP) [58]. In addition, we searched for upstream regulators of our genes of interest using Ingenuity Pathway Analysis (IPA, Ingenuity System Inc, USA). Upstream regulators are defined as genes, microRNAs, transcription factors or chemical compounds that affect the genes of interest through effects on expression, transcription, activation, molecular modification, transport or binding events according to the Ingenuity Knowledge Base, a large collection of observations in various experimental contexts [59]. A p-value of overlap < 0.01 was set as the significant threshold as default.

Local genetic covariance analysis using SUPERGNOVA

As a complementary approach to investigate pleiotropy between BD and risk-taking propensity, we estimated local genetic covariance using SUPERGNOVA [162]. This tool estimates the genetic similarity of complex traits in specific genomic regions using GWAS summary statistics and is robust to sample overlap [162]. Genetic covariance between two traits is estimated by minimizing the distance between the empirical covariance of *Z* scores. LD was estimated using the 1000 genomes project reference panel [163]. In order to control for sample overlap, the first K_i eigenvectors were used to transform and decorrelate Z scores in any given region *i*, where K_i is determined adaptively in SUPERGNOVA. After decorrelation, local genetic covariance was estimated using a weighted least squares regression in each region [162]. The software identifies genomic regions characterized by a significant local genetic covariance between two traits. P-values were adjusted based on FDR. As in the case of analyses with pleioFDR, ambiguous variants or variants located in regions with strong LD were excluded.

eQTL informed gene-based analysis

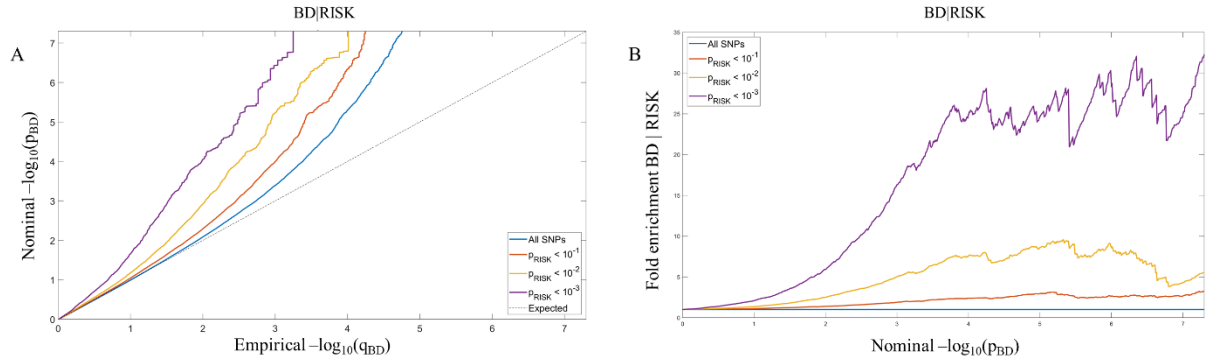
In order to investigate the functional effects of genetics variants associated with BD and risk-taking propensity, we conducted eQTL informed gene-based analysis using eMAGMA [164]. This method leverages tissue specific eQTL information across multiple human tissues to identify putative casual genes for a phenotype. eMAGMA provides tissue-specific annotation files while gene-based statistics were computed using MAGMA (v. 1.09) [165]. SNPs were assigned to genes based on their association with gene expression in the 13 brain tissues included in GTEx (v. 8) as well as in whole blood. Bonferroni-adjusted p-value thresholds were set accordingly to the number of genes included in MAGMA (p = 0.05/19,427 = 2.6e-06).

3.2.3 Results

Genetic overlap between BD and risk-taking propensity

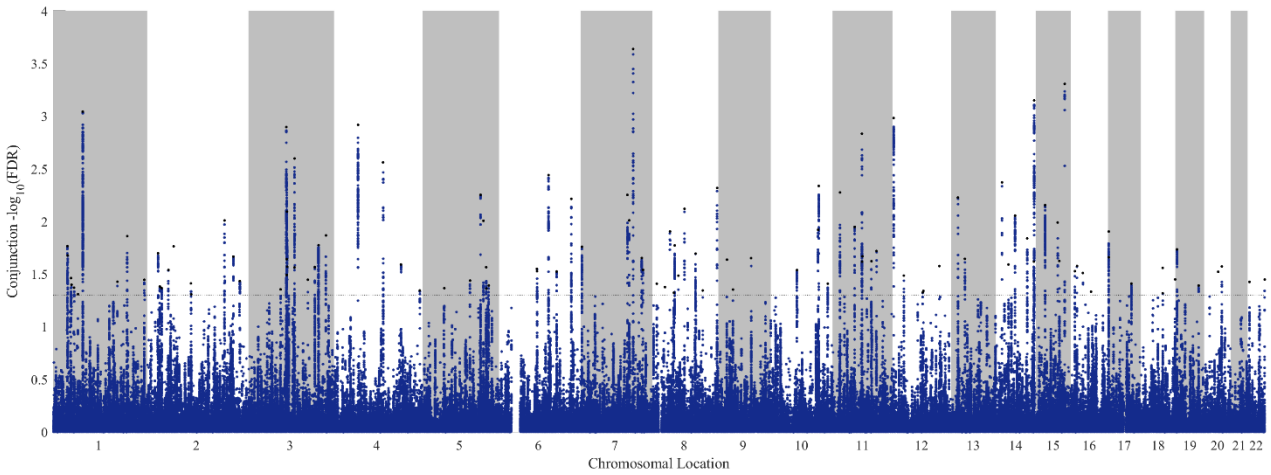
The conditional QQ plot and the fold enrichment plot showed significant cross-trait enrichment in variants associated with BD when conditioning on risk-taking propensity (Figure 3.1). We identified 102 independent genomic loci associated with both BD and risk-taking at a conjFDR < 0.05 (Figure 3.2, Table 3.1 and Appendix). Notably, 89 of these loci (87%) showed the same direction of effect on BD and risk-taking based on betas reported in the original GWAS (i.e. a variant associated with increased risk-taking propensity was also associated with increased predisposition to BD) (Table 3.1). Fifty of these SNPs were located in introns (49.0%), 4 in UTR or downstream regions (3.9%), 2 in exonic regions (2.0%), 34 in intergenic regions (33.3%) and 12 in non-coding RNAs (11.8%).

Figure 3.1. Conditional QQ plot and fold enrichment plot showing cross-trait enrichment between BD and risk-taking propensity



A: Conditional QQ plot. The progressive leftward deflection from the null line as levels of SNP associations with the secondary phenotype increase shows significant cross-trait enrichment between BD (primary phenotype) and risk-taking propensity (secondary phenotype). **B: Fold-enrichment plot.** The fold enrichment, calculated as the ratio between the –log10(p) cumulative distribution for a given stratum and the cumulative distribution for all SNPs, shows a significant enrichment for variants associated with BD conditioning on risk-taking propensity.

Figure 3.2 Manhattan plot showing genomics loci associated with BD and risk-taking propensity.



The figure shows 102 independent genomic loci associated with both BD and risk-taking propensity at a conjunctional false discovery rate < 0.05

Table 3.1. Independent genomic loci significantly associated with BD and risk-taking propensity at a conjunctional false discovery rate < 0.05

SNP	Nearest gene (Kb)	Functional category	A1/ A2	beta BD	p BD	beta risk	p risk	conjFDR	Specificity
rs1746662	*FNDC5*	intronic	T/C	0.05	1.5E-04	0.01	2.9E-05	0.017	BD
rs12138864	*PHC2*	intronic	T/C	0.03	2.2E-04	0.01	1.7E-06	0.021	BD
rs12096927	*RIMKLA* (4.6)	intergenic	T/C	0.04	5.3E-04	0.01	5.8E-06	0.035	BD
rs2367724	*KDM4A* (8.4)	intergenic	T/C	-0.04	2.6E-04	-0.01	4.7E-04	0.040	BD, SZ, ADHD
rs1417364	*NRD1:RP4-657D16.3*	ncRNA	A/G	0.06	3.7E-04	0.01	5.2E-04	0.043	BD
rs182823	*NFIA*	intronic	T/C	-0.03	9.8E-04	0.01	3.6E-04	0.049	BD
rs11210099	*RP4-660H19.1* (64.7)	intergenic	T/C	0.05	1.1E-06	0.01	2.0E-07	0.001	BD, SZ, ADHD

rs34194740	*RGS8 (4.4)*	intergenic	T/C	0.04	2.6E-04	0.01	4.3E-04	0.037	BD
rs823130	*NUCKS1*	intronic	T/C	0.04	9.2E-05	0.01	8.7E-05	0.014	BD, SZ
rs4146671	*SDCCAG8*	intronic	A/G	0.03	5.6E-04	0.01	1.1E-09	0.036	BD, SZ
rs11124327	*AC068490.2*	ncRNA	T/C	0.03	2.0E-04	0.01	7.6E-06	0.020	BD, SZ, ADHD
rs35605321	*CENPA* (14.7)	intergenic	T/G	-0.03	7.3E-04	-0.01	2.6E-04	0.041	BD, SZ
rs2194464	*GALNT14*	intronic	T/C	-0.03	7.7E-04	-0.01	2.8E-04	0.043	BD
rs55951536	*CAMKMT*	intronic	T/C	0.04	3.8E-04	0.01	6.2E-05	0.029	BD
rs7591022	*EML6*	intronic	T/C	0.04	1.5E-04	0.01	8.2E-05	0.017	BD
rs1433309	*AC092568.1* (51.4)	intergenic	A/G	-0.03	5.7E-04	-0.01	3.7E-04	0.039	BD
rs73041394	*ZNF804A*	intronic	A/G	-0.04	5.6E-05	-0.01	4.3E-05	0.010	BD, SZ
rs55811672	*MAP2 (19.0)*	intergenic	A/G	-0.04	1.7E-04	-0.01	1.8E-04	0.022	BD
rs2047134	*CUL3*	intronic	A/C	0.04	6.8E-05	0.01	4.1E-04	0.037	BD, SZ
rs1288974	*FOXP1*	intronic	A/G	-0.04	6.9E-04	0.01	4.1E-04	0.044	BD
rs9831123	*CADM2*	intronic	T/C	0.04	1.8E-06	0.01	8.0E-07	0.001	BD, SZ, ADHD
rs9681407	*MIR4795* (65.3)	intergenic	T/C	-0.04	3.4E-04	-0.01	8.5E-05	0.027	BD
rs836927	*RP11-115H18.1* (18.7)	intergenic	A/C	-0.04	9.9E-05	0.01	2.6E-04	0.027	BD, SZ
rs326359	*CD47 (10.8)*	intergenic	A/G	0.05	4.0E-07	0.01	6.1E-06	0.003	BD
rs12054405	*RP11-442N1.1* (38.2)	intergenic	A/G	0.05	5.6E-04	-0.01	2.5E-04	0.036	BD
rs359544	*PLCH1*	intronic	T/C	0.05	9.5E-05	0.01	2.6E-04	0.027	BD
rs4350923	*RP11-208P4.1* (1.5)	intergenic	T/C	-0.04	1.5E-04	-0.01	9.0E-05	0.017	BD
rs4434184	*SOX2-OT*	ncRNA	A/G	-0.05	1.0E-04	-0.02	1.4E-10	0.014	BD
rs535066	*RP11-320H14.1* (5.3)	intergenic	T/G	0.05	1.7E-06	0.01	8.1E-07	0.001	BD, SZ
rs2647256	*TET2* (0.6)	downstream	T/C	0.05	6.1E-06	0.02	3.3E-10	0.003	BD
rs11737121	*SLC10A7*	intronic	A/G	-0.06	1.8E-05	-0.01	2.3E-04	0.026	BD
rs7696225	*SORBS2*	intronic	A/C	-0.04	8.5E-04	-0.01	7.9E-05	0.045	BD
rs201587781	*EMB* (213.4)	intergenic	A/G	0.09	7.8E-04	0.02	7.2E-05	0.043	BD, SZ
rs13163662	*KCNN2*	intronic	A/G	0.04	4.5E-05	-0.01	4.1E-04	0.036	BD
rs13169274	*ETF1*	intronic	T/C	-0.04	2.0E-05	-0.01	9.7E-06	0.006	BD, SZ
rs76157183	*TCERG1*	intronic	T/C	0.09	9.5E-06	0.02	5.1E-05	0.010	BD
rs10053762	*AC091969.1*	ncRNA	A/C	-0.03	3.4E-04	-0.01	2.2E-04	0.027	BD, SZ
rs2195450	*GRIA1*	intronic	A/G	0.04	7.9E-04	0.01	5.7E-06	0.043	BD
rs10068495	*EBF1*	intronic	A/G	-0.04	7.0E-04	-0.01	1.8E-04	0.041	BD
rs852944	*RP1-288M22.2*	ncRNA	T/C	0.03	3.6E-04	-0.01	2.7E-04	0.028	BD
rs1487445	*RP11-436D23.1*	ncRNA	T/C	0.07	1.5E-15	0.01	1.1E-05	0.004	BD
rs7739294	*GOPC*	intronic	T/C	0.04	3.3E-04	0.01	3.0E-04	0.030	BD
rs6557271	*RGS17*	intronic	T/C	0.05	6.2E-06	0.01	2.4E-05	0.006	BD
rs11768212	*MAD1L1*	intronic	A/C	-0.04	1.6E-04	-0.01	7.2E-05	0.017	BD, ADHD
rs117450257	*SLC12A9:RP11-126L15.4*	ncRNA	A/G	-0.11	2.6E-06	-0.02	2.1E-05	0.006	BD, SZ
rs2470943	*RP11-325F22.2*	ncRNA	A/G	0.04	5.6E-05	0.01	4.4E-05	0.010	BD, SZ
rs10251192	*RP11-222O23.1* (117.0)	intergenic	T/C	-0.05	1.2E-07	-0.01	1.9E-07	0.000	BD, SZ
rs7785663	*DGKI*	UTR3	A/G	-0.04	2.4E-04	-0.01	3.0E-05	0.022	BD, SZ
rs80274100	*RAB19*	intronic	A/G	0.04	1.5E-04	0.01	2.8E-04	0.029	BD
rs2924726	*CSMD1*	intronic	A/G	0.04	1.6E-04	0.01	4.5E-04	0.039	BD
rs10106054	*RP11-468H14.2*	ncRNA	A/G	-0.04	4.1E-04	-0.01	5.1E-04	0.042	BD
rs78035175	*RP11-98P2.1*	intergenic	A/G	0.10	6.5E-05	-0.02	7.4E-05	0.012	BD

	(19.0)								
rs16883443	*AC098612.1* (56.4)	intergenic	T/G	0.03	2.5E-04	0.01	6.3E-04	0.048	BD
rs11777067	*FGFR1*	intronic	T/C	-0.04	1.2E-04	-0.01	1.2E-04	0.017	BD, SZ
rs10957894	*SNTG1*	intronic	A/G	-0.03	4.8E-04	-0.01	1.8E-04	0.033	BD
rs7813444	*RP11-21C4.4* (29.3)	intergenic	A/G	0.04	3.5E-05	0.01	8.5E-06	0.008	BD, SZ
rs4623479	*RUNX1T1*	intronic	T/C	0.04	1.6E-04	0.01	1.6E-04	0.020	BD, ADHD
rs7011741	*RP11-25D10.2* (18.3)	intergenic	A/G	0.03	8.5E-04	0.01	6.7E-05	0.045	BD
rs34853464	*TSNARE1*	intronic	T/C	0.04	1.6E-05	0.01	3.2E-07	0.005	BD, SZ
rs6474852	*FREM1*	intronic	A/G	-0.04	2.6E-04	-0.01	1.2E-04	0.023	BD
rs10967586	*RN7SL100P*	ncRNA	A/G	-0.06	9.4E-05	-0.01	5.6E-04	0.044	BD, SZ
rs10821122	*RNU6-829P* (19.8)	intergenic	T/C	-0.04	1.7E-04	-0.01	1.9E-04	0.022	BD, SZ
rs9888039	*PCDH15*	intronic	T/C	-0.04	2.0E-04	-0.01	2.8E-04	0.029	BD
rs7085104	*C10orf32-ASMT*	intronic	A/G	0.04	8.0E-05	-0.01	5.2E-05	0.012	BD, SZ
rs12761679	*SORCS3*	intronic	A/C	0.05	1.5E-05	0.01	4.1E-06	0.005	BD, SZ, ADHD
rs12359871	*RPS27P18* (50.8)	intergenic	T/C	-0.06	4.3E-04	-0.01	4.5E-04	0.039	BD
rs10082688	*ARNTL* (31.3)	intergenic	T/C	0.04	1.9E-05	0.01	1.6E-05	0.005	BD
rs11038655	*CTD-2210P24.4* (13.2)	intergenic	T/C	-0.07	7.2E-05	0.02	3.0E-05	0.011	BD
rs11227478	*RP11-867G23.10* (3.2)	intergenic	A/G	-0.06	2.3E-06	-0.01	1.3E-06	0.001	BD
rs4988321	*LRP5*	exonic	A/G	0.08	2.2E-04	-0.02	1.7E-04	0.021	BD
rs10831015	*GRM5*	intronic	A/C	0.04	2.7E-04	0.01	7.2E-05	0.024	BD
rs7932899	*CNTN5*	intronic	A/G	0.05	4.5E-05	0.01	1.5E-04	0.019	BD
rs61909095	*CACNA1C*	intronic	T/C	-0.08	9.4E-15	-0.01	1.6E-06	0.001	BD, SZ
rs10842271	*SOX5* (129.9)	intergenic	T/C	-0.03	4.1E-04	-0.01	3.4E-04	0.033	BD
rs7959452	*LYZ* (6.6)	intergenic	A/G	0.03	2.2E-04	0.01	6.2E-04	0.047	BD
rs11178282	*PTPRB*	intronic	T/C	0.05	7.7E-04	0.01	4.0E-04	0.046	BD
rs3764002	*WSCD2*	exonic	T/C	-0.04	3.3E-04	-0.01	9.7E-05	0.027	BD, ADHD
rs3885907	*ALOX5AP*	intronic	A/C	-0.04	2.3E-05	-0.01	6.7E-06	0.006	BD
rs7139704	*GNG5P5* (155.0)	intergenic	A/G	0.04	2.5E-04	0.01	1.5E-04	0.023	BD
rs34012672	*NPAS3* (9.8)	intergenic	T/C	-0.06	1.3E-05	-0.01	1.3E-05	0.004	BD, SZ, ADHD
rs3007061	*MDGA2* (70.2)	intergenic	T/C	-0.04	2.5E-04	-0.01	2.3E-04	0.026	BD, ADHD
rs8005321	*SYT16*	intronic	T/G	-0.04	2.1E-05	-0.01	4.2E-05	0.009	BD
rs72703614	*FOXN3*	intronic	A/G	-0.04	1.1E-04	-0.01	3.0E-05	0.014	BD
rs12892189	*LINC00637*	ncRNA	A/C	0.05	8.2E-07	0.01	2.4E-07	0.001	BD, SZ
rs4924676	*ZNF106*	intronic	T/C	0.07	2.0E-05	0.02	2.9E-05	0.007	BD, SZ
rs4327001	*CD276* (3.4)	intergenic	A/G	0.04	4.5E-05	0.01	5.4E-05	0.010	BD
rs12442456	*IREB2*	intronic	T/G	-0.05	2.7E-04	0.01	2.5E-05	0.024	BD, SZ
rs2071382	*FES*	intronic	T/C	-0.05	4.2E-08	-0.01	5.6E-07	0.000	BD, SZ
rs6500948	*RBFOX1*	intronic	A/G	-0.04	4.0E-04	-0.01	1.3E-04	0.030	BD, SZ
rs2352759	*GRIN2A*	intronic	T/C	0.03	3.3E-04	0.01	4.8E-05	0.027	BD
rs62029337	*PRKCB* (27.2)	intergenic	T/C	0.06	5.4E-05	0.01	3.1E-04	0.031	BD
rs55910718	*GINS3* (60.0)	intergenic	T/C	0.04	8.9E-04	0.01	1.6E-04	0.046	BD
rs7219635	*YWHAE*	intronic	T/C	-0.04	6.4E-06	-0.01	7.4E-05	0.012	BD, SZ
rs112562460	*TANC2:AC037445.1*	ncRNA	T/C	0.04	6.5E-04	0.01	1.8E-04	0.039	BD
rs9636107	*TCF4*	intronic	A/G	-0.03	3.5E-04	-0.01	1.1E-07	0.028	BD, SZ
rs12928	*PQLC1*	UTR3	A/G	-0.03	5.5E-04	-0.01	3.0E-04	0.036	BD, SZ
rs1736182	*THOP1*	intronic	T/G	-0.04	2.8E-05	0.01	1.4E-04	0.018	BD

rs2304204	*IRF3:BCL2L12*	UTR5	T/C	0.04	7.0E-04	0.01	1.4E-04	0.041	BD, SZ
rs1291112	*RN7SL156P* (1.4)	intergenic	T/C	-0.06	1.0E-04	-0.01	3.0E-04	0.030	BD
rs12624433	*SLC12A5*	intronic	A/G	0.05	3.6E-06	0.01	2.5E-04	0.027	BD
rs404060	*XXbac-B444P24.8* (21.9)	intergenic	T/C	0.03	6.1E-04	-0.01	3.0E-04	0.038	BD
rs13055562	*SHANK3*	intronic	A/G	0.04	8.4E-05	0.01	3.9E-04	0.036	BD

The table reports 102 linkage disequilibrium independent genomic loci associated with bipolar disorder and risk-taking propensity at a conjFDR < 0.05. Position denotes the chromosome and location of the lead SNP based on the hg19 assembly. Nearest gene and functional category have been annotated using FUMA (for SNPs located in intergenic regions, distance in Kb from the nearest gene is reported). Beta BD and beta risk show the direction of effect of the A1 allele in the original BD and risk-taking propensity GWAS datasets. The last column shows whether the genetic locus has been found to be specific for BD or whether it was also detected in the analyses conducted between risk-taking and either SZ or ADHD.

In order to assess specificity of loci shared between BD and risk-taking, conjFDR analyses were also conducted between risk-taking and SZ or ADHD. Among the 102 loci, 62 (61%) were specifically shared between risk-taking propensity and BD, while the others were also shared between risk-taking and SZ (n = 30), ADHD (n = 4) or both (n = 6) (Table 3.1). Among the 62 loci specifically shared between BD and risk-taking, 20 SNPs were found to significantly affect gene expression in at least one brain region, whole blood or both (Appendix). Sixteen variants were located in (*FNDC5, NRD1:RP4-657D16.3, FOXP1, PLCH1, SOX2-OT, KCNN2, EBF1, FREM1, GRM5, PTPRB, GRIN2A, THOP1* and *SLC12A5*) or near (*CD47, PRKCB* and *CD276*) genes part of the druggable genome or clinically actionable, and 17 in or near genes showing drug-gene interactions in DGIdb (Appendix). We identified 128 independent genomic loci associated with BD after conditioning on risk-taking propensity at a condFDR < 0.01 (Appendix). Among these, 45 loci (35%) were specific for BD, while 83 loci were also associated with SZ (n = 76), or SZ and ADHD (n = 7) after conditioning on risk-taking propensity. Among loci specific for BD, 15 are novel and are reported in Table 3.2. Eight SNPs were found to act as eQTLs in brain regions, whole blood or both. Three variants were located in genes part of the druggable genome (*HTR6, CAPN10:GPR35* and *ATP2B2*), and 4 in or near genes showing drug-gene interactions in DGIdb (Appendix).

Similarly, we identified significant enrichment in variants associated with risk-taking propensity when conditioning on BD. We reported 79 independent genomic loci associated with risk-taking propensity at a condFDR < 0.01. Among these, 26 loci (33%) were specific for risk-taking after

conditioning on BD, while 53 were also associated with risk-taking propensity after conditioning on SZ (n = 18), ADHD (n = 4) or both SZ and ADHD (n = 31). Of the 26 specific loci, 22 are novel and are reported in Table 3.3. Eight SNPs were found to act as eQTLs in brain regions or both brain tissues and whole blood. Three variants are located in genes part of the druggable genome (*GRIA1*, *SLC12A9* and *GRM5*) and 6 in genes showing drug-gene interactions in DGIdb (Appendix).

Table 3.2 Novel genomic loci associated with bipolar disorder at a condFDR < 0.01 conditioning on association with risk-taking propensity

SNP	Nearest gene (Kb)	Functional category	A1/A2	beta BD	p BD	condFDR BD|risk	RegDB Rank	CADD Score	eQTL	Gene	Region
rs10917509	*HTR6*	UTR5	T/C	0.05	7.3E-08	5.2E-03	2b	7.91	Yes	*HTR6*	Nucleus accumbens, whole blood
										NBL1	Nucleus accumbens
rs483252	*VAV3-AS1*	ncRNA	A/C	-0.06	9.9E-07	7.3E-03	3a	5.74	No	-	-
rs67050019	*RNU6-239P* (0.03)	upstream	A/G	0.08	3.7E-07	4.5E-03	5	6.76	No	-	-
rs4915346	*RP11-382E9.1*	ncRNA	A/G	-0.05	1.3E-05	6.6E-03	5	11.13	No	-	-
rs4972439	*SCRN3*	intronic	T/C	0.06	4.3E-07	8.0E-03	4	1.50	Yes	*SCRN3*	Whole blood
rs6433891	*AC068196.1:AC104820.2*	ncRNA	A/G	0.05	1.6E-07	3.1E-03	4	13.00	Yes	*UBE2E3*	Cerebellum, whole blood
rs4676412	*CAPN10:GPR35*	intronic	A/G	0.06	7.6E-08	7.8E-03	4	0.11	Yes	*ANKMY1*	Cortex
rs7644022	*ATP2B2*	intronic	A/C	0.05	2.5E-07	6.2E-03	5	3.51	No	-	-
rs78104110	*ZBTB20*	intronic	T/C	-0.13	2.1E-07	1.4E-03	5	5.22	No	-	-
rs2651566	*EMCN* (68.1)	intergenic	A/G	-0.04	4.3E-06	9.0E-03	7	2.23	No	-	-
rs11770210	*SCRN1*	intronic	A/G	0.07	6.4E-08	8.6E-03	5	1.14	Yes	*PLEKHA8*	Cerebellum, whole blood
										AC007285.6	Cerebellum
										WIPF3	Cortex
										SCRN1	Whole blood
rs10869262	*RP11-404E6.1* (11.0)	intergenic	A/G	0.05	7.8E-08	9.0E-03	7	1.19	Yes	*ANXA1*	Whole blood
										ALDH1A1	Whole blood
rs75888683	*SYT1*	intronic	T/G	0.12	1.1E-07	6.3E-03	6	3.32	Yes	*SYT1*	Spinal cord
rs8043792	*CDH8* (20.6)	intergenic	T/C	-0.04	2.0E-06	3.3E-03	6	4.88	No	-	-
rs4788865	*ARMC7*	intronic	T/G	-0.05	2.3E-07	6.8E-03	4	3.35	Yes	*NUP85*	Amygdala, anterior cingulate, caudate, cerebellum, cortex, hippocampus, hypothalamus, whole blood
										NTC5	Nucleus accumbens, putamen, spinal cord hypothalamus
										ITGB4	Putamen
										MRPS7	Whole blood
										SUMO2	Whole blood
										GGA3	Whole blood

Novel independent genomic loci associated with bipolar disorder conditioning on risk-taking propensity at a condFDR < 0.01, after exclusion of loci associated with either SZ or ADHD. Nearest gene and functional category have been annotated using FUMA (for SNPs located in intergenic regions, distance in Kb from the nearest gene is reported). Beta and p columns show the direction of effect of the A1 allele and p values from the original GWAS dataset. The RegBD rank was calculated using RegulomeDB based on known and predicted regulatory elements. The CADD score was computed in FUMA. In case the SNP is reported to be a significant eQTL in GTEx v.8 in brain regions or whole blood, the last two columns report regulated genes and relative region

Table 3.3. Novel genomic loci associated with risk-taking propensity at a condFDR< 0.01 conditioning on association with bipolar disorder

SNP	Nearest gene	Functional category	A1/A2	beta risk	p risk	condFDR risk|BD	RegDB Rank	CADD Score	eQTL	Gene	Region
rs1868402	*RP11-474G23.1:PPP3R1*	intronic	A/G	-0.01	8.3E-07	3.6E-03	1f	0.15	Yes	*PNO1* *PLEK*	Anterior cingulate, caudate, cerebellum Cerebellum
rs545200731	*AC062032.1*	ncRNA	T/C	0.04	5.3E-06	5.8E-03	6	1.08	No	-	-
rs34288552	*ERICH2* (6.0)	intergenic	A/G	0.01	2.0E-07	5.8E-03	5	7.33	Yes	*AC007405.6* *ERICH2*	Amygdala, anterior cingulate, cerebellum, cortex, frontal cortex, hypothalamus, susbtantia nigra Anterior cingulate, caudate
rs1014959	*ZNF804A*	intronic	A/G	-0.01	4.0E-05	8.3E-03	7	0.50	No	-	-
rs326353	*RP11-861A13.4*	ncRNA	T/C	-0.01	6.0E-06	2.7E-03	3a	3.28	Yes	*IFT57* *HHLA2* *CD47*	Whole blood Whole blood Whole blood
rs7628391	*RP11-208P4.1* (38.9)	intergenic	T/C	0.01	5.8E-06	4.0E-03	5	0.33	No	-	-
rs4696294	*RP11-424M21.1* (7.6)	intergenic	A/C	-0.01	2.9E-06	9.6E-03	6	0.02	Yes	*SH3D19* *RP11-164P12.5* *FAM160A1* *GATB* *RP11-164P12.3* *FAM160A1*	Caudate, cerebellum Cerebellum, whole blood Cerebellum, whole blood Cerebellum, cortex, frontal cortex, whole blood Cerebellum Cerebellum
rs76157183	*TCERG1*	intronic	T/C	0.02	5.1E-05	9.6E-03	5	0.08	No	-	-
rs2195450	*GRIA1*	intronic	A/G	0.01	5.7E-06	3.8E-03	4	16.32	No	-	-
rs852960	*RP1-288M22.2* (37.1)	intergenic	A/G	0.01	1.6E-05	5.7E-03	5	5.28	No	*OGFRL1*	Cerebellum
rs7758002	*RGS17*	intronic	T/G	-0.01	7.1E-07	1.3E-03	7	1.06	Yes	*MTRF1L* *RGS17*	Anterior cingulate, cerebellum, whole blood Cerebellum
rs117450257	*SLC12A9:RP11-126L15.4*	ncRNA	A/G	-0.02	2.1E-05	5.6E-03	5	0.14	No	-	-
rs80206917	*MKRN1*	intronic	T/C	0.01	2.3E-05	6.5E-03	2b	5.92	No	-	-
rs17055053	*RP11-98P2.1* (24.3)	intergenic	T/C	-0.02	5.1E-05	9.5E-03	4	14.95	No	-	-
rs7871821	*RP11-343J18.1* (39.6)	intergenic	T/C	0.01	5.5E-06	6.9E-03	5	1.18	Yes	*PBX3*	Cortex
rs7111300	*CTD-2210P24.4* (12.7)	intergenic	T/G	0.02	3.0E-05	7.0E-03	5	1.34	Yes	*CTD-2210P24.4*	Caudate, putamen
rs11827676	*GRM5*	intronic	A/C	0.01	3.7E-05	8.0E-03	6	3.66	No	-	-
rs3885907	*ALOX5AP*	intronic	A/C	-0.01	6.7E-06	2.9E-03	4	2.17	Yes	*ALOX5AP*	Whole blood
rs8005321	*SYT16*	intronic	T/G	-0.01	4.2E-05	8.6E-03	4	0.33	No	-	-
rs12927162	*CASC16*	ncRNA	A/G	-0.01	1.9E-06	4.9E-03	5	21.80	No	-	-
rs72841389	*TANC2*	intronic	A/G	0.01	5.4E-06	4.7E-03	7	4.83	Yes	*CYB561* *TANC2*	Anterior cingulate, caudate, cortex, frontal cortex, hippocampus, nucleus accumbens, putamen Cerebellum
rs6017733	*NCOA5*	intronic	A/G	-0.01	2.2E-06	5.7E-03	6	6.25	Yes	CD40	Cerebellum

The table reports 22 novel genetic loci associated with risk-taking propensity conditioning on bipolar disorder at a condFDR < 0.01, after excluding loci associated with risk-taking propensity conditioning on SZ or ADHD.

Functional enrichment of genes associated with BD and risk-taking propensity

We evaluated the functional enrichment for KEGG pathways and GO terms for genes in which variants jointly associated with BD and risk-taking propensity were located. Genes in which variants associated with risk-taking propensity and specifically BD were located were enriched for two KEGG pathways ("Glutamatergic synapse" and "Long-term potentiation"), the biological process "Glutamate receptor signaling pathway" GO term and four cellular component GO terms ("Postsynaptic specialization", "Neuron to neuron synapse", "Synaptic membrane", "Neuron spine") (Table 3.4). Genes in which variants specifically shared between BD and risk-taking were located showed a significant enrichment for drug targets with different clinical indications, including disorders related to the central nervous system (i.e. "mood disorders", "inflammatory disorders of the central nervous system" and "other degenerative disorders of the nervous system", Table 3.5). Using IPA, we identified 161 significant upstream regulators of genes in which variants associated with BD and risk-taking were located (including cross-disorder genes). Figure 3.3 shows a network of these genes including upstream regulators classified as "drugs". Upstream regulators of genes associated with BD and risk-taking included the antipsychotics haloperidol and flupentixol, as well as psychoactive substances such as cocaine, delta-9-tetrahydrocannabinol and nicotine. Several upstream regulators were found to be significantly associated with more than one gene in the network.

Table 3.4. Enrichment for KEGG pathways and GO terms for genes in which variants jointly associated with BD and risk-taking propensity were located

Pathway/GO term	p	FDR	ER	Genes
Variants associated with risk-taking and BD (without excluding cross-disorder variants associated with risk-taking propensity and either SZ or ADHD)				
KEGG pathways				
Glutamatergic synapse	3.8E-05	0.012	12.6	*CACNA1C, GRIA1, GRIN2A, GRM5, SHANK3*
Long-term potentiation	7.6E-05	0.012	17.2	*CACNA1C, GRIA1, GRIN2A, GRM5*
Biological process GO terms				
Cognition	4.9E-05	0.033	7.2	*DGKI, GRIA1, GRIN2A, GRM5, SHANK3, SLC12A5, SORCS3*
Regulation of membrane potential	7.7E-05	0.033	5.6	*CACNA1C, DGKI, GRIA1, GRIN2A, GRM5, KCNN2, SHANK3, YWHAE*
Cellular component GO terms				
Neuron spine	2.9E-04	0.013	8.4	*DGKI, GRIA1, KCNN2, SHANK3, ZNF804A*
Postsynaptic specialization	2.1E-06	1.9E-04	7.4	*CACNA1C, DGKI, GOPC, GRIA1, GRIN2A, GRM5, SHANK3, SORCS3, TANC2*
Neuron to neuron synapse	2.2E-06	1.9E-04	7.4	*CACNA1C, DGKI, GOPC, GRIA1, GRIN2A, GRM5, SHANK3, SORCS3, TANC2*
Synaptic membrane	1.5E-05	8.3E-04	5.9	*CACNA1C, CNTN5, DGKI, GOPC, GRIA1, GRIN2A, GRM5, SHANK3, SORCS3*
Glutamatergic synapse	0.0014	0.047	4.8	*DGKI, GRIA1, GRIN2A, SORCS3, TANC2, YWHAE*
Molecular function GO terms				
Glutamate receptor activity	1.4E-04	0.040	29.1	*GRIA1, GRIN2A, GRM5*
Variants specifically associated with risk-taking propensity and BD				
KEGG pathways				
Glutamatergic synapse	6.2E-05	0.020	17.5	*GRIA1, GRIN2A, GRM5, SHANK3*
Long-term potentiation	2.9E-04	0.047	22.3	*GRIA1, GRIN2A, GRM5*
Biological process GO terms				
Glutamate receptor signaling pathway	2.0E-05	0.017	24.4	*GRIA1, GRIN2A, GRM5, SHANK3*
Cellular component GO terms				
Postsynaptic specialization	2.6E-05	0.002	9.4	*GOPC, GRIA1, GRIN2A, GRM5, SHANK3, TANC2*
Neuron to neuron synapse	2.7E-05	0.002	9.3	*GOPC, GRIA1, GRIN2A, GRM5, SHANK3, TANC2*
Synaptic membrane	9.8E-05	0.006	7.4	*CNTN5, GOPC, GRIA1, GRIN2A, GRM5, SHANK3*
Receptor complex	6.7E-04	0.029	6.7	*GRIA1, GRIN2A, LRP5, PTPRB, SHANK3*
Molecular function GO terms				
Glutamate receptor activity	3.0E-05	0.008	48.9	*GRIA1, GRIN2A, GRM5*

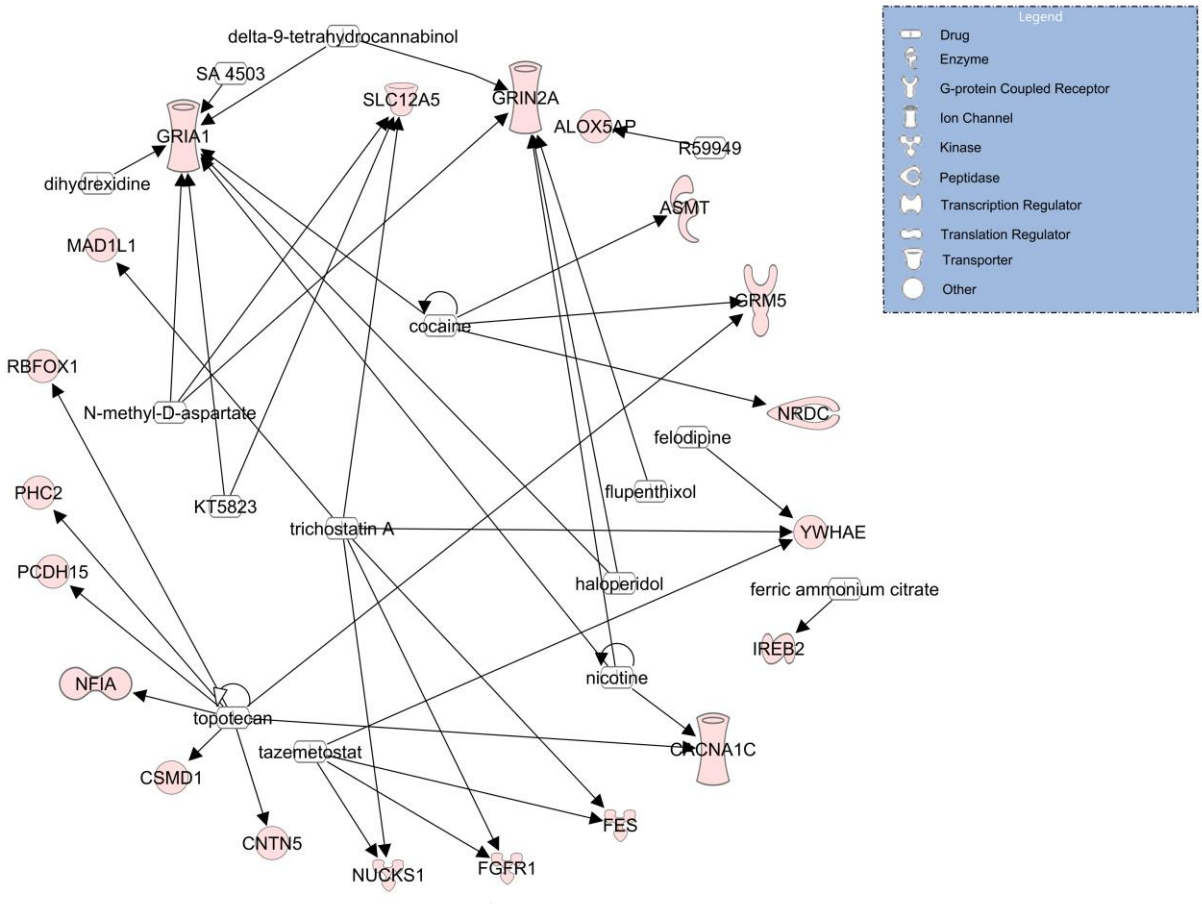
Abbreviations: ER, enrichment ratio; FDR, false discovery rate

Table 3.5. Enrichment for drug targets among genes in which variants jointly associated with BD and risk-taking propensity were located

Clinical indication	**Odds ratio**	**p**	**Targets and drugs**
Variants associated with risk-taking and BD (without excluding cross-disorder variants associated with risk-taking propensity and either SZ or ADHD)			
Drugs classified based on ATC codes			
Nervous system	7.22	0.007	*CACNA1C*: cinnarizine; *GRIA1*: enflurane, isoflurane, desflurane, sevoflurane, methoxyflurane, perampanel; *GRIN2A*: felbamate, memantine, acamprosate; *GRM5*: acamprosate
Drugs classified based on ICD-10 codes			
F30-F39 Mood [affective] disorders	8.10	0.005	*CACNA1C*: verapamil; *GRIA1*: farampator; *GRIN2A*: acamprosate; *GRM5*: adx-48621, acamprosate, adx10059, azd2066, grn-529, gsk-2210875, mglur5 antagonists (anxiety), novartis
G00-G09 Inflammatory diseases of the central nervous system	10.21	0.023	*GRM5*: adx-63365; KCNN2: dequalinium
G30-G32 Other degenerative diseases of the nervous system	6.50	0.009	*FGFR1*: mk-2461; *GRIA1*: gyki-52466; *GRIN2A*: memantine; *GRM5*: adx-63365, mk-3328
G40-G47 Episodic and paroxysmal disorders	5.11	0.036	*GRIN2A*: felbamate; *GRM5*: adx-63365, ly467711, ly525327; *SLC12A5*: clp-635
I20-I25 Ischaemic heart diseases	12.48	0.0002	*ALOX5AP*: am103; *CACNA1C*: amlodipine, nicardipine, nifedipine, r-56865, th-9229, verapamil; *FGFR1*: fgf-1; GRIA1: nbqx; *GRIN2A*: l-698532, nbqx; *GRM5*: rti-4229-982
I60-I69 Cerebrovascular diseases	5.03	0.037	*ALOX5AP*: am103; *CACNA1C*: th-9229, nimodipine; *GRIN2A*: dizocilpine, l-701324
I70-I79 Diseases of arteries, arterioles and capillaries	6.59	0.009	*ALOX5AP*: am103; *CACNA1C*: th-9229, nicardipine, nimodipine, verapamil, amlodipine; *FGFR1*: sar-106881; *PTPRB*: akb-9778
K55-K64 Other diseases of intestines	6.68	0.049	*CACNA1C*: trimebutine; *KCNN2*: trimebutine
M30-M36 Systemic connective tissue disorders	7.12	0.016	*GRIA1*: farampator; *GRIN2A*: acamprosate; GRM5: acamprosate, grn-529
Q90-Q99 Chromosomal abnormalities, not elsewhere classified	33.53	0.037	*GRM5*: afq056, ctep, mcn3377, rg-7090
R50-R69 General symptoms and signs	3.90	0.043	*GRIA1*: nbqx, sevoflurane, soretolide, ym-90k; *GRIN2A*: l-698532, nbqx, ym-90k; *GRM5*: azd2066, azd2516, ly467711, ly525327, rti-4229-982; *SLC12A5*: bumetanide
Variants specifically associated with risk-taking propensity and BD			
Drugs classified based on ATC codes			
Nervous system	9.43	0.012	*GRIA1:* enflurane, isoflurane, desflurane, sevoflurane, methoxyflurane, perampanel; *GRIN2A:* felbamate, memantine, acamprosate; *GRM5*: acamprosate
Drugs classified based on ICD-10 codes			
F10-F19 Mental and behavioural disorders due to psychoactive substance use	7.45	0.047	*GRIN2A*: acamprosate; *GRM5*: acamprosate

F30-F39 Mood [affective] disorders	10.57	0.009	*GRIA1*: farampator; *GRIN2A*: acamprosate; *GRM5*: adx-48621, acamprosate, adx10059, azd2066, grn-529, gsk-2210875, mglur5 antagonists (anxiety), novartis
G00-G09 Inflammatory diseases of the central nervous system	18.41	0.009	*GRM5*: adx-63365; *KCNN2*: dequalinium
G30-G32 Other degenerative diseases of the nervous system	8.50	0.015	*GRIA1*: gyki-52466; *GRIN2A*: memantine; *GRM5*: adx-63365, mk-3328
G40-G47 Episodic and paroxysmal disorders	10.24	0.009	*GRIN2A*: felbamate; *GRM5*: adx-63365, ly467711, ly525327; *SLC12A5*: clp-635
I20-I25 Ischaemic heart diseases	13.73	0.002	*ALOX5AP*: am103; *GRIA1*: nbqx; GRIN2A: l-698532, nbqx; *GRM5*: rti-4229-982
M30-M36 Systemic connective tissue disorders	14.26	0.004	*GRIA1*: farampator; *GRIN2A*: acamprosate; *GRM5*: acamprosate, grn-529
Q90-Q99 Chromosomal abnormalities, not elsewhere classified	56.00	0.024	*GRM5*: afq056, ctep, mcn3377, rg-7090
R50-R69 General symptoms and signs	9.12	0.007	*GRIA1*: nbqx, sevoflurane, soretolide, ym-90k; *GRIN2A*: l-698532, nbqx, ym-90k; *GRM5*: azd2066, azd2516, ly467711, ly525327, rti-4229-982; *SLC12A5*: bumetanide

Figure 3.3. Network of drugs that were found to be significant upstream regulators of genes in which variants shared between BD and risk-taking propensity were located



Local genetic correlation analysis using SUPERGNOVA

Using a complementary approach, we applied SUPERGNOVA to estimate local genetic covariance between BD and risk-taking propensity in specific genomic regions. Seventeen genomic regions characterized by a significant genetic covariance between BD and risk-taking propensity at an FDR < 0.05 are reported in Table3.6. Fifteen of these regions (88%) were overlapping with genomic loci identified with pleioFDR. Ten regions were specifically shared between risk-taking propensity and BD, while seven also showed a significant genetic covariance between risk-taking propensity and SZ (n=4), ADHD (n=2) or both disorders (n=1).

Table 3.6. Local genetic covariance analysis between BD and risk-taking propensity using SUPERGNOVA

Chr	Start	End	rho	var	p	FDR	Identified by pleioFDR	Specificity
1	32042540	34016219	0.0002	1.9E-09	1.9E-06	8.6E-04	Yes	BD
1	71822765	74326378	0.0003	4.1E-09	1.2E-05	3.3E-03	Yes	BD, SZ, ADHD
1	242700803	244105053	0.0003	3.0E-09	1.6E-08	9.5E-06	Yes	BD, SZ
2	22428680	23855977	0.0003	4.5E-09	7.0E-05	1.4E-02	Yes	BD, ADHD
3	85093629	86734415	0.0005	6.4E-09	3.8E-09	2.9E-06	Yes	BD, ADHD
4	45188855	47543891	0.0002	2.2E-09	3.1E-04	4.2E-02	Yes	BD
5	144584265	145803004	0.0001	1.2E-09	4.7E-05	1.2E-02	Yes	BD
6	97093295	98893182	0.0002	2.9E-09	6.0E-05	1.4E-02	Yes	BD
11	87827514	89208590	0.0002	1.8E-09	6.6E-06	2.3E-03	Yes	BD
12	2176265	2886299	0.0005	4.8E-09	2.4E-12	5.5E-09	Yes	BD, SZ
12	68742112	69826093	0.0002	2.5E-09	2.0E-04	3.2E-02	Yes	BD
13	31384910	32983250	0.0002	3.2E-09	7.0E-05	1.4E-02	Yes	BD
13	78807836	80252742	0.0002	2.2E-09	2.4E-04	3.5E-02	No	BD
14	102341650	104759919	0.0004	5.0E-09	1.5E-09	1.8E-06	Yes	BD, SZ
15	42222390	43473907	0.0002	3.0E-09	1.5E-04	2.5E-02	Yes	BD
17	820511	1480393	0.0003	3.4E-09	6.8E-06	2.3E-03	Yes	BD, SZ
19	10030690	11279257	0.0002	2.3E-09	7.9E-05	1.4E-02	No	BD

Regions with significant (FDR < 0.05) local genetic covariance among BD and risk-taking propensity estimated with SUPERGNOVA. rho: estimates of local genetic covariance; var: variance of local genetic covariance.; p: p-value of local genetic covariance; FDR, false discovery rate.

eQTL-informed gene-based analysis of variants associated with BD and risk-taking propensity

The eQTL-informed gene-based analysis showed 103 significant genes associated with BD in at least one brain region, 74 in whole blood, and 32 in both brain and whole blood (Appendix). Twenty-eight genes were associated with risk-taking propensity in at least one brain region, 14 in whole blood, and 6 in brain and whole blood. *CACNA1C* was significantly associated with both BD and risk-taking propensity in the cerebellar hemisphere (BD, Z = 6.48, p = 3.8E-14, adj p = 7.4E-10; risk-taking, Z = 4.66, p = 1.6E-06, adj p = 0.033). Notably, a genomic locus located in *CACNA1C* was also significantly associated with both phenotypes in the conjFDR analysis (Table 2.1) and in the local genetic covariance analysis. This gene is part of the druggable genome and a known target of calcium channel blockers. Two other genes significantly associated with both BD

and risk-taking in the conjFDR analysis were also associated with BD in the gene-based analysis: *SLC12A5* in caudate and hippocampus (most significant: hippocampus, Z = 4.87, adj p = 0.11) and FES in whole blood (Z = 4.57, adj p = 0.048) (Appendix). In addition, three genes associated with BD and risk-taking in the conjFDR analysis were also significantly associated with risk-taking in the eQTL-informed gene-based analysis: *CADM2* (most significant: hypothalamus, Z = 6.26, adj p = 3.8E-06), *RGS17* in cerebellum (Z = 4.88, adj p = 0.01) and *SDCCAG8* (most significant: cortex, Z = 6.15, adj p = 7.7E-06) and whole blood (Z = 6.27, adj p = 3.6E-06) (Appendix).

3.2.4 Discussion

In this study we leveraged large GWAS summary statistics to identify novel genetic variants associated with BD and risk-taking propensity as well as genetic loci shared between these two phenotypes using the condFDR/conjFDR method. Importantly, the large majority of the identified shared loci (87%) showed the same direction of effect, supporting previous evidence suggesting positive genetic correlation between these two phenotypes [144]. Among these loci, 62 (61%) were specifically shared between risk-taking propensity and BD, while the others were also shared between risk-taking and SZ or ADHD, two other traits previously shown to be genetically correlated with risk-taking [144]. In additional analyses, we computed local genetic covariance between BD and risk-taking as well as identified tissue-specific genes associated with the two traits through an eQTL-informed gene-based analysis in brain regions and whole blood. The *CACNA1C* gene was the only one to be significantly associated with both BD and risk-taking propensity using all approaches. This gene is part of the druggable genome and is a target of calcium channel blockers, a group of medications widely used for different cardiovascular indications such as hypertension and angina pectoris [166]. We found the same locus to be shared between risk-taking propensity and SZ, but not ADHD. Besides being previously associated with BD [143], as well as with alcohol dependence in patients with BD [167], *CACNA1C* has been consistently implicated in different psychiatric disorders such as SZ [168] and obsessive-compulsive disorder [169]. The

mechanisms underlying its putative role of a cross-disorders gene might include modulation of stress-coping behavior [170] and gene-environment interactions in response to adverse life events [171, 172]. The identification of shared genetic loci between BD and risk-taking may have relevant clinical implications. We suggest that patients with BD and increased risk-taking propensity may represent a specific sub-phenotype and benefit of more tailored treatment approaches. *CACNA1C*, the most robust locus identified in our study, encodes $Ca_V1.2\alpha$, the alpha-1 subunit of a voltage-dependent L-type calcium channel [173], which forms the pore through which ions pass into the cell. Therefore, patients with BD and increased risk-taking propensity might show better response to drugs acting on calcium signaling, such as calcium channel blockers. Intriguingly, increased intracellular calcium ion concentration, with or without stimulation by agonists such as thrombin or serotonin has been reported in peripheral cells from patients with BD [174] and shown to be normalized by *in vitro* treatment with lithium [175] or carbamazepine [176]. Recent studies also showed dysregulation in calcium signaling in hippocampal dentate gyrus-like neurons derived from induced pluripotent stem-cells of patients with BD compared with controls [177]. The hyperexcitability phenotype of these neurons was selectively reversed by lithium treatment only in neurons derived from patients who also responded to lithium treatment [177]. In addition, *CACNA1C* was part of a glutamatergic network suggested to mediate lithium response in a recent epigenome pathway analysis [178] and knockdown of this gene in fibroblasts from patients with BD was found to alter circadian rhythm amplitude and eliminate lithium's ability to amplify rhythms [179].

However, it must be noted that calcium channel blockers have been previously used in patients with BD without clear results. Verapamil has been the first calcium channel blocker suggested to be useful in the treatment of mania [180-182]. While a recent meta-analysis did not support clinical efficacy of verapamil in mania, the small number of studies and the lack of high-quality data from randomized trials do not allow to draw definitive conclusions [183]. In the last few years, the interest in therapies targeting calcium channels has grown considerably [183] and new studies are

currently being designed to clarify the potential for drug repurposing [184]. A recent population study including 142,691 participants from Sweden with a diagnosis of BD, SZ or nonaffective psychosis found exposure to L-type calcium channel blockers to be associated with reduced rates of psychiatric hospitalization and self-harm [185]. Importantly, genetic variants might modulate the effect of calcium-channel blockers. A recent double-blind pharmacoMRI study recruited healthy men genotyped for the *CACNA1C* rs1006737 variant who were randomized to a single 60 mg dose of the brain-permeable calcium channel blocker nimodipine or placebo [186]. Participants treated with nimodipine showed decreased frontal cortical and parietal cortical activity and improved working memory performance during the N-back task. The decrease in frontal cortical activity was more pronounced in carriers of the rs1006737 risk allele [186]. Calcium channel blockers have also started to be studied as potential adjunctive treatment options for cognitive impairment in patients with SZ. In a recent double-blind, randomized, placebo-controlled trial, patients with SZ randomized to 5 mg of the nonselective brain-permeable calcium channel blocker isradipine for 6 weeks showed improvement in verbal memory and attention dysfunction measured with the Stroop test compared with patients randomized to placebo [187]. As genetic variants may affect $Ca_V1.2\alpha$ expression and activity [188], an ongoing trial will evaluate whether *CACNA1C* polymorphisms and gene expression may affect response to calcium channel blockers in young adults with mood instability [184]. This trial might provide elements to support or confute the hypothesis that participants might show differential response to calcium channel blockers based on their level of risk-taking propensity, as participants will undergo cognitive testing aimed at assessing impulsivity, behavioral inhibition and reward learning [184].

While we found a relevant overlap between genomic loci shared between risk-taking propensity and the three psychiatric disorders we investigated, around half of the loci were specifically shared between risk-taking propensity and BD (Table 3.1). Similar to cross-disorder genes, these loci were enriched for KEGG pathways related to postsynaptic specialization and long-term potentiation, with GO terms related to postsynaptic specialization and synapses (Table 3.4) as well as for targets of

drugs used for mood disorders, substance use disorders and other disorders of the central nervous system (Table 3.5).

Besides the identification of loci jointly associated with BD and risk-taking propensity, another aim of our study was to identify novel loci associated with these phenotypes. By leveraging pleiotropic enrichment between these two traits, we identified 128 loci associated with BD after conditioning on risk-taking propensity, including 15 loci which were novel and specific for BD, and 79 associated with risk-taking propensity conditioning on BD, including 22 novel loci identified when conditioning specifically on BD and not SZ or ADHD. One novel locus specifically associated with BD was rs10917509 in the UTR5 region of *HTR6,* which encodes a G protein-coupled serotonin receptor and is a druggable gene as well as a known target of different antipsychotics and antidepressants. Another locus with rs75888683 as the lead SNP is located in the *SYT1* gene which encodes synaptotagmin-1, a synaptic vesicle membrane protein that serves as a calcium sensor and is implicated in vesicular trafficking and exocytosis [189]. In mouse cortical neurons, a breakpoint mutant version of the DISC1 protein (which is encoded by a known susceptibility gene for BD and SZ) was shown to disrupt vesicle transport via defective assembly between the kinesin-1 adaptor FEZ1 and the cargo protein Synaptotagmin-1 [190], with this effect found to be rescued by *in vitro* treatment with the mood stabilizer lithium 2 mM for 48 hours [190]. Three novel loci specifically associated with BD, four with risk-taking propensity and six with both phenotypes (Tables 3.1, 3.2 and 3.3) were located in non-coding RNAs. LncRNAs have been increasingly implicated in psychiatric disorders [191] and related phenotypes, such as lithium response [192], highlighting the need to improve our understanding of the role of these molecules in brain processes.

Among loci associated with risk-taking propensity, only 33% were identified when conditioning specifically on BD, while a relevant number of loci (39%) were associated with risk-taking when conditioning on all investigated psychiatric disorders and therefore show extensive pleiotropic profiles. Some of these loci might be worth of investigation as potential therapeutic targets as they were found to be located in genes part of the druggable genome (e.g *CGREF1,* which has been

recently associated with non-response to antidepressants [193], or *TET2* which has been implicated in the potential antidepressants effect of metformin in a recent preclinical study [194]). Another interesting locus associated with risk-taking propensity when conditioning on all psychiatric phenotypes was found in the *NPAS3* gene, which encodes a transcription factor regulating genes involved in key neuronal processes such as postnatal hippocampal neurogenesis [195]. *NPAS3* was first identified as a candidate risk gene for psychiatric disorders through the study of a balanced chromosomal translocation, t(9,14)(q34.2;q13), associated with SZ and learning disability [196, 197]. Interactions between risk and protective haplotypes at this gene have been suggested to contribute to susceptibility to both SZ and BD [198] and variants located in this gene have been consistently associated with BD at a nominal $p < 0.05$ in different GWAS [199]. In addition, a group of SNPs in the first intron (top SNP = rs4982029, p = 3.96E-06) showed pleiotropic effects on BD, SZ and major depressive disorder [200]. Besides reduced adult hippocampal neurogenesis [201], mice deficient for *NPAS3* also show abnormalities in glutamate, dopamine and serotonin signaling [202]. All these effects might underlie the association we observed between *NPAS3* and risk-taking propensity, as this trait has been found to be positively associated with hippocampal glutamate [134, 136] and monoamine levels [135] and negatively associated with gray matter volume in the amygdala and hippocampus [133].

Results from this study have to be interpreted in light of a number of limitations. As in other studies conducted using GWAS, it cannot be excluded that the identified lead SNPs may be in LD with other causal SNPs. No assessment of risk-taking propensity in participants included in the BD GWAS was conducted. Identified SNPs only explained a small proportion of variance of the BD phenotype. Additionally, a cohort from UK Biobank is included in the PGC BD freeze 3 cohort. Therefore, we cannot exclude that overlapping participants may inflate the cross-trait enrichment statistics. Finally, as our investigation of the potential functional role of identified variants was largely based on *in-silico* methods, functional characterization based on independent experimental data, as well replication of the loci in independent cohorts, is needed to confirm and further assess

the putative role of these variants in the shared polygenic architecture between BD and risk-taking propensity. In conclusion, we observed pleiotropic enrichment between BD and risk-taking propensity and identified 102 loci shared between these two phenotypes, 87% of which showed the same direction of effect and 61% of which were specifically shared between the two traits. Our findings dissect for the first-time genetic factors shared between risk-taking propensity and BD and lay the basis for future investigation of treatment approaches targeting molecular mechanisms involved in both traits.

3.3 Genetic loci shared between psychiatric disorders and telomere length

3.3.1 Genetic determinants of LTL

As previously mentioned, patients with BD, SZ and MDD may show features suggestive of accelerated cellular aging such as shorter LTL. However, contrasting results have also been reported and there is scarce knowledge on the factors that might increase or rather counteract accelerated cellular aging in these patients. As in the case of mental disorders, LTL has a strong genetic component. The largest GWAS of LTL was conducted in 472,174 well-characterized participants in the UK Biobank [203]. This study identified 197 variants associated with LTL at 138 genomic loci (108 of which were new). In addition, genetically determined LTL was associated with multiple biological traits (e.g. bone marrow function) as well as a number of diseases spanning neoplastic, vascular and inflammatory disorders [203]. While both mental disorders and LTL are heritable traits, the specific genes involved independently, or shared among different traits, are only partially known. Few studies have tried to assess whether the observed relationship between mental disorders and LTL might be affected by genetic determinants. In a previous study, we used two-sample mendelian randomization analysis to evaluate the bidirectional association between genetically determined LTL (using summary statistics from a GWAS including genetic data for 37,684 individuals [204]) and predisposition to BD (using data from PGC BD freeze 2, including 20,352 cases and 31,358 controls [142] and reported negative results [108]. Consistently, another study did not find any significant association between polygenic risk for BD, MDD or SZ and LTL in a sample including 351 participants characterized for depression using self-reported measures [205]. However, a recent study conducted in the larger UK Biobank cohort for which LTL measurements are now available, reported a PRS for depression to be associated with shorter telomeres (β = -0.006, adjusted p = 0.001) [206], suggesting the existence of a possible link between mental disorders and genetically predicted LTL. Thanks to the development of analytical methods based on pleiotropy, novel genetic variants associated with severe mental disorders have

been identified by leveraging related traits. This approach has never been applied to TL. We aimed to investigate whether 1) there is a significant pleiotropy between psychiatric disorders and TL, and 2) shared genetic loci might predispose patients to accelerated cellular aging or rather play a counteractive role.

3.3.2 Methods

GWAS samples

We conducted a cross-trait analysis using the largest publicly available datasets for BD, SZ, MDD and LTL. GWAS summary statistics for BD, SZ and MDD were obtained from the Psychiatric Genomics Consortium (PGC) [20-22]. The BD sample included 41,917 cases from 57 cohorts collected in Europe, North America and Australia and 371,549 controls of European origin [149]. The SZ sample included 53,386 cases and 77,258 controls of European origin [21], while the MDD sample 170,756 cases and 329,443 controls. GWAS summary statistics for genetically determined LTL were obtained for 472,174 UK Biobank participants [203]. For all GWAS datasets, quality control procedures, including adjustment for population stratification, were performed by the original studies. Analyses were conducted on autosomal variants common to GWAS on psychiatric traits and LTL, after exclusion of ambiguous variants (A/T and C/G) or variants located in regions characterized by strong LD such as the MHC region (chr6:25119106-33854733), chromosome 8p23.1 (chr8:7200000–12500000) and the *MAPT* gene (chr17:40000000–47000000).

Global genetic correlation analysis

Global genetic correlation analysis was conducted using LDSC [207]. To this aim, summary statistics were converted into the LDSC format, while LD Scores were computed using 1000 Genomes European data [110, 207]. The cross-trait LDSC method represents an extension of single-trait LDSC to estimate heritability and genetic correlation from GWAS summary statistics. As explained in Section 3.1, this method allows studying the genetic correlation globally,

considering the average of the shared signals across the genome (including the contribution of SNPs that do not reach genome-wide significance [110]), considering possible sample overlap and population stratification.

Conditional and conjunctional false discovery rate analysis

To identify shared loci between genetically predicted LTL and mental disorders, we used the condFDR/conjFDR method implemented in pleioFDR [112, 113], as described in Section 3.2.2. The conjFDR method is an extension of condFDR aimed at discovering SNPs associated with two phenotypes simultaneously. The threshold for significant conjFDR associations was set at 0.05, as in previous studies [111, 153-155]. We checked for correlation of *Z* scores among intergenic SNPs using the function implemented in pleioFDR. While we detected low correlation coefficients between LTL and BD (0.003), SZ (0.007) or MDD (0.011), we still controlled results for sample overlap using the function implemented in pleioFDR consisting in decorrelation of vectors of *Z* scores based on the Mahalanobis Transformation [113].

Definition of genomic loci and functional annotation

Independent significant genetic loci were defined according to the FUMA protocol [156], as described in Section 3.2.2. The direction of allelic effects for significant variants was evaluated by comparing betas reported in the original GWAS. We searched whether SNPs acted eQTLs in brain regions based on genotyping and gene expression data (obtained from a range of 114 - 209 samples) from GTEx v.8 [159]. We reported cis eQTLs in a +/- 1Mb cis window around the TSS and significant based on FDR. For genes with significant eQTLs found to be associated with lower LTL and increased predisposition to mental disorders (i.e. genes for which expression levels are modified by the identified SNPs) we tested the functional enrichment for GO terms and Panther pathways using WebGestalt [160] with default options, adjusting results based on FDR. In addition, we investigated whether proteins encoded by the identified genes showed significant protein-protein

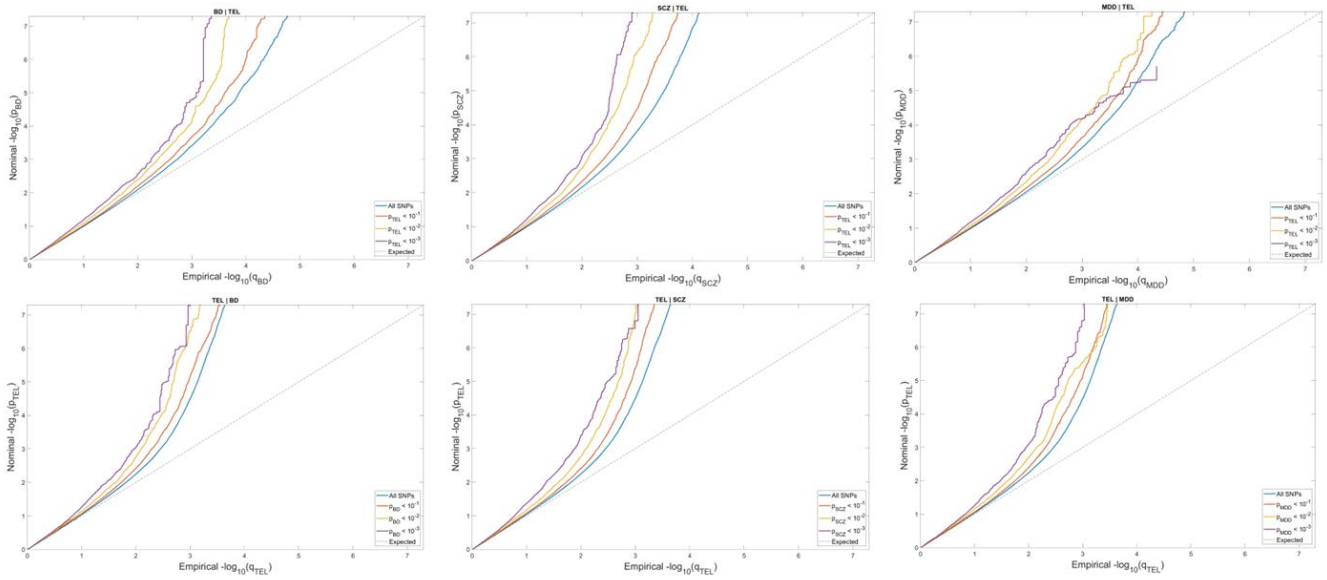
interaction (PPI) enrichment using STRING. A significant PPI indicates that the identified proteins have more interactions among themselves than would be expected for a random set of proteins of the same size and degree distribution drawn from the genome.

3.3.3. Results

Among mental disorders, only MDD showed a significant negative global genetic correlation with LTL (r_g = -0.11, p = 1.4E-08). Conversely, global genetic correlation between LTL and BD (r_g = -0.03, p = 0.17) or SZ (r_g = 0.00, p = 0.98) was not significant.

On the other hand, conditional QQ plots suggested cross-phenotype polygenic enrichment between all mental disorders and genetically determined LTL (Figure 3.4).

Figure 3.4. Conditional QQ plots suggesting cross-phenotype polygenic enrichment between mental disorders and LTL



A total of 16 genetic loci were shared between BD and LTL at a conjFDR < 0.05 (Table 3.7). Of 18 lead SNPs, 7 were associated with increased risk of BD and shorter LTL (while 11 with increased risk of BD and increased LTL).

Table 3.7 Loci associated with risk of BD and LTL

Chr	Start locus	Stop locus	Lead SNP	Gene	EA	OA	beta LTL	beta BD	conjFDR
1	149999764	150514149	rs11588837	Intergenic	A	G	0.01	0.06	0.037
1	163582980	163766672	rs2345964	Intergenic	A	G	0.01	0.05	0.032
1	226613126	226702300	rs1299858	Intergenic	T	C	**-0.02**	**0.05**	**0.020**
2	210043728	210322212	rs34842775	Intergenic	A	C	0.01	0.04	0.033
3	52277445	52838402	rs12629701	*PBRM1*	T	C	0.01	0.06	0.035
6	11920763	12037477	rs11968174	Intergenic	T	C	**0.01**	**-0.07**	**0.033**
7	129663496	129685597	rs11556924	*ZC3HC1*	C	**T**	**-0.01**	**0.04**	**0.042**
10	64451233	64556238	rs10822056	Intergenic	C	**T**	**0.01**	**-0.05**	**0.011**
10	106453550	106560225	rs7909129	*SORCS3*	A	**G**	**0.01**	**-0.05**	**0.027**
15	74099922	74161676	rs4886412	Intergenic	A	C	-0.01	-0.04	0.011
15	84703470	85344550	rs11638445	Intergenic	C	A	0.01	0.06	0.009
16	69141138	69432250	rs12919664	*TERF2*	T	C	-0.02	-0.05	0.002
18	52297945	52504252	rs117201218	*RAB27B*	T	G	-0.02	-0.13	0.038
18	52297945	52504252	rs56162185	*RAB27B*	C	T	-0.01	-0.04	0.031
20	33224174	33360785	rs6059976	*PIGU*	G	A	-0.01	-0.04	0.045
20	35488246	35503978	rs75438122	Intergenic	T	C	**-0.02**	**0.11**	**0.013**
20	35488246	35503978	rs1291117	Intergenic	A	G	-0.02	-0.06	0.047
20	62127121	62129566	rs310619	*EEF1A2*	G	A	**0.01**	**-0.04**	**0.047**

Loci reported in bold are concordant with the hypothesis of higher predisposition to BD being associated with shorter LTL. Abbreviations: Chr, chromosome; EA, effect allele; OA, other allele

Six of the 18 lead SNPs were found to act as eQTLs for different genes in at least one brain region (Table 3.8). However, only the intergenic SNP rs10822056, suggested to act as an eQTL for the *ADO* gene in the caudate brain region, was associated with increased predisposition to BD and shorter LTL, while all the other SNPs acting as eQTLs were associated with the two traits with a concordant direction of effect (increased predisposition to BD and longer LTL).

Table 3.8 Functional effect of lead SNPs associated with BD and LTL

lead SNP	RDB score	RDB rank	eQTL in brain regions (GTEx v. 8)
rs11588837	0.55	1f	*VPS45* (frontal cortex)
rs2345964	0.63	5	-
rs1299858	0.59	5	-
rs34842775	0.18	7	-
rs12629701	0.18	7	*GNL3* (cerebellum, frontal cortex, hypothalamus, putamen); *RP5-966M1.7* (cerebellum, cortex, putamen); *PPM1M* (cerebellum); *NEK4* (cerebellum); *GLYCTK* (cerebellum); *ITIH4* (cortex, hypothalamus, putamen); *POC1A* (putamen)
rs11968174	0.53	5	-
rs11556924	0.22	1f	-

rs10822056	0.63	6	*ADO* (caudate)
rs7909129	0.13	5	-
rs4886412	0.13	5	-
rs11638445	0.59	5	*GOLGA2P7* (amygdala, anterior cingulate cortex, caudate, cerebellum, cortex, frontal cortex, hippocampus, hypothalamus, nucleus accumbens, putamen); *CSPG4P12* (anterior cingulate cortex, cerebellum, cortex, frontal cortex, hippocampus, hypothalamus, putamen); *LINC00933* (anterior cingulate cortex, caudate, cortex); *GOLGA6L5P* (anterior cingulate cortex, caudate, cortex, frontal cortex, putamen, substantia nigra); *NMB* (caudate); *DNM1P51* (cortex, frontal cortex); *RP11-182J1.14* (cortex), *EFTUD1P1* (hypothalamus)
rs12919664	0.18	7	*VPS4A* (anterior cingulate cortex, caudate, cortex, frontal cortex, hypothalamus, nucleus accumbens, putamen); *TERF2* (cerebellum, cortex); *SNTB2* (cerebellum), *NIP7* (nucleus accumbens); *UTP4* (nucleus accumbens)
rs117201218	0.43	6	-
rs56162185	0.18	7	-
rs6059976	0.39	5	*MAP1LC3A* (anterior cingulate cortex, caudate, cerebellum, cortex, hypothalamus, nucleus accumbens); *MYH7B* (cerebellum); *ACSS2* (cerebellum, cortex); *EDEM2* (cortex); *MMP24-AS1* (cortex)
rs75438122	0.18	7	-
rs1291117	0.71	3a	-
rs310619	0.61	4	-

Abbrevations: RDB, RegulomeDB

A total of 52 loci were shared between SZ and LTL (Table 3.9). Of the 55 lead SNPs, 33 were associated with increased risk of SZ and shorter LTL.

Table 3.9 Loci associated with risk of SZ and LTL

Chr	Start locus	Stop locus	Lead SNP	Gene	EA	OA	beta LTL	beta SZ	conjFDR
1	92664966	93035020	rs10874656	*GFI1*	T	C	**0.01**	**-0.05**	**0.043**
1	146919919	146984386	rs1874422	Intergenic	A	G	-0.01	-0.05	0.035
1	149999764	150514149	rs11588837	Intergenic	A	G	0.01	0.06	0.026
1	153768740	154162493	rs7521047	NUP210L	T	C	0.01	0.04	0.038
1	163582980	163766672	rs2345964	Intergenic	A	G	0.01	0.05	0.022
1	207917499	208049502	rs4844621	*C1orf132*	A	G	**-0.01**	**0.05**	**0.012**
1	226694849	226694849	rs58787117	Intergenic	A	G	-0.01	-0.06	0.032
2	48178775	48324044	rs11891807	*AC079807.4*	T	G	**-0.01**	**0.04**	**0.036**
2	53864496	54497500	rs7583622	*GPR75-ASB3*	G	A	**-0.01**	**0.05**	**0.015**
2	53864496	54497500	rs7567556	*ACYP2*	C	T	**0.07**	**-0.11**	**0.022**
2	58872553	58991868	rs7591382	*LINC01122*	T	C	**0.01**	**-0.04**	**0.023**
3	48446237	49631585	rs12107252	*CELSR3*	T	C	-0.01	-0.06	0.013
3	52277445	52838402	rs12629701	*PBRM1*	T	C	0.01	0.06	0.024
4	48342682	48697149	rs34386102	Intergenic	T	C	**-0.01**	**0.04**	**0.041**

4	102766892	102931290	rs34208976	*BANK1*	G	T	-0.01	-0.04	0.013
4	105375274	105443381	rs10034519	*CXXC4*	A	C	**-0.01**	**0.04**	**0.018**
4	153018256	153101286	rs35296212	*RP11-18H21.2*	T	G	0.01	0.04	0.025
6	11957303	12038979	rs209809	Intergenic	G	T	**-0.01**	**0.05**	**0.046**
6	24905311	24998665	rs77386029	*FAM65B*	C	T	0.03	0.12	0.025
7	23600173	23881813	rs798641	Intergenic	G	A	**0.02**	**-0.06**	**0.022**
8	70943083	70990615	rs3750228	*PRDM14*	T	C	-0.02	-0.05	0.037
9	34081331	34130435	rs11557154	*DCAF12*	C	T	0.03	0.05	0.043
9	96181075	96381916	rs564	*FAM120A*	T	C	0.01	0.04	0.028
9	138378856	138378856	rs2078266	*PPP1R26*	A	G	0.01	0.07	0.022
10	78741559	78763297	rs11001965	*KCNMA1*	G	A	**0.01**	**-0.04**	**0.030**
10	104697781	104741114	rs12414777	*CNNM2*	C	T	**-0.01**	**0.08**	**0.010**
10	106003861	106076414	rs17883150	*GSTO1*	G	A	**-0.01**	**0.04**	**0.023**
10	106453550	106560225	rs7909129	*SORCS3*	A	G	**0.01**	**-0.05**	**0.009**
11	46330604	47207362	rs61882672	Intergenic	C	A	**0.01**	**-0.09**	**0.001**
11	47925962	49248150	rs10838843	Intergenic	G	T	**0.01**	**-0.07**	**0.048**
12	53730164	54028059	rs34169640	*RP11-793H13.8*	A	G	**0.02**	**-0.12**	**0.032**
12	57486647	57492996	rs4559	*STAT6*	C	T	**0.01**	**-0.04**	**0.029**
12	110229434	110229434	rs117145318	*TRPV4*	C	A	**0.02**	**-0.12**	**0.039**
12	122804256	123144293	rs7952868	*CLIP1*	A	G	**0.02**	**-0.04**	**0.020**
12	123421902	123897177	rs73230058	*PITPNM2*	C	T	**-0.01**	**0.06**	**0.028**
12	123421902	123897177	rs1727302	*PITPNM2*	G	A	**-0.02**	**0.07**	**1.E-07**
13	79855297	80159615	rs3187338	*RBM26*	C	T	0.01	0.05	0.048
14	104332759	104363528	rs10139856	Intergenic	T	C	**-0.01**	**0.05**	**0.027**
15	38820606	38869666	rs28582094	*RASGRP1*	A	G	**0.01**	**-0.04**	**0.029**
15	78712119	78858400	rs16969894	*IREB2*	C	T	**-0.01**	**0.07**	**0.001**
15	82827938	83406857	rs783522	*CPEB1*	A	G	-0.01	-0.05	0.019
15	84703470	85344550	rs11638445	Intergenic	C	A	0.01	0.06	0.007
15	91416550	91429042	rs4702	*FURIN*	G	A	**-0.01**	**0.08**	**0.040**
16	68285847	68419298	rs61593058	*PRMT7*	T	C	-0.01	-0.06	0.003
16	69141138	69432250	rs8049057	*RNU6-22P*	G	T	-0.02	-0.04	0.014
16	90109372	90120171	rs3743824	*URAHP*	G	A	**-0.01**	**0.05**	**0.001**
18	4930206	5038613	rs4798275	*RP11-172F10.1*	G	A	**-0.01**	**0.04**	**0.047**
18	9129337	9414607	rs2902839	*RP11-888D10.3*	C	T	-0.02	-0.08	0.034
20	32903904	33294945	rs6059779	*ITCH*	C	T	0.01	0.04	0.015
20	62127121	62171556	rs1741617	*EEF1A2*	T	C	**0.02**	**-0.05**	**0.006**
20	62127121	62171556	rs310653	*SRMS*	T	C	**0.01**	**-0.04**	**0.020**
22	29162506	29358802	rs6005928	Intergenic	T	C	-0.01	-0.04	0.019
22	41411804	41613303	rs4822000	*RP11-12M9.4*	T	C	**0.01**	**-0.04**	**0.004**
22	50162136	50321623	rs138832	*BRD1*	A	G	**0.01**	**-0.05**	**0.026**
22	50978504	50982272	rs58111256	*CTA-384D8.35*	C	T	**0.02**	**-0.08**	**0.008**

Loci reported in bold are concordant with the hypothesis of higher predisposition to SZ being associated with shorter LTL. Abbreviations: Chr, chromosome; EA, effect allele; OA, other allele

Twenty-eight of the 55 lead SNPs were found to act as eQTLs for different genes in at least one brain region (Table 3.10).

Table 3.10 Functional effect of lead SNPs associated with SZ and LTL

Lead SNP	RDB score	RDB rank	eQTL in brain regions (GTEx v. 8)
rs10874656	0.61	4	*EVI5* (amygdala, caudate, cortex, hyppocampus, hypothalamus, putamen, substantia nigra); *RP4-621B10.8* (cerebellum, cortex, frontal cortex); *FAM69A* (cerebellum); *C1orf146* (cerebellum)
rs1874422	0.23	5	-
rs11588837	0.55	1f	*VPS45* (frontal cortex)
rs7521047	0.48	3a	*CREB3L4* (caudate); *SLC27A3* (cerebellum)
rs2345964	0.63	5	-
rs4844621	0.61	4	*CD46* (amygdala, anterior cingulate cortex, caudate, cerebellum, cortex, frontal cortex, hyppocampus, hypothalamus, nucleus accumbens, putamen, substantia nigra)
rs58787117	0.13	5	-
rs11891807	0.89	5	*FOXN2* (caudate, cerebellum, frontal cortex, nucleus accumbens, putamen)
rs7583622	0.16	5	-
rs7567556	0.13	5	-
rs7591382	0.18	7	-
rs12107252	0.55	1f	*NCKIPSD* (anterior cingulate cortex, caudate, cerebellum, cortex, frontal cortex, nucleus accumbens, putamen); *WDR6* (caudate, cerebellum, cortex, frontal cortex, nucleus accumbens, putamen); *CCDC71* (cerebellum cerebellum); *PFKFB4* (cerebellum); *TREX1* (cortex, nucleus accumbens)
rs12629701	0.18	7	*GNL3* (cerebellum, frontal cortex, hypothalamus, putamen); RP5-966M1.7 (cerebellum, cortex, putamen); *PPM1M* (cerebellum); *NEK4* (cerebellum); *GLYCTK* (cerebellum); *ITIH4* (cortex, hypothalamus, putamen); *POC1A* (putamen)
rs34386102	0.61	4	-
rs34208976	0.05	5	-
rs10034519	0.22	6	-
rs35296212	0.13	5	-
rs209809	0.61	4	-
rs77386029	1.00	5	*GPLD1* (cortex)
rs798641	0.13	5	*FAM221A* (caudate, nucleus accumbens)
rs3750228	0.13	5	-
rs11557154	0.13	5	*UBAP1* (substantia nigra)
rs564	0.80	2b	-
rs2078266	0.38	3a	-
rs11001965	0.35	5	-
rs12414777	0.18	7	*AS3MT* (amygdala, anterior cingulate cortex, caudate, cerebellum, cortex, frontal cortex, hypothalamus, nucleus accumbens, putamen, substantia nigra); *RPARP-AS1* (caudate, cerebellum, cortex, nucleus accumbens); *BORCS7* (cerebellum, cortex); *RPL22P17* (cerebellum); *RP11-724N1.1* (cerebellum)
rs17883150	0.61	4	*RP11-127L20.3* (amygdala, anterior cingulate cortex, caudate, cerebellum, cortex, frontal cortex, hippocampus, hypothalamus, nucleus accumbens, putamen); *GSTO2* (amygdala, anterior cingulate cortex, caudate, cerebellum, cortex, frontal cortex, hippocampus, hypothalamus, nucleus accumbens, putamen); *ITPRIP* (cortex)
rs7909129	0.13	5	
rs61882672	0.61	4	*C11orf49* (cerebellum)
rs10838843	0.08	6	*FOLH1* (caudate, cerebellum, nucleus accumbens, putamen)

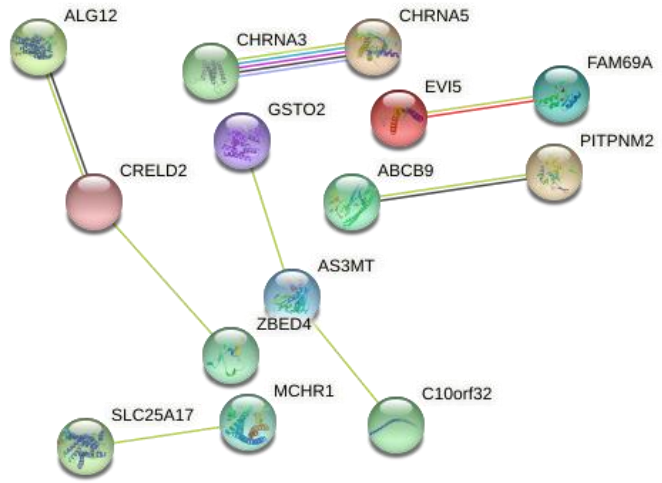
rs34169640	0.59	5	-
rs4559	0.83	2b	-
rs117145318	0.18	7	-
rs7952868	0.13	5	-
rs73230058	0.00	5	*ABCB9* (cerebellum); *KMT5A* (cerebellum)
rs1727302	0.61	4	*PITPNM2* (cerebellum); *RP11-282O18.3* (cerebellum); *KMT5A* (cerebellum); *ZCCHC8* (cerebellum); *CCDC62* (cerebellum)
rs3187338	0.37	3a	*RBM26* (cerebellum); *LINC01068* (cerebellum)
rs10139856	0.49	5	*TDRD9* (caudate, cerebellum, cortex)
rs28582094	0.16	6	-
rs16969894	0.39	5	*CHRNA3* (caudate, nucleus accumbens); *CHRNA5* (nucleus accumbens)
rs783522	0.68	5	*GOLGA2P10* (amygdala, caudate, cerebellum); *GOLGA6L9* (anterior cingulate cortex, caudate, cerebellum, cortex, frontal cortex, hippocampus, nucleus accumbens); *GOLGA6L10* (caudate, cerebellum, cortex, frontal cortex, hippocampus, putamen, substantia nigra); *CSPG4P10* (caudate, cerebellum); *ADAMTS7P1* (cerebellum); *RPS17* (cortex, frontal cortex, hippocampus); *CPEB1* (cortex); *AP3B2* (cortex)
rs11638445	0.59	5	*GOLGA2P7* (amygdala, anterior cingulate cortex, caudate, cerebellum, cortex, frontal cortex, hypothalamus, nucleus accumbens, putamen); *CSPG4P12* (anterior cingulate cortex, cerebellum, cortex, frontal cortex, hippocampus, hypothalamus, nucleus accumbens, putamen); *DNM1P51* (cortex, frontal cortex); *EFTUD1P1* (hypothalamus); *GOLGA6L5P* (anterior cingulate cortex, caudate, cortex, frontal cortex, putamen, substantia nigra); *LINC00933* (anterior cingulate cortex, caudate, cortex); *NMB* (caudate); *RP11-182J1.14* (cortex)
rs4702	0.61	4	*FURIN* (frontal cortex)
rs61593058	0.14	6	*PRMT7* (caudate, cortex, frontal cortex, nucleus accumbens, putamen, substantia nigra)
rs8049057	0.09	1d	*COG8* (cortex, frontal cortex); *NIP7* (frontal cortex, nucleus accumbens, putamen); *SNTB2* (cerebellum); *TERF2* (cerebellum); *UTP4* (nucleus accumbens); *VPS4A* (anterior cingulate cortex, caudate, cortex, frontal cortex, nucleus accumbens, putamen)
rs3743824	0.61	4	-
rs4798275	0.13	5	-
rs2902839	0.55	1f	-
rs6059779	0.61	4	*ACSS2* (cerebellum); *EDEM2* (cortex); *ITCH* (cortex); *MAP1LC3A* (anterior cingulate cortex, caudate, cerebellum, cortex, frontal cortex, hypothalamus, nucleus accumbens, putamen); *MMP24-AS1* (cortex, nucleus accumbens, substantia nigra); *MYH7B* (cerebellum)
rs1741617	0.61	4	-
rs310653	0.61	4	*PTK6* (caudate)
rs6005928	0.32	5	-
rs4822000	0.18	7	*MCHR1* (cerebellum); *RP11-12M9.4* (cerebellum); *SLC25A17* (cerebellum, nucleus accumbens); *ZC3H7B* (cerebellum)
rs138832	0.55	1f	*ALG12* (hippocampus, nucleus accumbens); *CRELD2* (hypothalamus); *RP3-522J7.6* (cerebellum); *ZBED4* (cerebellum)
rs58111256	0.70	4	-

Abbreviations: RDB, RegulomeDB

Genes modulated by SNPs associated with increased predisposition to SZ and shorter LTL were

enriched for the nicotine pharmacodynamics pathway (FDR = 0.049, genes: *CHRNA3* and *CHRNA5*) as well as for the ammonium ion binding molecular function GO term (FDR = 0.045, genes: *CHRNA3*, *CHRNA5* and *PITPNM2*). Proteins encoded by the identified genes also showed significant protein-protein interaction enrichment (PPI enrichment p-value: 1.02E-05, Figure 3.5).

Figure 3.5 Protein-protein interaction network for genes with significant eQTLs among SNPs associated with increased predisposition to SZ and shorter LTL



Finally, 12 loci were shared between MDD and LTL (Table 3.11). Of the 13 lead SNPs, 10 were associated with increased risk of MDD and shorter LTL.

Table 3.11 Loci associated with risk of MDD and LTL

Chr	Start locus	Stop locus	Lead SNP	Gene	EA	OA	Beta LTL	Beta MDD	conjFDR
1	151364199	151449138	rs4971040	Intergenic	A	C	**0.02**	**-0.03**	**0.006**
2	58878085	59039998	rs7596101	*LINC01122*	A	G	**-0.01**	**0.02**	**0.027**
3	49609477	49890967	rs148383796	*IP6K1*	A	G	**-0.01**	**0.03**	**0.035**
4	164483214	164570327	rs11729015	*MARCH1*	A	C	**0.01**	**-0.02**	**0.032**
5	145463497	145704064	rs17104395	*CTC-359M8.1*	T	C	**-0.01**	**0.03**	**0.045**
10	106453550	106560225	rs7909129	*SORCS3*	A	G	**0.01**	**-0.02**	**0.027**
11	47401448	49555740	rs7107356	Intergenic	A	G	**0.01**	**-0.02**	**0.049**
11	47401448	49555740	rs116941111	*OR4A42P*	T	C	**-0.03**	**0.07**	**0.009**
11	118569414	118712509	rs564091	*AP002954.4*	A	G	**0.01**	**-0.03**	**0.006**
14	64649894	64877135	rs944047	*ESR2*	T	C	0.01	0.02	0.041
15	38820606	38925195	rs56059718	*RASGRP1*	A	C	**-0.01**	**0.02**	**0.033**
18	51764473	51832407	rs4940321	Intergenic	A	G	0.02	0.02	0.020
18	52464388	52504252	rs2008551	*RAB27B*	T	C	0.01	0.02	0.006

Loci reported in bold are concordant with the hypothesis of higher predisposition to MDD being associated with shorter LTL. Abbreviations: Chr, chromosome; EA, effect allele; OA, other allele

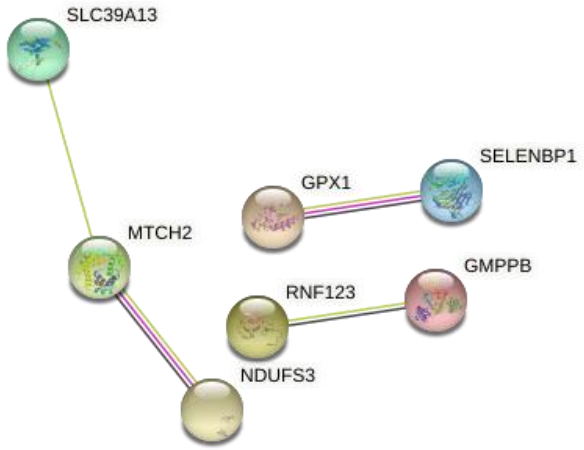
Of the 13 lead SNPs, six were found to act as eQTLs for different genes in at least one brain region (Table 3.12).

Table 3.12 Functional effect of lead SNPs associated with MDD and LTL

Lead SNP	RDB score	RDB rank	eQTL in brain regions (GTEx v. 8)
rs4971040	0.40	3a	*POGZ* (cerebellum, cortex, frontal cortex, nucleus accumbens, putamen); *SELENBP1* (cortex)
rs7596101	0.41	5	-
rs148383796	0.13	5	*AMT* (anterior cingulate cortex, caudate, cerebellum, cortex, frontal cortex, Hyppocampus, nucleus accumbens, putamen, substantia nigra); *CCDC71* (amygdala); *DALRD3* (cerebellum); *FAM212A* (cerebellum); *GMPPB* (amygdala, anterior cingulate cortex, caudate, cerebellum, cortex, frontal cortex, hyppocampus, nucleus accumbens bens, putamen, substantia nigra); *GPX1* (caudate, cerebellum, cortex, frontal cortex, nucleus accumbens); *P4HTM* (cerebellum, cortex); *RBM6* (cerebellum, cortex, frontal cortex); *RNF123* (cerebellum, nucleus accumbens); *RP11-694I15.7* (cerebellum)
rs11729015	0.18	7	-
rs17104395	0.13	5	-
rs7909129	0.13	5	-
rs7107356	0.50	6	*C1QTNF4* (cerebellum); *MTCH2* (cerebellum, cortex, nucleus accumbens, Putamen); *NDUFS3* (cerebellum); *RP11-750H9.5* (cerebellum); *SLC39A13* (cerebellum)
rs116941111	0.13	5	*FOLH1* (cortex)
rs564091	0.59	5	*RP11-158I9.8* (amygdala, anterior cingulate cortex, caudate, cerebellum, cortex, frontal cortex, hyppocampus, hypothalamus, nucleus accumbens, putamen, substantia nigra)
rs944047	0.88	3a	-
rs56059718	0.13	5	-
rs4940321	0.16	6	*POLI* (anterior cingulate cortex, caudate, cerebellum, cortex, frontal cortex, hypothalamus, nucleus accumbens, putamen); *STARD6* (cortex)
rs2008551	0.35	6	-

Five of the six eQTLs were associated with increased predisposition to MDD and shorter LTL. Genes modulated by these SNPs were not significantly enriched for GO terms or molecular pathways. However, proteins encoded by these genes showed a significant PPI (PPI enrichment p-value: 0.002, Figure 3.6).

Figure 3.6 Protein-protein interaction network for genes with significant eQTLs among SNPs associated with increased predisposition to MDD and shorter LTL



3.3.4 Discussion

In this study, we explored pleiotropy between severe mental disorders and genetically determined LTL. Using global genetic correlation, we found only MDD to be significantly associated with shorter LTL (r_g = -0.11, p = 1.4E-08). This result is in line with a recent study suggesting shorter LTL in individuals with depression in UK Biobank as well as a significant association between a PRS for depression and shorter LTL [206]. However, using a method able to identify specific genetic loci between two traits, rather than just investigating genetic correlation at a global level, we identified significant cross-trait enrichment between all the investigated severe mental disorders (MDD, BD and SZ) and genetically determined LTL. Our study identified for the first time specific genetic loci shared between mental disorders and LTL, with the highest number of loci being identified for SZ. Interestingly, a high percentage of loci among identified loci showed lead SNPs with a direction of effect unexpected based on the hypothesis that severe mental disorders might be characterized by accelerated cellular aging. Specifically, 61% (11/18), 40% (22/55) and 23% (3/13) were associated with increased risk of BD, SZ or MDD, respectively, and longer LTL. BD showed the highest percentage of loci with an unexpected direction of effect. Interestingly, among mental disorders, BD is the one for which the most conflicting results have been reported as regards to shorter LTL compared with individual without mental illness. Indeed, a number of studies has observed longer LTL in patients with BD compared with controls [31, 108]. While treatment with

the mood stabilizer lithium has been suggested to exert a potential counteractive effect on telomere shortening [69, 70], it might also be the case that some genetic variants might protect patients with BD from accelerated telomere shortening. Among variants associated with increased risk of BD and shorter TL, we found the rs12919664 SNP located in the *TERF2* gene. This gene encodes a telomere specific protein which is a component of the telomere nucleoprotein complex and plays a key role in the protective activity of telomeres. As previously mentioned, SZ was the mental disorder for which we identified the highest number of genetic loci shared with LTL (52 loci with 55 lead SNPs). Around half of these SNPs were found to act as significant eQTLs for a variety of genes in at least one brain region. Finally, MDD was the disorder for which we identified the smaller number of SNPs shared with LTL. However, it was also the disorder for which the large majority of SNPs showed the expected direction of effect (the allele associated with increased predisposition to MDD was also associated with shorter LTL). This observation is in line with the finding of a significant negative global genetic correlation between MDD and LTL. On the other hand, methods able to identify specific genetic loci shared between two traits even in the absence of a global genetic correlation, have proved to be more useful for BD and SZ. Based on the direction of effect of identified variants, shorter TL in patients with SZ or BD could be at least partly counteracted by genetic factors. Interestingly, a locus on chr 10 (106453550-106560225), with rs7909129 as the lead SNP and located in the *SORCS3* gene, was associated with shorter LTL and increased predisposition to all three mental disorders. This gene has been previously implicated in different mental disorders [146, 208, 209] as well as in Alzheimer's disease [209, 210]. The protein encoded by this gene is a member of the vacuolar protein sorting 10 (Vps10) family of receptors, which represent cargos of the retromer complex and are involved in protein trafficking and intracellular/intercellular signaling in neuronal and non-neuronal cells [211, 212]. The retromer is a complex of proteins that control the reverse transport of molecules from the endosomes trans-Golgi network or to the cell surface, thus potentially playing a relevant role in different neurodegenerative diseases. Besides their roles as cargo proteins of the retromer complex, members of the Vps10

receptor family such as SORCS3 have been shown to modulate neurotrophic signaling pathways [212]. Based on this evidence, SORCS3 represents an interesting target that might be involved in the molecular mechanisms underlying accelerated cellular aging in severe mental disorders. In addition, four loci with rs11588837, rs11638445, rs12629701 and rs2345964 as lead SNPs, were associated with longer LTL and predisposition to both BD and SZ. Three of these variants are significant eQTLs for a variety of genes in different brain regions. Among genes modulated by these variants, rs11588837 is able to affect the expression of *VPS45* (a gene encoding another protein involved in trafficking through the endosomal system [213]) in the frontal cortex.

Taken together, our results support the existence of shared genetic loci between severe mental disorders and LTL and point to the retromer complex and intracellular protein trafficking as interesting molecular mechanisms potentially underlying the shared genetic bases between these traits.

3.4 Gender differences in genetic loci shared between mental disorders and metabolic traits

3.4.1 Introduction

As previously mentioned, patients with severe mental disorders show excess mortality and decreased life expectancy, mainly due to a high prevalence of comorbid chronic disorders such as cardiovascular disorders. High rates of metabolic risk factors greatly contribute to the increased incidence of cardiovascular disorders in patients with severe mental disorders. Indeed, patients with BD show increased frequency of overweight and obesity (41% compared to 27% in general population in US) [214, 215] and a three-fold higher risk of type 2 diabetes (T2D) [216] compared to the general population. Obesity exerts a negative impact on the course of BD, as this comorbidity is associated with higher episode frequency, rates of disability, suicide attempts, psychiatric and medical comorbidities as well as cognitive impairment and white matter abnormalities [217]. Conversely, a lower body mass index (BMI) has been associated with positive response to lithium treatment, suggesting a potential interplay between BMI and molecular targets involved in the mechanism of action of this mood stabilizer. Although a link between mental disorders and metabolic traits has been established, the molecular mechanisms underlying this comorbidity have only recently started to be investigated and are still largely unknown. The factors underlying the association between mental disorders and metabolic risk factors are manyfold and include, among others, lifestyle factors (e.g. diet, physical activity, smoking habits) and metabolic adverse effects of psychotropic drugs. However, shared genetic determinants between mental disorders and metabolic traits might also play a role. A few studies have started to investigate pleiotropic loci shared between psychiatric disorders and BMI, with different analytical methods [218-221]. To our knowledge, no study investigating shared genetic determinants between mental disorders and metabolic phenotypes (or any other phenotype) has considered the effect of gender. However, there are substantial differences between men and women in body composition, muscle mass, adipose distribution, glucose homeostasis, incidence of metabolic disorders as well as genetic determinants of metabolic traits [222, 223]. Therefore, the aim of the present study was to investigate whether

shared genetic determinants between severe mental disorders and metabolic traits might be associated with metabolic abnormalities in a gender-specific way. We conducted our analyses in larger datasets compared to previous studies and evaluated the potential functional role and druggability of identified genetic variants and related genes.

3.4.2 Methods

GWAS samples

We used the latest release of GWAS summary statistics for BD, SZ and MDD from the Psychiatric Genomics Consortium (PGC) [20-22] as described in Section 3.3.2. GWAS summary statistics for BMI (434,794 women and 374,756 men) and waist-to-hip ratio adjusted for BMI (^{BMIadj}WHR, 379,501 women and 315,284 men) were obtained from GIANT consortium and UK Biobank [223]. For all GWAS datasets, quality control procedures, including adjustment for population stratification, were performed by the original studies. Analyses were conducted on autosomal variants common to GWAS on psychiatric traits and LTL, after exclusion of ambiguous variants (A/T and C/G) or variants located in regions characterized by strong LD such as the MHC region (chr6:25119106-33854733), chromosome 8p23.1 (chr8:7200000–12500000) and the *MAPT* gene (chr17:40000000–47000000).

Global genetic correlation analysis and conjunctional false discovery rate analysis

Cross-trait global genetic correlation analysis was conducted using LDSC [110, 207] as described in Section 3.3.2.

To identify shared loci between mental disorders and metabolic traits, we used the condFDR/conjFDR method implemented in pleioFDR [112, 113], as described in Section 3.2.2. The threshold for significant conjFDR associations was set at 0.05, as in previous studies [111, 153-155]. Results were controlled for sample overlap using the decorrelation of vectors of *Z* scores based on the Mahalanobis Transformation [113].

Definition of genomic loci and functional annotation

Independent significant genomic loci were defined according to the FUMA protocol [156], as described in Section 3.2.2. The direction of allelic effects for significant variants was evaluated by comparing betas reported in the original GWAS. Genes in which genetic variants significantly associated with a mental disorder and a metabolic trait with a concordant direction of effect were located were tested for functional enrichment for GO terms using WebGestalt [160] with default options, adjusting results based on FDR. We tested the functional enrichment for GO terms using WebGestalt [160] with default options, adjusting results based on FDR. In addition, genes in which significantly associated variants were located were searched in the Drug Gene Interaction Database (DGIdb) [161] to assess whether they are known targets of existing drugs (drug-gene interactions) or 'potentially druggable' based on their involvement in selected pathways, molecular functions or gene families.

3.4.3 Results

Using LDSC regression, we found heterogeneity in the direction of effect of global genetic correlation (r_g) patterns, especially for BD and SZ, as shown in Table 3.13.

Table 3.13. Global genetic correlation analysis between psychiatric and metabolic traits

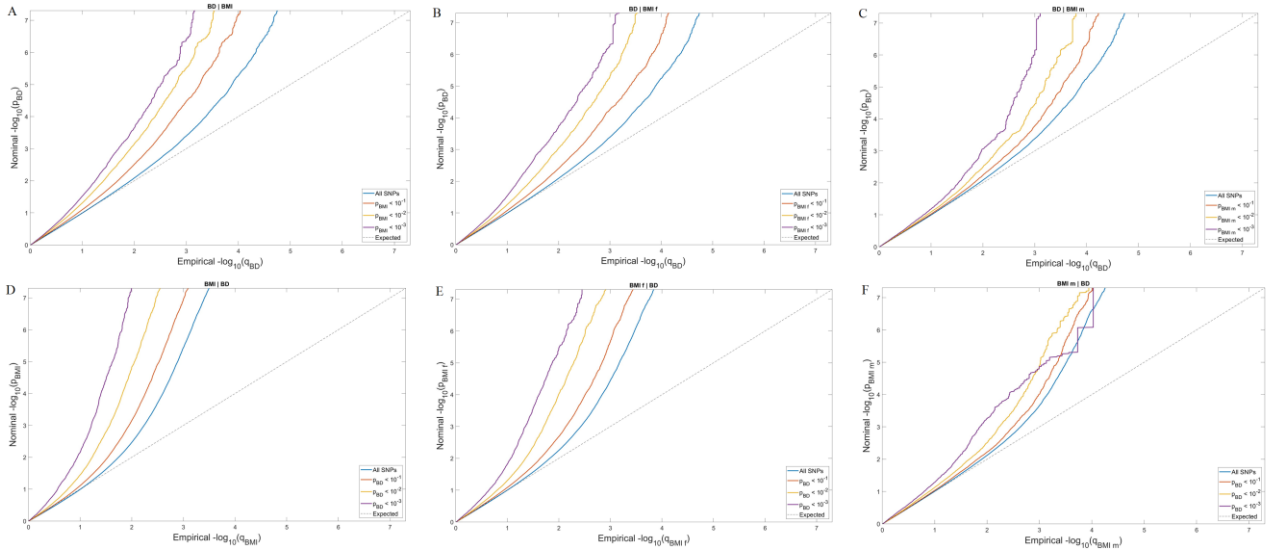
	BD		**SZ**		**MDD**	
Phenotype	**r_g**	**p**	**r_g**	**p**	**r_g**	**p**
BMI (All)	-0.04	0.033	-0.11	$1.6E^{-12}$	**0.11**	5.6E-11
BMI Women	-0.05	0.015	-0.11	$1.5E^{-12}$	**0.12**	4.5E-10
BMI Men	**0.07**	**0.008**	-0.06	0.003	**0.14**	4.8E-11
^{BMIadj}WHR (All)	**0.05**	**0.010**	0.03	0.059	**0.10**	3.8E-09
^{BMIadj}WHR Women	0.04	0.087	-0.02	0.286	**0.07**	1.5E-04
^{BMIadj}WHR Men	**0.07**	**0.008**	-0.06	0.003	**0.14**	4.8E-11

Significant results in the expected direction of effect (positive association between increased predisposition to the mental disorders and BMI or ^{BMIadj}WHR) are reported in bold.

The conditional QQ plot showed significant cross-trait enrichment in variants associated with mental disorders when conditioning on metabolic traits. As an example, Figure 3.7 shows conditional QQ plots for BD conditioned on the BMI GWAS in the whole sample, the BMI GWAS

in women and the BMI GWAS in men, as well as QQ plots for BMI in the whole sample, BMI in women and BMI in men, when conditioning on BD.

Figure 3.7 Conditional QQ plots suggesting cross-phenotype polygenic enrichment between mental disorders and metabolic phenotypes



The progressive leftward deflection from the null line as levels of SNP associations with the secondary phenotype increase shows significant cross-trait enrichment between primary and secondary phenotype. A: BD conditioned on BMI; B: BD conditioned on BMI in women; C: BD conditioned on BMI in men; D: BMI conditioned on BD; E: BMI in women conditioned on BD; F: BMI in men conditioned on BD

Using conjFDR, we identified a high number of loci shared between mental disorders and metabolic traits and, consistently with LDSC regression, we observed mixed patterns of direction of effect for SZ and BD, while MDD showed a higher rate of variants with concordant direction of effect (Figure 3.8). Overall, SZ was the disorder found to share the highest number of genetic loci with metabolic traits, followed by BD and MDD. However, when considering the direction of effect, for MDD, in the large majority of loci, the allele associated with increased risk for the psychiatric disorder was also associated with increased BMI or ^{BMIadj}WHR (Table 3.14).

Table 3.14 Overall number of shared genetic loci between mental disorders and metabolic traits

	SZ		BD		MDD	
Sample	**SNP (loci)**	**SNP concordant dir. (%)**	**SNP (loci)**	**SNP concordant dir. (%)**	**SNP (loci)**	**SNP concordant dir. (%)**
BMI	727 (539)	277 (38%)	301 (272)	137 (46%)	289 (257)	203 (70%)
BMI Women	538 (429)	211 (39%)	233 (218)	112 (48%)	233 (212)	168 (72%)
BMI Men	87 (80)	44 (51%)	30 (28)	16 (53%)	30 (28)	22 (73%)
^{BMIadj}WHR	230 (192)	116 (50%)	90 (86)	56 (62%)	59 (55)	45 (76%)
^{BMIadj}WHR Women	157 (135)	74 (47%)	69 (63)	41 (59%)	41 (40)	28 (68%)
^{BMIadj}WHR Men	91 (84)	46 (51%)	35 (33)	17 (49%)	27 (26)	20 (74%)

Abbreviations: Concordant dir, concordant direction of effect between mental disorders and metabolic traits; SNP, single nucleotide polymorphism

Substantial gender differences in terms of global genetic correlation, number of identified loci, number of loci with concordant direction of effect and genes to which genomic loci were mapped were observed (Figure 3.9). A higher number of loci shared with psychiatric disorders was associated with higher BMI or ^{BMIadj}WHR exclusively in women.

Figure 3.8. Shared SNPs between mental disorders and metabolic traits

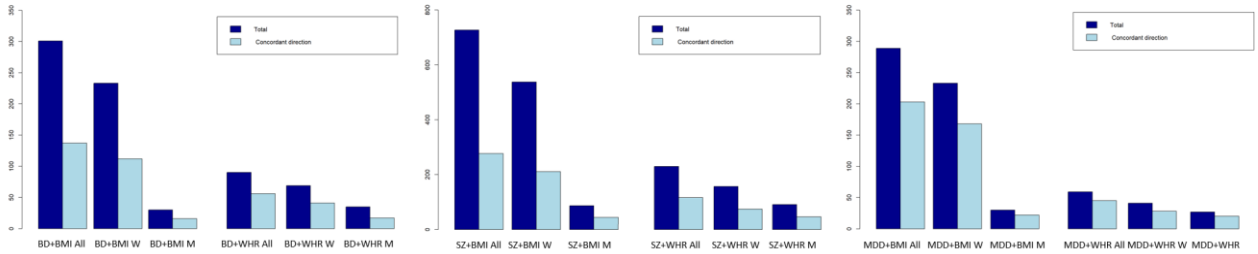
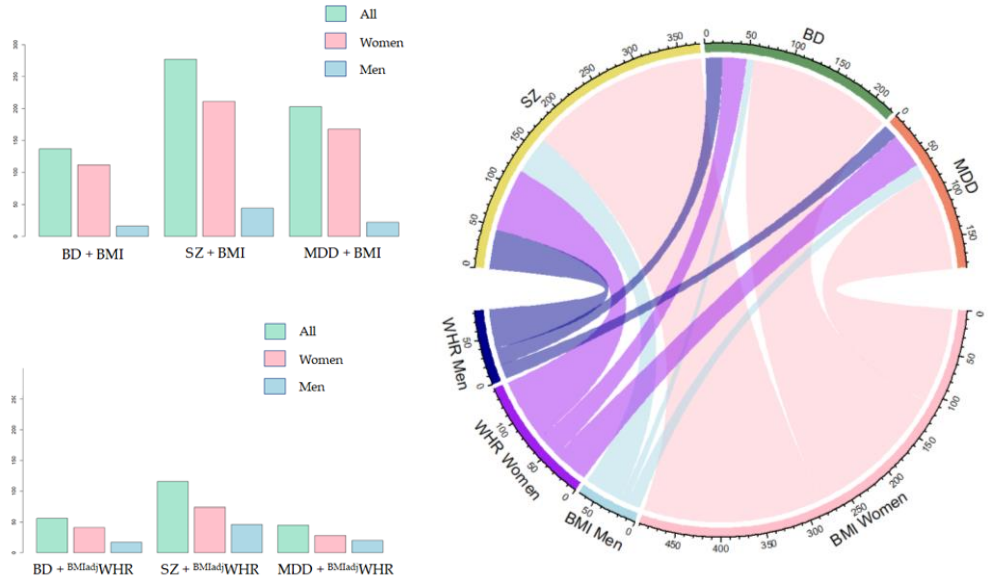


Figure 3.9 Bar plots and chord diagram showing the number of loci associated with mental disorders and increased BMI or ^{BMIadj}WHR in women or in men



Functional enrichment of genes shared between mental disorders and metabolic traits

Genes to which genetic variants associated with increased risk for SZ and increased BMI in women were mapped were enriched for different biological processes (Table 3.15) and cellular components GO terms (Table 3.16). Conversely, genes in which genetic variants associated with increased risk for SZ and increased BMI in men were located were not enriched for any significant GO term.

Table 3.15. Biological processes GO terms showing enrichment among loci associated with SZ and increased BMI in women

Gene Set	Description	Ratio	p	FDR
GO:0010975	regulation of neuron projection development	5.63	5.2E-08	4.4E-05
GO:0098742	cell-cell adhesion via plasma-membrane adhesion molecules	5.95	2.0E-05	0.006
GO:0001764	neuron migration	8.27	2.2E-05	0.006
GO:0061564	axon development	4.01	8.7E-05	0.017
GO:0097485	neuron projection guidance	5.49	1.0E-04	0.017
GO:0035051	cardiocyte differentiation	7.59	1.4E-04	0.020
GO:0050769	positive regulation of neurogenesis	3.99	1.9E-04	0.023
GO:0016358	dendrite development	5.7	2.3E-04	0.023
GO:0030900	forebrain development	4.28	2.4E-04	0.023
GO:0031345	negative regulation of cell projection organization	6.12	4.4E-04	0.038
GO:0099177	regulation of trans-synaptic signaling	3.85	5.3E-04	0.041
GO:0042692	muscle cell differentiation	4.22	6.0E-04	0.043

Table 3.16. Cellular component GO terms showing enrichment among loci associated with SZ and increased BMI in women

Gene Set	Description	Ratio	p	FDR
GO:0044309	neuron spine	6.81	6.9E-05	0.012
GO:0099572	postsynaptic specialization	4.30	2.1E-04	0.012
GO:0098984	neuron to neuron synapse	4.29	2.2E-04	0.012

Loci in which genetic variants associated with increased risk for MDD and increased BMI in women were located were enriched for different cellular components (Table 3.17) GO terms.

Table 3.17. Cellular component GO terms showing enrichment among loci associated with MDD and increased BMI in women

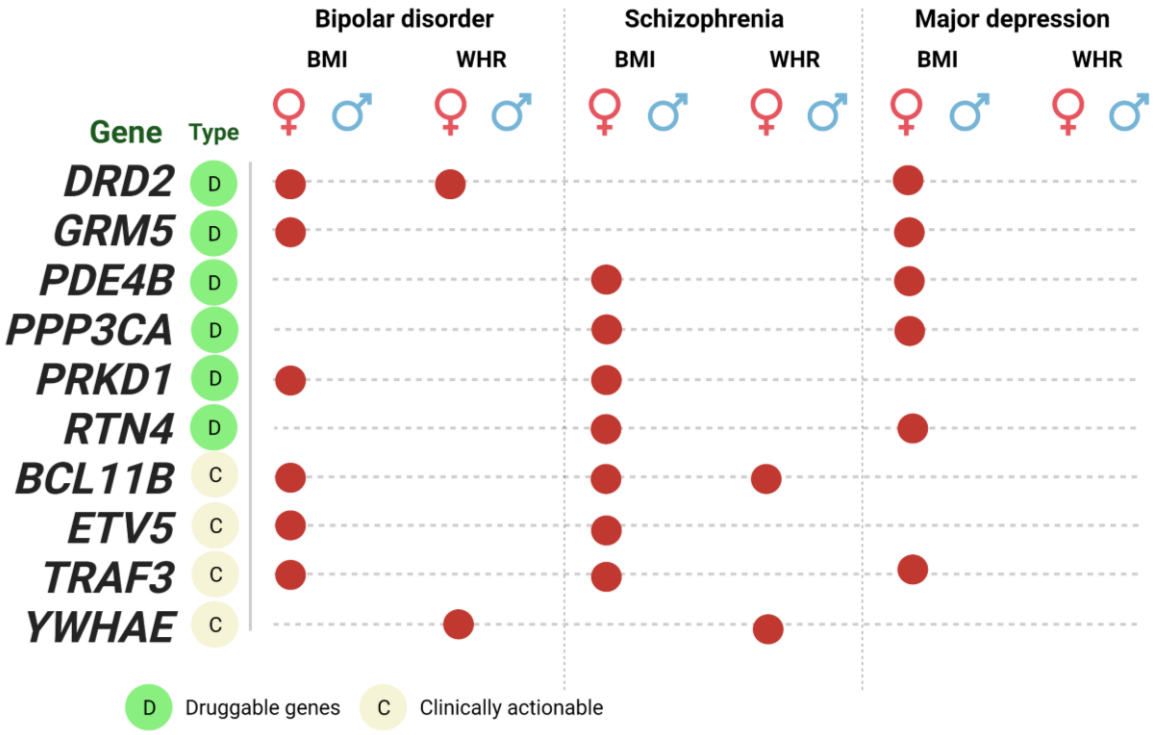
Gene Set	Description	Ratio	p	FDR
GO:0099572	postsynaptic specialization	**6.52**	**6.3E-07**	**5.6E-05**
GO:0098984	neuron to neuron synapse	6.50	6.5E-07	5.6E-05
GO:0097060	synaptic membrane	4.69	4.0E-05	0.002
GO:0098793	presynapse	3.76	5.3E-04	0.023
GO:0044309	neuron spine	6.04	1.4E-03	0.045
GO:0098978	glutamatergic synapse	4.03	1.6E-03	0.045

Conversely, genes in which genetic variants associated with increased risk for MDD and increased BMI in men were located were not enriched for any significant GO term. Finally, genes in which genetic variants associated with increased risk for BD and increased BMI in women or in men were located were not enriched for any significant GO term. In addition, genes in which genetic variants associated with increased risk for any severe mental disorder and increased ^{BMIadj}WHR were not enriched for any significant GO term.

Identification of Druggable genes

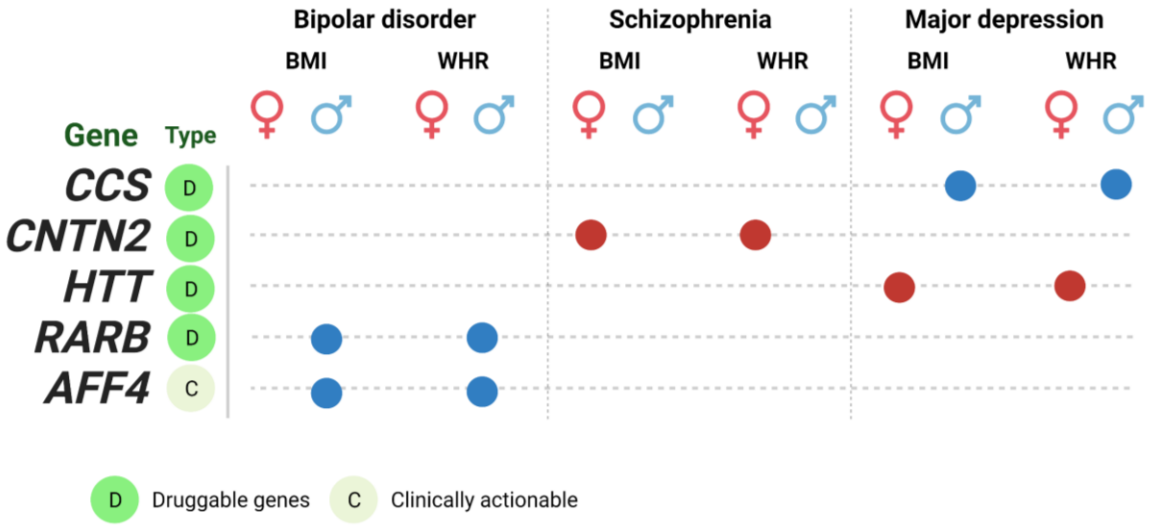
A total of 23 loci identified as significantly shared between severe mental disorders and increased BMI or ^{BMIadj}WHR in either women or men were found to encompass genes part of the druggable genome or clinically actionable. Loci located in 10 druggable genes were associated with different mental disorders and one or more metabolic phenotypes in a gender-specific way (exclusively in women). These genes are reported in Figure 3.10.

Figure 3.10. Druggable or clinically actionable genes associated with multiple mental disorders and increased BMI or ^{BMIadj}WHR exclusively in women



In addition, we identified 5 druggable or clinically actionable genes associated with the same psychiatric disorder and different metabolic phenotypes in a gender-specific way (2 specific for women and 3 for men). These genes are shown in Figure 3.11.

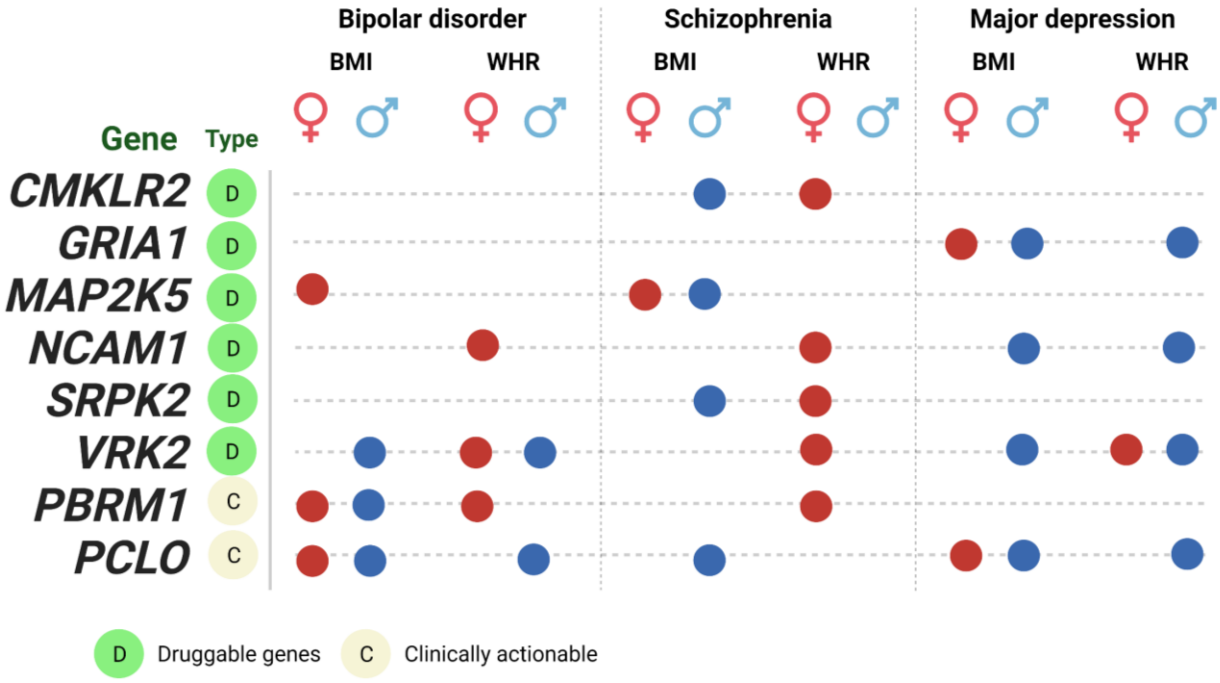
Figure 3.11. Druggable or clinically actionable genes associated with the same mental disorder and different metabolic phenotypes in a gender-specific way



Finally, loci located in 8 druggable or clinically actionable genes were associated with multiple

mental disorders or metabolic traits in a not gender-specific way (Figure 3.12).

Figure 3.12. Druggable or clinically actionable genes associated with different mental disorders or metabolic phenotypes in a not gender-specific way



3.4.4 Discussion

In this study, we explored for the first time pleiotropy between severe mental disorders and metabolic traits taking into consideration the effect of gender. Specifically, we aimed to assess whether genetic loci associated with predisposition to severe mental disorders might also be associated with increased BMI or ^{BMIadj}WHR in a gender-specific way. Overall, compared with previous studies, we identified a higher number of genetic loci shared between severe mental disorders and the investigated metabolic phenotypes. Of note, we identified relevant differences in the direction of effect of these loci across severe mental disorders. Specifically, in the case of SZ and BD a large part of the identified loci was found to be associated with predisposition to mental disorders and lower BMI or ^{BMIadj}WHR. Conversely, in the case of MDD the majority of loci was found to act in the expected direction of effect, based on the observation that patients with mental disorders show increased frequency of cardiometabolic disturbances. This finding is in line with previous results [219, 220] and suggests that the study of the association between mental disorders

and metabolic traits needs to be conducted with analytical methods able to assess the contribution at specific loci rather than just the genetic correlation at a global level, as this method does not allow to identify signals confined to particular genomic regions or in opposing directions at different loci. Indeed, when evaluating global genetic correlation, only MDD was significantly and positively associated with increased BMI and ^{BMIadj}WHR in the whole sample as well as in the gender stratified samples. Conversely, we observed mixed patterns of effects for SZ and BD. We therefore applied the conjFDR approach to evaluate whether global r_g patterns might mask considerable heterogeneity in the bivariate local r_g across the genome.

We observed substantial gender differences in terms of global genetic correlation, number of identified loci, number of loci with concordant direction and genes to which genomic loci were mapped. When evaluating loci with concordant direction of effect (i.e. loci associated with increased predisposition to mental disorders and increased BMI or ^{BMIadj}WHR), we found loci associated with increased predisposition to SZ or MDD and increased BMI in women (but not in men) to be enriched for a number of GO terms related to neuronal functions.

These results have to be interpreted in light of some limitations. First, common genetic variants only explain a small part of the comorbidity between mental and metabolic disorders. Indeed, several psychotropic drugs used for the management of mental disorders have relevant metabolic adverse effects. Lifestyle factors such as diet, physical activity and alcohol intake also play a relevant role. These factors might also be affected by gender. However, our results suggest that shared genetic determinants might also play a role in the observed increased frequency of metabolic disorders in patients with severe mental disorders and that some of these shared genetic determinants are gender-specific. Future developments of this work might include replication of the identified loci with a different analytical method that estimates local genetic correlation between different traits and allows to evaluate the effect of potential confounding phenotypes (e.g. inflammatory markers, exposure or response to medication).

4 Conclusions and future directions

In this work, we used different experimental and analytical approaches to investigate molecular and genetic determinants of severe mental disorders, with a specific focus on cellular aging and pleiotropy. We explored different aspects of cellular aging in severe mental disorders, such as its interplay with inflammatory markers and the role of genetic factors regulating TL. While the hypothesis of a relationship between reduced TL and severe mental disorders is corroborated by a number of studies, our transdiagnostic approach allowed to observe substantial differences between disorders. We observed shorter TL to characterize patients with MDD and SZ, while patients with BD showed longest TL compared to non-psychiatric controls. We hypothesize this finding to be related to the fact that all patients were treated with lithium at the time of sampling, as this mood stabilizer has been previously hypothesized to exert neuroprotective properties and a counteractive effect on telomere shortening [68-70, 108]. However, genetic factors might also play a role. To explore this hypothesis, we investigated the potential interplay between genetic variants, severe mental disorders and LTL using the largest available genome-wide summary statistics. All three severe mental disorders showed substantial pleiotropy with genetically-determined LTL, but we observed different scenarios based on the investigated disorder as regards to the direction of effect of the identified variants. As regards to BD, among the 18 genetic variants we found to be shared between this disorder and LTL, 11 were associated with increased predisposition to BD while exerting a protective effect on telomere shortening. Intriguingly, some of these variants might be able to affect mechanisms involved in the neuroprotective effects of lithium. To this regard, different SNPs that we found to be associated with both BD and LTL, acts as eQTLs and are therefore able to affect gene expression in different brain regions. The T allele of the rs12629701 SNP, which we observed to be associated with increased predisposition to BD and longer LTL, increases expression of different genes, including the guanine nucleotide-binding protein-like 3 (GNL3) gene in cerebellum, frontal cortex, hypothalamus and putamen. Intriguingly, the *GNL3* gene is located in a locus on chromosome 3 which has been recently shown to be associated with

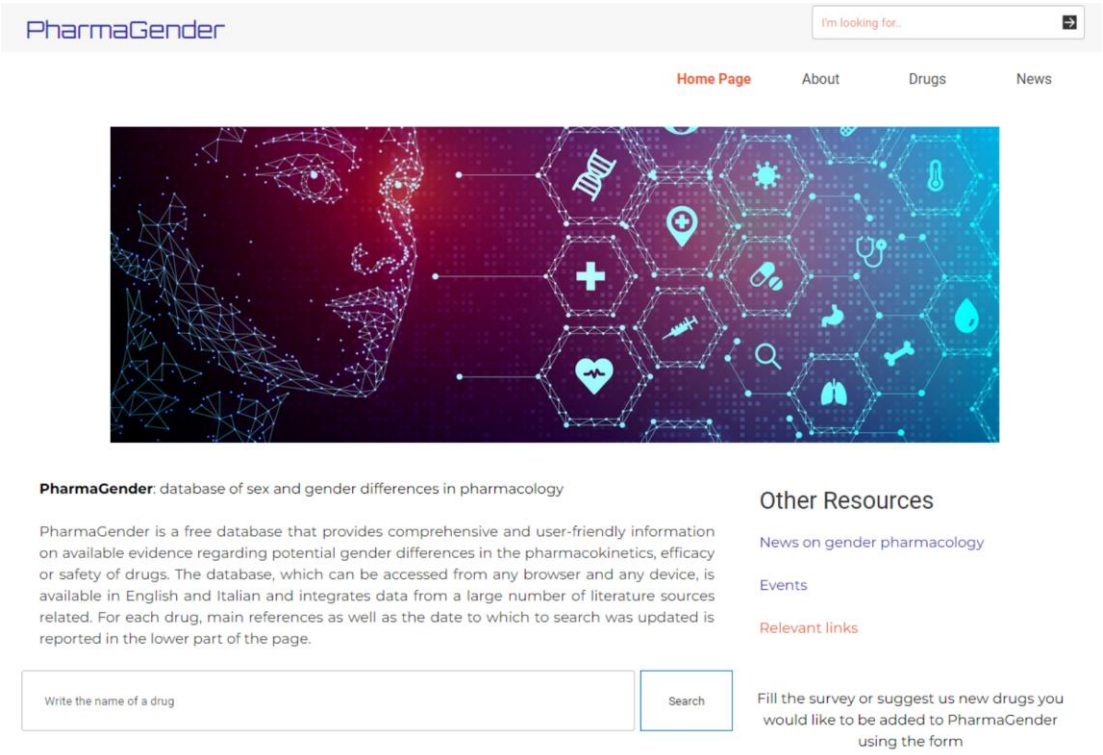
lithium-induced proliferation. Specifically, increasing the expression of *GNL3* using clustered regularly interspaced short palindromic repeats interference (CRISPRi) in primary human neural precursors cells (NPC) from fetal brain tissue has been shown to increase NPC proliferation in response to lithium [224]. Conversely, decreasing expression of *GNL3* decreased lithium-induced proliferation. Future developments of our study will include testing the moderating effect of the identified genetic variants on the putative protective effects of lithium on accelerated cellular aging in cellular models or peripheral cells derived from patients with BD characterized for lithium response.

Using global genetic correlation analysis, MDD was the only disorder to show a significant negative global genetic correlation with LTL (r_g = -0.11, p = 1.4E-08). Accordingly, the direction of effect of the large majority of shared genetic variants (77%) associated with MDD also predisposed to shorter LTL (thus showing a direction of effect in line with the hypothesis of a genetic predisposition to both MDD and accelerated cellular aging). The high rate of concordance in the direction of effect of variants predisposing to MDD and shorter LTL is in line with the more consistent results reported by studies investigating cellular aging in this disorder. In fact, while controversial results have been reported for BD, the majority of available studies found shorter LTL in patients with MDD compared with controls, as also observed by our group in different and independent samples [31, 105, 225]. However, results from longitudinal studies are needed to further disentangle the potential relationships between cellular aging and depression severity, course and response to psychotropic treatments.

In this thesis, we also conducted two studies using state-of-the-art analytical approaches to investigate shared genetic bases between mental disorders and related traits (risk-taking propensity and the two metabolic traits BMI and ^{BMIadj}WHR). We showed that some of the loci shared between mental disorders and related phenotypes are located in genes part of the druggable genome or clinically actionable, that might be further investigated as potential pharmacological targets. Future developments of these studies will include evaluation of these loci using analytical approaches that

allow to incorporate the effect of potentially confounding traits (e.g. inflammatory markers and exposure to medication). In addition, we plan to validate in the cohort presented in Section 2 the identified pleiotropic loci. In the latter study we showed substantial gender differences in global genetic correlation patterns as well as in the number of specific genetic loci shared between mental disorders and metabolic traits. However, adverse effects of psychotropic medications also play a relevant role in the comorbidity between mental disorders and metabolic disturbances. In order to contribute to spread the knowledge on the importance of sex and gender differences in the efficacy and safety of drugs, we are developing a free resource to access updated information on this relevant topic: the PharmaGender database. The pilot version of this resource has been funded by the "Centro Studi Nazionale su Salute e Medicina di Genere" and is currently being developed (Figure 4.1).

Figure 4.1. PharmaGender database interface



The database will be freely accessible from computers, tablets or smartphones and will contain curated information on sex and gender differences in the pharmacokinetics, efficacy and safety of

drugs. Information will be extracted from the summary of product characteristics as well as from a systematic review of the scientific literature.

To conclude, accelerated cellular aging and inflammation might play a role in the pathogenesis of severe mental disorders as well as in response to pharmacological treatment. Elucidating the shared genetic bases between severe mental disorders and genetically predicted markers of cellular aging, as well as age-related disorders such as metabolic disturbances, might allow us to discover novel drug targets and define subgroups of patients that might benefit of more tailored treatment strategies, moving toward precision medicine in severe mental disorders.

Appendix Table 1. Functional characterization of independent genomic loci associated with bipolar disorder and risk-taking propensity

							Significant eQTL in GTEx V. 8	
SNP	**Nearest gene (Kb)**	**RegDB Rank**	**CADD Score**	**Druggable categories**	**Drug-gene interactions**	**Specificity**	**Gene**	**Brain region**
rs1746662	*FNDC5*	4	13.09	Druggable genome	-	BD	*RP5-1174N9.2* *S100PBP*	Caudate, whole blood Whole blood
rs12138864	*PHC2*	1f	1.66	-	-	BD	*A3GALT2*	Cerebellum, whole blood
rs12096927	*RIMKLA* (4.6)	5	10.66	-	-	BD	-	-
rs2367724	*KDM4A* (8.4)	5	1.17	Druggable genome	CHEMBL2094532, CHEMBL1504762, pralidoxime iodide, ranolazine hydrochloride, CHEMBL1255836, minaprine hydrochloride, CHEMBL502057, cycloheterphyllin, CHEMBL1728638, CHEMBL256062	BD, SZ, ADHD	*ARTN* *CCDC24*	Cerebellum Whole blood
rs1417364	*NRD1:RP4-657D16.3*	5	1.01	Druggable genome	-	BD	*TXNDC12*	Whole blood
rs182823	*NFIA*	5	2.71	-	-	BD	-	-
rs11210099	*RP4-660H19.1* (64.7)	6	5.64	-	-	BD, SZ, ADHD	-	-
rs34194740	*RGS8 (4.4)*	3a	2.08	-	CHEMBL1917204	BD	*APOBEC4*	Cerebellum
rs823130	*NUCKS1*	4	1.39	-	-	BD, SZ	*PM20D1* *RAB29* *SLC41A1* *NUCKS1* *RAB7B*	Anterior cingulate, caudate, cortex, frontal cortex, hippocampus, hypothalamus, NAc, putamen, spinal cord, substantia nigra, whole blood Cerebellum, hypothalamus, whole blood Cerebellum, hippocampus, whole blood Cerebellum, whole blood NAc
rs4146671	*SDCCAG8*	7	6.01	-	-	BD, SZ	*SDCCAG8*, *CEP170*	Whole blood Whole blood
rs11124327	*AC068490.2*	7	2.34	-	-	BD, SZ, ADHD	-	-
rs35605321	*CENPA* (14.7)	5	0.83	-	-	BD, SZ	-	-
rs2194464	*GALNT14*	5	1.99	-	Mitoxantrone, sorafenib, cisplatin, fluorouracil	BD	-	-
rs55951536	*CAMKMT*	5	1.46	-	-	BD	*CAMKMT*	Whole blood
rs7591022	*EML6*	5	0.06	-	-	BD	-	-
rs1433309	*AC092568.1* (51.4)	7	4.71	-	-	BD	-	-

rs73041394	*ZNF804A*	5	9.69	-	Lithium	BD, SZ	-	-
rs55811672	*MAP2 (19.0)*	7	2.89	-	Estramustine, melatonin, docetaxel, colchicine, paclitaxel	BD	-	-
rs2047134	*CUL3*	3a	2.16	Clinically actionable	-	BD, SZ	*CUL3*	Cortex, hippocampus
rs1288974	*FOXP1*	3a	1.11	Clinically actionable	-	BD	-	-
rs9831123	*CADM2*	5	0.77	-	Alcohol	BD, SZ, ADHD	*CADM2*	Caudate, putamen
rs9681407	*MIR4795* (65.3)	5	0.15	-	-	BD	*POU1F1* *CHMP2B*	Putamen Whole blood
rs836927	*RP11-115H18.1* (18.7)	5	0.65	-	-	BD, SZ	*LINC01990*	Caudate, putamen, NAc
rs326359	*CD47 (10.8)*	4	0.08	Druggable genome	ALX-148, magrolimab, ABT-510	BD	*CD47, IFT57*	Whole blood
rs12054405	*RP11-442N1.1* (38.2)	3a	6.12	-	-	BD	-	-
rs359544	*PLCH1*	5	0.14	Druggable genome	-	BD	-	-
rs4350923	*RP11-208P4.1* (1.5)	5	4.67	-	-	BD	-	-
rs4434184	*SOX2-OT*	3a	20.30	Clinically actionable	-	BD	-	-
rs535066	*RP11-320H14.1* (5.3)	6	0.33	-	-	BD, SZ	*GABRA2*	Hypothalamus
rs2647256	*TET2* (0.6)	4	3.36	-	Decitabine, azacitidine, hydrochlorotiazide	BD	-	-
rs11737121	*SLC10A7*	5	3.38	-	-	BD	-	-
rs7696225	*SORBS2*	5	4.68	-	-	BD	-	-
rs201587781	*EMB* (213.4)	7	6.29	-	-	BD, SZ	-	-
rs13163662	*KCNN2*	5	0.78	Druggable genome	Apamin, tubocurarine, dequalinium	BD	-	-
rs13169274	*ETF1*	7	1.38	-	-	BD, SZ	*ETF1*	Whole blood
rs76157183	*TCERG1*	5	0.08	-	-	BD	-	-
rs10053762	*AC091969.1*	5	5.06	-	-	BD, SZ	*LINC01470*	Caudate
rs2195450	*GRIA1*	4	16.32	-	Perampanel, talampanel, piracetam, CX516, tianeptine, tezampanel, NBQXM, zonampanel, MK-8777, selurampanel	BD	-	-
rs10068495	*EBF1*	7	1.28	Clinically actionable	-	BD	-	-
rs852944	*RP1-288M22.2*	6	0.80	-	-	BD	-	-
rs1487445	*RP11-436D23.1*	5	3.27	-	-	BD	-	-
rs7739294	*GOPC*	5	7.63	-	-	BD	*DCBLD1*	Whole blood

rs6557271	*RGS17*	5	3.94	-	-	BD	*RGS17*	Cerebellum
rs11768212	*MAD1L1*	2b	2.05	-	Paclitaxel, carbotaxel	BD, ADHD	*MRM2* *AC110781.3*	Caudate NAc
rs117450257	*SLC12A9:RP11-126L15.4*	5	0.14	Druggable genome	-	BD, SZ	-	-
rs2470943	*RP11-325F22.2*	5	0.14	-	-	BD, SZ	*RP11-325F22.2* *LHFPL3-AS2*	Whole blood Whole blood
rs10251192	*RP11-222O23.1* (117.0)	7	0.45	-	-	BD, SZ	-	-
rs7785663	*DGKI*	6	1.57	-	-	BD, SZ	-	-
rs80274100	*RAB19*	6	3.88	-	-	BD	-	-
rs2924726	*CSMD1*	5	0.30	-	Hydrochlorothiazide, oxaliplatin	BD	-	-
rs10106054	*RP11-468H14.2*	6	1.33	-	-	BD		
rs78035175	*RP11-98P2.1* (19.0)	5	2.56	-	-	BD	-	-
rs16883443	*AC098612.1* (56.4)	6	0.31	-	-	BD		
rs11777067	*FGFR1*	1f	4.41	Druggable genome	CHEMBL89363, CHEMBL1231606, palifermin; rogaratinib, pemigatinib, FP-1039, E-7090, derazantinib, erdafitinib	BD, SZ	*RPS20P22* *PLPP5* *DDHD2* *BAG4* *RP11-350N15.5*	Cerebellum Cerebellum, cortex, NAc Cerebellum, NAc Whole blood Whole blood
rs10957894	*SNTG1*	5	1.87	-	-	BD	-	-
rs7813444	*RP11-21C4.4* (29.3)	6	5.15	-	-	BD, SZ	-	-
rs4623479	*RUNX1T1*	7	0.68	Clinically actionable	-	BD, ADHD	*RUNX1T1*	Putamen
rs7011741	*RP11-25D10.2* (18.3)	5	1.47	-	-	BD	-	-
rs34853464	*TSNARE1*	5	1.07	-	-	BD, SZ	-	-
rs6474852	*FREM1*	5	3.96	Druggable genome	-	BD	*CER1*	Cerebellum
rs10967586	*RN7SL100P*	5	8.63	-	-	BD, SZ	*CAAP1* *IFT74*	Cerebellum Cortex
rs10821122	*RNU6-829P* (19.8)	6	0.29	-	-	BD, SZ	*RP11-165J3.6*	Whole blood
rs9888039	*PCDH15*	5	1.03	-	-	BD	-	-
rs7085104	*C10orf32-ASMT*	4	8.18	-	Melatonin	BD, SZ	*AS3MT*	Amygdala, anterior cingulate, caudate, cerebellum, cortex, frontal cortex, hippocampus, hypothalamus, NAc, putamen, spinal cord, substantia nigra, whole blood
							BORCS7	Anterior cingulate, caudate, cerebellum, cortex, frontal cortex, hippocampus, hypothalamus, NAc, putamen, spinal cord, substantia nigra, whole blood
							RPARP-AS1	Caudate, accumens

							RPL22P17	Cerebellum
							RP11-724N1.1	Cerebellum
							ARL3	Cerebellum
							CALHM2	Whole blood
							CNNM2	Whole blood
rs12761679	*SORCS3*	6	4.17	-	-	BD, SZ, ADHD	-	-
rs12359871	*RPS27P18* (50.8)	5	0.90	-	-	BD	-	-
rs10082688	*ARNTL* (31.3)	7	0.16	-	-	BD	-	-
rs11038655	*CTD-2210P24.4* (13.2)	7	1.13	-	-	BD	*CTD-2210P24.4*	Caudate, putamen
rs11227478	*RP11-867G23.10* (3.2)	5	0.31	-	-	BD	*RP11-867G23.8*	Cerebellum
							RP11-867G23.10	
							RP11-755F10.1	Cerebellum
							LRFN4	Cerebellum, NAc, putamen
							CTSF	Cerebellum, whole blood
								Whole blood
rs4988321	*LRP5*	4	24.40	-	-	BD	-	-
rs10831015	*GRM5*	6	2.11	Druggable genome	Dipraglurant, raseglurant, basimglurant, STX107, AZD2066, RG7342, mavoglurant, CHEMBL2164552, CHEMBL2164551, CHEMBL292065	BD	-	-
rs7932899	*CNTN5*	7	0.80	-	-	BD	-	-
rs61909095	*CACNA1C*	3a	0.13	Druggable genome	Barnidipine, lacidipine, drotaverine, benidipine, manidipine, ritodrine, isradipine, levamlodipine, clevidipine, efonidipine	BD, SZ	-	-
rs10842271	*SOX5* (129.9)	3a	0.83	-	-	BD	-	-
rs7959452	*LYZ* (6.6)	5	0.24	-	Propanol, triacetylchitotriose, chitodextrin, CHEMBL541253, arsanilic acid, sucrose, aspartic acid	BD	*YEATS4*	Anterior cingulate, caudate, cerebellum, cortex, frontal cortex, hippocampus, hypothalamus, NAc, putamen, whole blood
							LYZ	Caudate, cortex, hippocampus, putamen, spinal cord, whole blood
							RP11-1143G9.5	Whole blood
rs11178282	*PTPRB*	5	2.52	Druggable genome	CHEMBL379000, razuprotafib, sunitinib	BD	-	-
rs3764002	*WSCD2*	4	28.10	-	-	BD, ADHD	-	-
rs3885907	*ALOX5AP*	4	2.17	-	Fiboflapon, fiboflapon sodium	BD	*ALOX5AP*	Whole blood
rs7139704	*GNG5P5* (155.0)	4	3.02	-	-	BD	-	-
rs34012672	*NPAS3* (9.8)	5	0.68	-	-	BD, SZ, ADHD	-	-

rs3007061	*MDGA2* (70.2)	3a	7.07	-	Milnacipram, fluvoxamine, paroxetine	BD, ADHD	*MDGA2*	Cerebellum
rs8005321	*SYT16*	4	0.33	-	-	BD		
rs72703614	*FOXN3*	5	2.67	-	-	BD		
rs12892189	*LINC00637*	4	1.95	-	-	BD, SZ	*PPP1R13B* *APOPT1* *XRCC3* *KLC1* *RP11-73M18.8* *TDRD9* *BAG5*	Caudate Caudate, hippocampus Whole blood Whole blood Whole blood Whole blood Whole blood
rs4924676	*ZNF106*	3a	2.09	Druggable genome	-	BD, SZ	*GANC* *CAPN3*	Anterior cingulate, putamen, whole blood Cerebellum, whole blood
rs4327001	*CD276* (3.4)	2a	0.51	Druggable genome	Enoblituzumab	BD	*C15orf59-AS1*	Spinal cord
rs12442456	*IREB2*	6	0.00	-	-	BD, SZ	-	-
rs2071382	*FES*	4	10.02	Druggable genome	Lorlatinib, hesperadin, dasatinib, SP-600125, fostamatinib, linifanib	BD, SZ	*FES*	Whole blood
rs6500948	*RBFOX1*	3a	0.17	-	-	BD, SZ	-	-
rs2352759	*GRIN2A*	4	7.46	Druggable genome	Memantine, philanthoxin, dizocilpine, dextromethorphan, tenocyclidine, felbamate, dextromethorphan, glycine, selfotel, N-Methyl-D-Aspartic Acid	BD	-	-
rs62029337	*PRKCB* (27.2)	3a	1.58	Druggable genome	Phosphorylethanolamine, tocopherol acetate, (+)-alpha-tocopheryl succinate, enzastaurin, ruboxistaurin, vitamin E, bisindolymaleimide IX, bryostatin, enoxolone, sincalide	BD	-	-
rs55910718	*GINS3* (60.0)	3a	3.20	-	-	BD	-	-
rs7219635	*YWHAE*	2a	1.06	-	CHEMBL4244843, insulin, phenethylisothiocyanate	BD, SZ	-	-
rs112562460	*TANC2:AC037445.1*	5	4.81	-	-	BD	*CYB561* *TANC2*	Caudate, cortex, frontal cortex, NAc, putamen Cerebellum
rs9636107	*TCF4*	5	5.05	-	-	BD, SZ	-	-
rs12928	*PQLC1*	5	1.62	-	-	BD, SZ	*AC139100.3* *PQLC1*	Cortex Whole blood
rs1736182	*THOP1*	4	2.65	Druggable genome	Nemonoxacin, icofungipen, karenitecin	BD	*THOP1* *ZNF554*	Cerebellum Cerebellum
rs2304204	*IRF3:BCL2L12*	4	11.47	-	-	BD, SZ	*IRF3* *PRR12* *CPT1C*	Cerebellum, hypothalamus Cerebellum, frontal cortex Cerebellum

rs1291112	*RN7SL156P* (1.4)	4	12.07	-	-	BD	-	-
rs12624433	*SLC12A5*	2a	4.24	Druggable genome	Bumetanide	BD	*SLC12A5* *CD40*	Caudate, hippocampus, putamen Cerebellum, whole blood
rs404060	*XXbac-B444P24.8* (21.9)	1f	2.01	-	-	BD	-	-
rs13055562	*SHANK3*	5	2.37	-	-	BD	*RABL2B*	Whole blood

The table reports functional characterization for the 102 linkage disequilibrium independent genomic loci associated with bipolar disorder and risk-taking propensity at a conjFDR < 0.05. Nearest gene and functional category have been annotated using FUMA (for SNPs located in intergenic regions, distance in Kb from the nearest gene is also reported). The RegBD rank (from 1 to 7, with 1 being associated with highest evidence of functional effects) was calculated using RegulomeDB based on known and predicted regulatory elements including regions of DNase hypersensitivity, binding sites of transcription factors and promoter regions that regulate transcription. The CADD score, which predicts how deleterious a variant is on protein structure/function was computed in FUMA, based on 63 annotations. Higher scores indicate more deleterious SNP, with a suggested threshold of 12.37 for a SNP to be considered deleterious. Nearest genes were searched in DGIdb in order to assess whether they are part of the druggable genome (druggable categories) or known targets of drugs (drug-gene interactions). In case more than 10 drug-gene interactions were found, the top 10 based on their interaction score in DGIdb are reported. The specificity reports whether the locus has been found to be specific for BD and risk or if it was detected in the analyses between SZ and risk or ADHD and risk at a conjFDR < 0.05. In case the SNP is reported to be a significant eQTL in GTEx v.8 in brain regions or whole blood, the last two columns report regulated genes and relative regions.

Abbreviations: ADHD, attention deficit hyperactivity disorder; BD, bipolar disorder; NAc, nucleus accumbens; SNP, single nucleotide polymorphism; RegBD, Regulome DB, SZ, schizophrenia

Appendix Table 2. Functional characterization of independent genomic loci associated with bipolar disorder after conditioning on risk-taking propensity at condFDR < 0.01

SNP	Position	Nearest gene (Kb)	Functional category	A1 / A2	beta BD	p BD	condFDR BD|risk	RegDB Rank	CADD Score	Druggable categories	Drug-gene interactions	Novel	Specific
rs10917509	1:19992066	*HTR6*	UTR5	T/C	0.05	7.3E-08	5.2E-03	2b	7.91	Druggable genome	Cyproheptadine, risperidone, fluperlapine, loxapine, amoxapine, idalopirdine, amitriptyline, cerlapiridine, metitepine, BRL-15,572	Yes	BD
rs1284373	1:33355923	*HPCA*	intronic	T/C	-0.05	5.1E-05	9.5E-03	3a	0.95	-	-	Yes	BD, SZ
rs61774748	1:41841503	*FOXO6*	intronic	T/G	-0.05	9.8E-07	3.0E-03	6	17.19	-	-	1	BD, SZ
rs2126180	1:61105668	*RP11-776H12.1*	ncRNA	A/G	0.06	1.6E-09	1.7E-04	3a	1.00	-	-	2	BD, SZ
rs11210099	1:73429567	*RP4-660H19.1* (64.7)	intergenic	T/C	0.05	1.1E-06	8.9E-04	6	5.64	-	-	3	BD, SZ, ADHD
rs483252	1:108510358	*VAV3-AS1*	ncRNA	A/C	-0.06	9.9E-07	7.3E-03	3a	5.74	-	Setipiprant, carbacyclin, iloprost, AM-461, cloprostenol, vidupiprant, asapiprant, nedocromil, dinoprostone, treprostinil	Yes	BD
rs67050019	1:154267953	*RNU6-239P* (0.03)	upstream	A/G	0.08	3.7E-07	4.5E-03	5	6.76	-	-	Yes	BD
rs4845399	1:154866093	*KCNN3* (23.3)	intergenic	T/C	0.06	5.6E-08	8.2E-03	5	4.11	Druggable genome	Dequalinium, riluzole, tubocurarine, apamin	Yes	BD, SZ
rs10737496	1:163745389	*RP4-640E24.1* (6.5)	intergenic	T/C	-0.05	7.2E-09	1.4E-04	5	5.80	-	-	2	BD, SZ
rs4915346	1:199122192	*RP11-382E9.1*	ncRNA	A/G	-0.05	1.3E-05	6.6E-03	5	11.13	-	-	Yes	BD
rs733760	2:21534298	*AC067959.1*	ncRNA	T/G	-0.05	7.2E-08	4.5E-03	5	0.81	-	-	4	BD, SZ
rs2339519	2:22604140	*AC068490.2:AC096570.2*	ncRNA	A/G	0.05	1.9E-07	1.9E-03	6	5.46	-	-	4	BD, SZ, ADHD
rs1506536	2:28182006	*MRPL33:BRE*	intronic	T/C	-0.05	4.6E-07	9.6E-04	3a	18.95	-	-	1	BD, SZ
rs57681866	2:57975714	*CTD-2026C7.1* (6.9)	intergenic	A/G	-0.10	2.3E-07	2.7E-03	5	18.49	-	-	5	BD, SZ
rs4619651	2:97416153	*LMAN2L* (10.4)	intergenic	A/G	-0.07	4.8E-11	5.1E-05	5	0.83	-	-	5	BD, SZ
rs17183814	2:166152389	*SCN2A*	exonic	A/G	-0.10	2.7E-08	1.9E-03	5	19.83	Druggable genome	Chloroprocaine hydrochloride, BKTR-171, elpetrigine, mexiletine hydrochloride, ethotoin, hexylcaine hydrochloride, orphenadrine hydrochloride, evenamide, lidocaine hydrochloride, procaine hydrochloride	5	BD
rs1869374	2:169481472	*CERS6*	intronic	T/G	-0.06	3.7E-08	1.7E-03	7	1.23	-	-	2	BD
rs4972439	2:175261443	*SCRN3*	intronic	T/C	0.06	4.3E-07	8.0E-03	4	1.50	-	-	Yes	BD
rs6433891	2:181969709	*AC068196.1:AC104820.2*	ncRNA	A/G	0.05	1.6E-07	3.1E-03	4	13.00	-	-	Yes	BD

rs1429423	2:185868877	*ZNF804A* (864.7)	intergenic	T/C	-0.06	3.9E-07	4.0E-04	6	2.29	-	Lithium	6	BD, SZ
rs13014947	2:193742999	*PCGEM1* (101.4)	intergenic	A/G	-0.05	1.1E-07	7.5E-03	7	4.67	-	-	5	BD, SZ
rs2719164	2:194437889	*AC074290.1* (157.4)	intergenic	A/G	0.05	4.8E-08	5.7E-03	5	0.30	-	-	5	BD, SZ
rs139272730	2:211182602	*MYL1* (2.7)	intergenic	T/C	-0.17	1.7E-07	6.3E-03	6	0.08	-	-	Yes	BD, SZ
rs4676412	2:241553492	*CAPN10:GPR35*	intronic	A/G	0.06	7.6E-08	7.8E-03	4	0.11	Druggable genome	Metformin, tacrolimus, zaprinast, lodoxamide, bumetanide, furosemide, CHEMBL1256291, CHEMBL107513, luteolin, myricetin	Yes	BD
rs7644022	3:10510618	*ATP2B2*	intronic	A/C	0.05	2.5E-07	6.2E-03	5	3.51	Druggable genome	-	Yes	BD
rs4328757	3:36938180	*TRANK1*	intronic	T/C	0.07	8.4E-13	5.1E-08	5	1.09	-	-	5	BD, SZ
rs59212827	3:44769620	*ZNF501* (1.5)	intergenic	A/G	-0.05	4.0E-07	8.1E-03	7	0.03	-	-	1	BD
rs2276834	3:52325759	*GLYCTK-AS1*	splicing	A/G	0.06	2.1E-11	2.5E-06	2b	14.80	-	-	7	BD, SZ
rs6806239	3:70488207	*RP11-231I13.2* (126.4)	intergenic	T/G	0.07	2.6E-08	7.1E-04	6	2.78	-	-	2	BD, SZ
rs4452341	3:85787986	*CADM2*	intronic	A/G	-0.05	1.1E-06	8.8E-04	5	1.26	-	Alcohol	8	BD, SZ, ADHD
rs7621447	3:86684769	*RP11-331K15.1* (138.6)	intergenic	A/C	0.04	4.0E-05	8.0E-03	7	0.33	-	-	8	BD, SZ, ADHD
rs696366	3:107757060	*CD47* (5.1)	intergenic	A/C	-0.05	4.5E-08	7.0E-05	5	1.80	Druggable genome	ALX-148, magrolimab, ABT-150	5	BD, SZ
rs78104110	3:114133266	*ZBTB20*	intronic	T/C	-0.13	2.1E-07	1.4E-03	5	5.22	-	-	Yes	BD
rs67428377	3:155354340	*PLCH1*	intronic	A/C	-0.05	2.2E-05	5.8E-03	5	1.18	Druggable genome	-	Yes	BD, SZ
rs10937241	3:185822774	*ETV5*	intronic	A/G	-0.06	4.3E-06	9.8E-03	5	0.67	Druggable genome	Trametinib	9	BD
rs535066	4:46240287	*RP11-320H14.1* (5.3)	intergenic	T/G	0.05	1.7E-06	1.2E-03	6	0.33	-	-	Yes	BD, SZ
rs2651566	4:101507968	*EMCN* (68.1)	intergenic	A/G	-0.04	4.3E-06	9.0E-03	7	2.23	-	-	Yes	BD
rs2647256	4:106201556	*TET2* (0.6)	downstream	T/C	0.05	6.1E-06	2.7E-03	4	3.36	-	Decitabine, azacitidine, hydrochlorothiazide	Yes	BD, SZ
rs2635209	4:118425913	*AC092661.1*	ncRNA	T/C	-0.05	6.1E-08	8.0E-03	7	0.65	-	-	10	BD
rs112481526	4:123076007	*KIAA1109*	intronic	A/G	-0.06	1.9E-09	7.0E-04	5	2.04	-	-	2	BD
rs11737121	4:147268639	*SLC10A7*	intronic	A/G	-0.06	1.8E-05	5.0E-03	5	3.38	-	-	Yes	BD, SZ
rs28565152	5:7542911	*ADCY2*	intronic	A/G	0.07	2.0E-09	1.7E-04	5	0.43	Druggable genome	CHEMBL401844, colfrosin, aurothioglucose, capecitabine	5	BD
rs6865469	5:78849505	*Y_RNA* (18.7)	intergenic	T/G	0.06	1.7E-08	4.6E-03	5	4.46	-	-	2	BD
rs6887473	5:80961069	*SSBP2*	intronic	A/G	-0.06	8.8E-09	2.7E-03	6	3.07	-	-	5	BD
rs12519857	5:113733109	*KCNN2*	intronic	T/G	0.04	2.6E-05	6.8E-03	7	2.10	Druggable genome	Apamin, tubocurarine, dequalinium	Yes	BD, SZ
rs13169274	5:137855305	*ETF1*	intronic	T/C	-0.04	2.0E-05	5.5E-03	7	1.38	-	-	2	BD, SZ

rs75623709	5:145870577	*TCERG1*	intronic	T/G	-0.07	5.9E-06	3.2E-03	6	2.71	-	-	Yes	BD, SZ
rs4958592	5:152288222	*AC091969.1*	ncRNA	A/G	-0.04	8.3E-06	9.4E-03	5	0.02	-	-	10	BD, SZ
rs7702334	5:165701326	*CTB-63M22.1* (108.0)	intergenic	T/G	-0.04	4.5E-06	6.2E-03	7	5.72	-	-	3	BD
rs72841199	5:169284998	*DOCK2*	intronic	A/G	0.06	2.9E-11	3.2E-05	6	15.42	-	-	2	BD
rs829473	6:72440951	*RNU4-66P* (78.6)	intergenic	A/C	-0.04	1.6E-05	5.5E-03	6	1.00	-	-	5	BD, SZ
rs13208578	6:98572976	*RP11-436D23.1*	intronic	T/C	0.07	4.7E-13	2.3E-08	5	13.04	-	-	1	BD, SZ
rs9371601	6:152790573	*SYNE1*	intronic	T/G	0.05	7.0E-08	4.0E-03	6	0.81	-	-	11	BD, SZ
rs6927659	6:153397299	*RGS17*	intronic	T/G	0.05	1.5E-06	1.1E-03	7	2.06	-	-	11	BD, SZ
rs6456095	6:166984094	*RPS6KA2*	intronic	T/C	-0.06	5.6E-09	2.0E-03	6	3.62	Druggable genome	CHEMBL573107	5	BD
rs12154473	7:1982181	*MAD1L1*	intronic	A/G	-0.06	2.4E-09	6.7E-04	4	1.36	-	Paclitaxel, carboplatin	12	BD, SZ, ADHD
rs113779084	7:11871787	*THSD7A*	UTR5	A/G	0.08	1.4E-13	5.6E-06	4	16.30	-	-	5	BD
rs6954854	7:21492589	*SP4*	intronic	A/G	-0.06	5.9E-10	4.2E-05	7	5.05	-	-	2	BD
rs12672003	7:24647222	*MPP6*	intronic	A/G	-0.09	2.7E-09	2.9E-05	6	1.30	-	-	2	BD, SZ
rs11770210	7:29993998	*SCRN1*	intronic	A/G	0.07	6.4E-08	8.6E-03	5	1.14	-	-	Yes	BD
rs10487648	7:82583609	*PCLO*	exonic	A/C	-0.06	7.8E-07	9.3E-03	6	13.19	Clinically actionable	-	13	BD, SZ
rs117450257	7:100446237	*SLC12A9:RP11-126L15.4*	ncRNA	A/G	-0.11	2.6E-06	1.6E-03	5	0.14	Druggable genome	-	1	BD, SZ
rs11764361	7:105043229	*SRPK2* (3.5)	intergenic	A/G	0.06	3.5E-09	1.6E-04	5	14.76	Druggable genome	Purvalanol B, adenine	5	BD, SZ
rs62474680	7:115016799	*RP11-222O23.1* (126.6)	intergenic	A/G	-0.06	6.8E-08	9.9E-05	5	2.81	-	-	Yes	BD, SZ
rs6946056	7:131870597	*PLXNA4*	intronic	A/C	-0.05	3.7E-08	3.4E-03	4	0.12	-	-	2	BD, SZ
rs10255167	7:140676153	*CCT4P1* (21.6)	intergenic	A/G	0.07	1.6E-08	2.8E-03	4	0.94	-	-	5	BD, SZ
rs6557904	8:26106100	*RP11-98P2.1* (6.3)	intergenic	T/C	-0.10	4.0E-05	8.0E-03	2b	0.39	-	-	Yes	BD, SZ
rs73560982	8:34214305	*RP1-84O15.2* (10.1)	intergenic	T/C	-0.12	6.6E-09	1.8E-03	5	1.54	-	-	2	BD, SZ
rs7813444	8:65437506	*RP11-21C4.4* (29.3)	intergenic	A/G	0.04	3.5E-05	7.5E-03	6	5.15	-	-	Yes	BD, SZ
rs34853464	8:143363277	*TSNARE1*	intronic	T/C	0.04	1.6E-05	4.7E-03	5	1.07	-	-	14	BD, SZ
rs6992333	8:144993377	*PLEC*	exonic	A/G	-0.06	1.6E-09	9.0E-04	4	3.77	-	-	2	BD
rs10973223	9:37121837	*ZCCHC7*	intronic	T/C	-0.06	2.2E-07	5.4E-03	3a	0.37	-	-	2	BD, SZ
rs10869262	9:76102010	*RP11-404E6.1* (11.0)	intergenic	A/G	0.05	7.8E-08	9.0E-03	7	1.19		-	Yes	BD
rs11137399	9:141068624	*TUBBP5*	ncRNA	T/C	-0.07	2.9E-08	1.4E-04	4	2.51	Druggable genome	-	2	BD
rs10828679	10:18711288	*CACNB2*	intronic	A/G	0.08	6.2E-08	5.8E-03	4	1.14	-	Isradipine, nimodipine, felodipine, nisoldipine, gabapentin, bepridil hydrochloride, nifedipine, nilvadipine, atagabalin, imagabalin	2	BD, SZ

rs2154393	10:62326687	*ANK3*	intronic	T/C	0.12	1.2E-11	6.2E-06	5	0.77	-	-	5	BD
rs10761661	10:64525135	*ALDH7A1P4* (24.0)	intergenic	T/C	0.05	4.6E-08	2.9E-03	5	0.05	-	-	2	BD, SZ
rs2496038	10:106511954	*SORCS3*	intronic	T/G	0.05	2.6E-06	1.6E-03	6	1.83	-	-	10	BD, SZ, ADHD
rs2273738	10:111648659	*XPNPEP1*	intronic	T/C	0.09	1.6E-11	7.2E-06	6	1.85	-	Tosedostat	5	BD
rs1351522	11:13268386	*ARNTL* (29.8)	intergenic	T/C	-0.04	2.4E-06	1.5E-03	7	1.12	-	-	8	BD, SZ
rs1482742	11:23250967	*RP11-266A24.1* (26.3)	intergenic	T/G	-0.04	2.3E-05	9.6E-03	7	2.52	-	-	Yes	BD, SZ
rs144225206	11:45844797	*CTD-2210P24.6*	ncRNA	A/G	0.08	5.0E-06	3.1E-03	5	2.45	-	-	Yes	BD, SZ
rs174594	11:61619829	*FADS2*	intronic	A/C	-0.07	4.4E-13	5.9E-06	5	2.05	-	Linolenic acid	5	BD
rs4672	11:64009879	*FKBP2*	exonic	A/G	0.10	3.4E-09	9.1E-04	4	20.50	-	-	2	BD
rs12577917	11:66182417	*RP11-867G23.10*	ncRNA	T/C	0.05	3.7E-08	2.8E-04	2b	0.65	-	-	5	BD, SZ
rs11602121	11:70559878	*SHANK2*	intronic	T/C	-0.06	2.2E-10	8.9E-05	2b	2.85	-	-	5	BD
rs12289486	11:79092527	*TENM4*	intronic	T/C	0.08	3.3E-08	2.5E-03	5	6.82	-	-	15	BD
rs308800	11:88230512	*GRM5-AS1:GRM5* (7.2)	intergenic	T/C	0.06	2.5E-06	3.0E-03	5	0.33	-	Dipraglurant, CHEMBL292065, LY54694, raseglurant, basimglurant, CHEMBL88612, CHEMBL381055, acamprosate, AZD2066, rufinamide	3	BD, SZ
rs12806504	11:99089993	*CNTN5*	intronic	A/G	0.06	1.0E-06	2.7E-03	6	6.33	-	-	3	BD, SZ
rs10848637	12:2316554	*CACNA1C*	intronic	A/C	0.07	5.5E-14	2.3E-08	7	7.76	-	Verapamil, nicardipine, amlodipine besylate, elpetrigine, benidipine, imagabalin, isradipine, nifedipine, felodipine, atagabalin	5	BD, SZ
rs75888683	12:79478068	*SYT1*	intronic	T/G	0.12	1.1E-07	6.3E-03	6	3.32	-	Cocaine	Yes	BD
rs17680262	12:110354536	*TCHP*	UTR3	T/C	0.09	2.7E-07	9.5E-03	5	0.53	-	-	4	BD, SZ
rs4075692	13:31323342	*ALOX5AP*	intronic	A/G	0.05	1.3E-07	1.7E-04	6	0.70	-	Fiboflapon	Yes	BD, SZ
rs4884463	13:54035129	*AL450423.1* (93.0)	intergenic	A/G	-0.05	2.9E-07	1.1E-03	2b	2.66	-	-	3	BD
rs7982263	13:80061074	*NDFIP2*	intronic	T/C	-0.05	5.2E-08	3.8E-04	4	0.08	-	-	Yes	BD, SZ
rs35306827	13:113869045	*CUL4A*	intronic	A/G	-0.07	3.6E-09	1.1E-03	4	1.15	Clinically actionable	Lenalidomide, thalidomide, pomalidomide	2	BD
rs11844034	14:33420212	*NPAS3*	intronic	A/G	0.05	1.2E-05	4.0E-03	5	5.67	-	-	16	BD, SZ, ADHD
rs10131905	14:62425610	*CTD-2277K2.1*	ncRNA	A/C	-0.05	8.9E-07	7.5E-04	7	2.88	-	-	Yes	BD, SZ
rs2693698	14:99719219	*BCL11B*	intronic	A/G	-0.05	2.0E-08	4.6E-03	2b	8.09	-	-	2	BD, SZ
rs12892189	14:104319989	*LINC00637*	ncRNA	A/C	0.05	8.2E-07	7.0E-04	4	1.95	-	-	1	BD, SZ
rs35958438	15:38973793	*RP11-275I4.2*	ncRNA	A/G	-0.06	3.8E-08	7.4E-04	5	0.71	-	-	2	BD
rs4447398	15:42904904	*STARD9*	intronic	A/C	0.08	2.6E-09	2.2E-05	4	0.04	-	-	5	BD, SZ
rs72743329	15:74048178	*C15orf59* (3.1)	intergenic	T/C	-0.04	1.5E-05	6.7E-03	4	3.05	-	-	Yes	BD, SZ
rs62011735	15:83581018	*HOMER2*	intronic	A/C	-0.06	2.1E-08	3.2E-03	3a	0.41	-	-	2	BD, SZ

rs748455	15:85149575	*ZSCAN2*	intronic	T/C	0.07	5.0E-11	4.1E-06	5	3.27	-	-	5	BD, SZ
rs4702	15:91426560	*FURIN*	UTR3	A/G	-0.06	3.5E-09	8.0E-06	4	17.36	Druggable genome	Decanoic acid, pirfenidone	2	BD, SZ
rs28455634	16:9230816	*C16orf72* (15.3)	intergenic	A/G	-0.06	2.6E-10	2.5E-04	5	4.35	-	-	2	BD, SZ
rs7201930	16:9958655	*GRIN2A*	intronic	T/C	-0.06	1.9E-08	2.3E-04	3a	0.79	Druggable genome	Neboglamine, amantadine, acamprosate calcium, neramexane mesylate, dizocilpine, N-Methyl-D-Aspartic Acid, dextromethorphan polistirex, indantadol, apimostinel, AV-101	5	BD, SZ
rs17808510	16:23821996	*PRKCB* (25.3)	intergenic	A/G	-0.06	3.3E-05	7.3E-03	7	1.41	Druggable genome	GSK-690693, enzastaurin, midostaurin, ruboxistaurin, CEP-2563, quercetin, balanol, sotrastaurin, CHEMBL1236539, UCN-01	17	BD, SZ
rs11644048	16:29885698	*SEZ6L2*	intronic	A/G	-0.05	5.8E-07	2.3E-03	4	0.44	-	-	Yes	BD, SZ
rs8043792	16:61660554	*CDH8* (20.6)	intergenic	T/C	-0.04	2.0E-06	3.3E-03	6	4.88	-	-	Yes	BD
rs35251956	16:89654800	*CPNE7*	intronic	T/C	-0.06	7.2E-08	1.2E-03	4	0.50	-	-	2	BD
rs9896486	17:1252843	*YWHAE*	intronic	T/G	0.05	5.9E-08	8.9E-05	5	1.95	-	Insulin, Phenethylisothiocyanate, CHEMBL4244843	18	BD, SZ
rs4790841	17:1835482	*RTN4RL1* (2.5)	intergenic	T/C	0.07	3.1E-08	3.1E-03	4	0.15	Druggable genome	-	2	BD, SZ
rs61554907	17:38220432	*THRA*	intronic	T/G	0.09	1.6E-08	9.9E-04	4	15.25	Druggable genome	Liothyronine sodium, dextrothyroxine, sobetirome, liothyronine, liotrix, tiratricol, dextrothyroxine sodium, levothyroxine, dronedarone, lithium	12	BD
rs12940636	17:53400110	*HLF*	UTR3	T/C	-0.05	2.9E-06	2.2E-03	4	20.30	Clinically actionable	-	5	BD, SZ
rs4788865	17:73115508	*ARMC7*	intronic	T/G	-0.05	2.3E-07	6.8E-03	4	3.35	-	-	Yes	BD
rs8090457	18:51539487	*AC090666.1* (73.5)	intergenic	A/G	-0.05	6.6E-08	7.8E-03	6	7.75	-	-	3	BD
rs28865701	18:77620911	*KCNG2* (2.8)	intergenic	A/G	-0.04	7.6E-06	6.9E-03	5	0.20	-	Tedisamil, dalfampridine, nerispiridine, Guanidine hydrochloride	8	BD, SZ
rs1736195	19:2786557	*THOP1*	intronic	T/C	0.05	1.3E-05	4.2E-03	4	5.18	Druggable genome	Nemonoxacin, icofungipen, karenitecin	Yes	BD, SZ
rs7408675	19:13089890	*DAND5* (4.3)	intergenic	A/G	0.05	3.2E-07	7.7E-03	5	0.48	-	Methyldopa	1	BD
rs112219496	19:19358086	*NCAN*	intronic	A/G	0.07	6.4E-08	3.3E-03	5	0.38	-	Hyalunorate sodium, dextrose, thiodigalactoside	5	BD, SZ
rs67712855	20:43682551	*STK4*	intronic	T/G	0.07	4.2E-11	2.5E-06	3a	1.49	Druggable genome	Bosutinib, cerdulatinib, hesperadin	5	BD, SZ
rs1569723	20:44742064	*CD40* (4.9)	intergenic	A/C	-0.05	3.9E-07	9.2E-04	1f	1.50	Druggable genome	Teneliximab, dacetuzumab, iscalimab, PG-102, hydroquinone,	4	BD, SZ

											fludarapine, ravagalimab, streptozocin, APX-005M, bleselumab		
rs237460	20:48033127	*KCNB1*	intronic	T/C	0.06	4.3E-09	1.1E-03	5	0.41	-	Tedisamil, guanidine hydrochloride, dalfampridine, nerispirdine	2	BD, SZ
rs13044225	20:60865815	*OSBPL2*	intronic	A/G	-0.05	8.5E-09	2.0E-03	5	3.84	-	SNAP-7941, CHEMBL178707, CHEMBL214957, CHEMBL2110360, haloperidol, BMS-830216	2	BD
rs6519227	22:41119899	*MCHR1* (41.1)	intergenic	A/G	0.05	2.9E-08	3.4E-03	3a	3.71	-	-	5	BD, SZ
rs2038061	22:43397861	*PACSIN2*	intronic	A/G	-0.05	6.3E-08	2.3E-03	2b	0.15	-	Mercaptopurine, methotrexate	3	BD, SZ

The table reports functional characterization for the linkage-disequilibrium independent genomic loci associated with bipolar disorder conditioning on risk-taking propensity at a condFDR < 0.01. Nearest gene and functional category have been annotated using FUMA (for SNPs located in intergenic regions, distance in Kb from the nearest gene is also reported). Beta BD shows the direction of effect of the A1 allele in the original GWAS dataset. The RegBD rank (from 1 to 7, with 1 being associated with highest evidence of functional effects) was calculated using RegulomeDB based on known and predicted regulatory elements including regions of DNase hypersensitivity, binding sites of transcription factors and promoter regions that regulate transcription. The CADD score, which predicts how deleterious a variant is on protein structure/function was computed in FUMA. Higher scores indicate more deleterious SNP, with a suggested threshold of 12.37 for a SNP to be considered deleterious. Nearest genes were located were searched in DGIdb in order to assess whether they are part of the druggable genome (druggable categories) or known targets of drugs (drug-gene interactions). In case more than 10 drug-gene interactions were found, the top 10 based on their interaction score in DGIdb are reported. The 'novel' column indicates whether the genomic loci are novel or have been found to be associated with BD by previous studies indicated in supplementary references.
Abbreviations: ADHD, attention deficit hyperactivity disorder; BD, bipolar disorder; SNP, single nucleotide polymorphism; RegBD, Regulome DB; SZ, schizophrenia

Appendix Table 3. Functional characterization of independent genomic loci associated with risk-taking propensity conditioning on BD at condFDR < 0.01

SNP	Position	Nearest gene (Kb)	Functional category	A1 / A2	beta risk	p risk	condFDR risk|BD	RegDB Rank	CADD Score	Druggable categories	Drug-gene interactions	Novel	Specific
rs785272	1:33311507	*S100PBP*	intronic	T/C	0.01	1.4E-05	4.5E-03	5	6.36	-	-	19	BD, SZ, ADHD
rs10914678	1:33767228	*ZNF362:AL513327.1* (0.9)	downstream	T/G	0.01	3.5E-08	3.0E-04	1b	0.15	-	-	19	BD, SZ, ADHD
rs11210630	1:42852612	*RIMKLA*	intronic	T/C	0.01	3.0E-06	2.8E-03	3a	1.15	-	-	19	BD, SZ
rs4649972	1:73444790	*RP4-660H19.1* (80.0)	intergenic	A/C	-0.01	6.8E-08	1.3E-04	5	1.82	-	-	Yes	BD, SZ, ADHD
rs2595944	1:204966749	*NFASC*	intronic	A/G	0.01	1.0E-06	8.7E-03	5	0.05	-	-	19	BD
rs984983	1:208034955	*C1orf132*	ncRNA	T/C	-0.02	4.2E-07	2.8E-03	4	2.82	-	-	19	BD, SZ, ADHD
rs58560561	1:243537729	*SDCCAG8*	intronic	T/G	-0.01	2.3E-10	1.8E-06	5	3.38	-	-	19	BD, SZ, ADHD
rs11124322	2:22442392	*AC068490.2*	ncRNA	A/G	0.01	3.2E-06	1.8E-03	5	5.08	-	-	Yes	BD, SZ, ADHD
rs71437484	2:23595043	*AC012506.4* (3.1)	intergenic	T/C	0.02	5.5E-07	3.5E-03	5	0.93	-	-	19	BD, SZ
rs12617392	2:27336827	*CGREF1*	intronic	A/C	-0.01	2.8E-08	6.7E-04	4	0.70	Druggable genome	-	19	BD, SZ, ADHD
rs564207	2:45136742	*RP11-89K21.1* (10.6)	intergenic	T/C	-0.01	2.9E-07	7.2E-03	6	3.19	-	-	19	BD
rs359243	2:60475509	*AC007381.3* (102.2)	intergenic	T/C	-0.01	2.9E-08	6.2E-03	5	5.73	-	-	19	BD, SZ, ADHD
rs1868402	2:68409037	*RP11-474G23.1:PPP3R1*	intronic	A/G	-0.01	8.3E-07	3.6E-03	1f	0.15	-	Myristic acid, voclosporin	Yes	BD
rs977950	2:145746816	*TEX41*	ncRNA	A/C	-0.01	1.6E-06	5.4E-03	5	0.08	-	-	19	BD, ADHD
rs545200731	2:147644489	*AC062032.1*	ncRNA	T/C	0.04	5.3E-06	5.8E-03	6	1.08	-	-	Yes	BD
rs34288552	2:171661486	*ERICH2* (6.0)	intergenic	A/G	0.01	2.0E-07	5.8E-03	5	7.33	-	-	Yes	BD
rs1014959	2:185472113	*ZNF804A*	intronic	A/G	-0.01	4.0E-05	8.3E-03	7	0.50	-	Lithium	Yes	BD
rs35811586	2:233743794	*NGEF*	UTR3	T/C	0.02	7.7E-07	8.2E-03	4	10.99	-	-	Yes	BD, SZ
rs283914	3:17330649	*TBC1D5*	intronic	T/C	0.01	1.0E-08	7.3E-04	5	2.78	-	-	19	BD, SZ, ADHD
rs6793141	3:25202977	*AC133680.1*	ncRNA	A/G	-0.01	7.6E-08	4.4E-03	7	0.27	-	-	Yes	BD, SZ, ADHD
rs7649685	3:82538109	*RP11-260O18.1* (25.3)	intergenic	A/G	-0.01	4.8E-07	6.0E-03	7	0.85	-	-	Yes	BD, ADHD
rs17516683	3:85585431	*CADM2*	intronic	A/G	-0.02	4.2E-29	4.5E-08	7	2.72	-	Alcohol	19	BD, SZ, ADHD
rs326353	3:107853648	*RP11-861A13.4*	ncRNA	T/C	-0.01	6.0E-06	2.7E-03	3a	3.28	-	-	Yes	BD
rs7628391	3:163680497	*RP11-208P4.1* (38.9)	intergenic	T/C	0.01	5.8E-06	4.0E-03	5	0.33	-	-	Yes	BD
rs4434184	3:181422854	*SOX2-OT*	ncRNA	A/G	-0.02	1.4E-10	9.0E-07	3a	20.30	Clinically actionable	-	19	BD, SZ, ADHD
rs279846	4:46329886	*GABRA2*	intronic	T/C	-0.01	4.1E-08	9.1E-05	7	1.81	Druggable genome	Halazepam, bromazapem, isoguvacine, primidone, diazepam, picrotoxin, AZD7325, talbutal, hexobarbital, quazepam	19	BD, SZ
rs992493	4:106180264	*TET2*	intronic	T/C	0.02	2.2E-10	1.3E-06	5	4.44	Clinically actionable	Decitabine, azacitidine, hydrochlorothiazide	19	BD, SZ, ADHD
rs4696294	4:152713089	*RP11-424M21.1* (7.6)	intergenic	A/C	-0.01	2.9E-06	9.6E-03	6	0.02	-	-	Yes	BD

rs3849046	5:137851192	*ETF1*	intronic	T/C	0.01	5.2E-06	2.5E-03	4	1.90	-	-	19	BD, SZ
rs76157183	5:145833478	*TCERG1*	intronic	T/C	0.02	5.1E-05	9.6E-03	5	0.08	-	-	Yes	BD
rs2195450	5:152871009	*GRIA1*	intronic	A/G	0.01	5.7E-06	3.8E-03	4	16.32	Druggable genome	Zonampanel, MK-8777, selurampanel, mibampator, becampanel, cyclothiazide, NBQX, CX516, sevoflurane, desflurane	Yes	BD
rs852960	6:72205635	*RP1-288M22.2* (37.1)	intergenic	A/G	0.01	1.6E-05	5.7E-03	5	5.28	-	-	Yes	BD
rs1487445	6:98565211	*RP11-436D23.1*	ncRNA	T/C	0.01	1.1E-05	3.8E-03	5	3.27	-	-	19	BD, SZ
rs4027745	6:109131493	*RP3-354J5.3* (7.4)	intergenic	T/C	0.01	1.3E-08	4.1E-03	5	1.16	-	-	19	BD, SZ, ADHD
rs7758002	6:153440770	*RGS17*	intronic	T/G	-0.01	7.1E-07	1.3E-03	7	1.06	-	-	Yes	BD
rs117450257	7:100446237	*SLC12A9:RP11-126L15.4*	ncRNA	A/G	-0.02	2.1E-05	5.6E-03	5	0.14	Druggable genome	-	Yes	BD
rs2470939	7:104581510	*RP11-325F22.2*	ncRNA	A/G	0.01	2.0E-05	5.5E-03	4	2.86	-	-	19	BD, SZ
rs10262103	7:114091844	*FOXP2*	intronic	A/C	0.02	8.5E-13	2.2E-06	5	5.22	-	-	19	BD, SZ, ADHD
rs4275159	7:115067269	*RP11-222O23.1* (76.2)	intergenic	A/G	-0.01	2.8E-09	1.1E-05	5	1.21	-	-	19	BD, SZ, ADHD
rs2351138	7:137071390	*DGKI*	UTR3	T/C	-0.01	2.7E-05	6.5E-03	5	1.05	-	-	Yes	BD, SZ
rs80206917	7:140159389	*MKRN1*	intronic	T/C	0.01	2.3E-05	6.5E-03	2b	5.92	-	-	Yes	BD
rs17055053	8:26088094	*RP11-98P2.1* (24.3)	intergenic	T/C	-0.02	5.1E-05	9.5E-03	4	14.95	-	-	Yes	BD
rs7829912	8:33479228	*RP11-317N12.1*	ncRNA	T/C	0.01	6.3E-08	1.4E-03	5	4.15	-	-	20	BD, SZ, ADHD
rs7845911	8:38135412	*WHSC1L1*	intronic	T/C	0.01	2.8E-05	6.7E-03	5	0.20	Clinically actionable	-	Yes	BD, SZ
rs62519839	8:65497573	*BHLHE22* (1.4)	intergenic	T/C	-0.02	6.8E-11	3.9E-05	4	11.71	-	-	19	BD, SZ, ADHD
rs1051920	8:81438420	*ZBTB10*	UTR3	T/C	0.02	1.5E-10	5.3E-05	5	0.70	-	-	19	BD, SZ, ADHD
rs34819186	8:143363229	*TSNARE1*	intronic	A/C	0.01	6.4E-08	1.3E-04	5	0.00	-	-	Yes	BD, SZ, ADHD
rs12115650	9:126367705	*DENND1A*	intronic	A/G	-0.01	1.4E-07	5.6E-03	5	11.68	-	-	19	BD, ADHD
rs7871821	9:128992756	*RP11-343J18.1* (39.6)	intergenic	T/C	0.01	5.5E-06	6.9E-03	5	1.18		-	Yes	BD
rs10823790	10:73338253	*CDH23*	intronic	A/G	0.01	7.2E-08	5.3E-03	5	0.76	-	Methylphenidate	Yes	BD, SZ, ADHD
rs9630089	10:98968967	*ARHGAP19-SLIT1*	intronic	A/G	-0.01	2.3E-08	3.2E-04	5	0.57	-	etoposide, hydrochlorothiazide	19	BD, SZ, ADHD
rs12244388	10:104640052	*C10orf32-ASMT:AS3MT*	intronic	A/G	0.01	1.5E-05	4.7E-03	5	1.83	-	Melatonin, ademetionine	Yes	BD, SZ, ADHD
rs12761679	10:106512727	*SORCS3*	intronic	A/C	0.01	4.1E-06	2.1E-03	6	4.17	-	-	Yes	BD, SZ
rs3901919	11:13237023	*ARNTL* (61.2)	intergenic	A/C	0.01	3.9E-06	2.1E-03	2b	0.09	-	-	19	BD
rs7126178	11:29016502	*RP11-115J23.1*	ncRNA	A/G	-0.01	6.5E-08	7.0E-03	5	0.87	-	-	20	BD, SZ, ADHD
rs7111300	11:45806624	*CTD-2210P24.4* (12.7)	intergenic	T/G	0.02	3.0E-05	7.0E-03	5	1.34	-	-	Yes	BD
rs11227478	11:66173400	*RP11-867G23.10* (3.2)	intergenic	A/G	-0.01	1.3E-06	1.0E-03	5	0.31	-	-	Yes	BD, SZ
rs11827676	11:88263465	*GRM5*	intronic	A/C	0.01	3.7E-05	8.0E-03	6	3.66	Druggable genome	Dipraglurant, CHEMBL292065, Ly545694, raseglurant, basimglurant, CHEMBL88612, CHEMBL381055,	Yes	BD

											acamprosate, AZD2066, rufinamide		
rs11226321	11:104221759	*RP11-886D15.1* (94.8)	intergenic	T/C	-0.02	2.8E-08	4.3E-03	7	1.84	-	-	19	BD, SZ, ADHD
rs61909095	12:2301189	*CACNA1C*	intronic	T/C	-0.01	1.6E-06	1.2E-03	3a	0.13	-	Verapamil, nicardipine, amlodipine besylate, elpetrigine, benidipine, imagabalin, israpidine, nifedipine, felodipine, atagabalin	19	BD, SZ
rs3885907	13:31314455	*ALOX5AP*	intronic	A/C	-0.01	6.7E-06	2.9E-03	4	2.17	-	Fiboflapon	Yes	BD
rs36063234	14:33409812	*NPAS3*	intronic	T/C	-0.01	1.5E-07	2.4E-04	4	3.51	-	-	Yes	BD, SZ, ADHD
rs8005321	14:62458832	*SYT16*	intronic	T/G	-0.01	4.2E-05	8.6E-03	4	0.33	-	-	Yes	BD
rs3783845	14:89867481	*FOXN3:RP11-33N16.2*	ncRNA	T/C	-0.01	1.5E-06	1.1E-03	6	0.70	-	-	19	BD, SZ
rs6575642	14:98556621	*RP11-61O1.1*	ncRNA	A/G	-0.01	2.0E-08	5.7E-03	7	0.41	-	-	19	BD, SZ, ADHD
rs6576006	14:104322394	*LINC00637:CTD-2134A5.4*	ncRNA	A/C	0.01	1.3E-07	2.2E-04	4	1.09	-	-	19	BD, SZ
rs4924675	15:42681057	*RP11-164J13.1:CAPN3*	ncRNA	A/G	0.02	1.2E-05	4.0E-03	1f	9.51	Druggable genome	-	Yes	BD, SZ
rs7164399	15:74012895	*CD276* (6.0)	intergenic	T/C	0.01	3.5E-05	7.7E-03	4	4.63	Druggable genome	Enoblituzumab	19	BD
rs12442456	15:78751962	*IREB2*	intronic	T/G	0.01	2.5E-05	6.4E-03	6	0.00	-		Yes	BD, SZ
rs2071382	15:91428197	*FES*	intronic	T/C	-0.01	5.6E-07	6.0E-04	4	10.02	Druggable genome	Hesperadin, lorlatinib, fostamatinib, linifanib, SP-600125, dasatinib	Yes	BD, SZ, ADHD
rs2352759	16:10215483	*GRIN2A*	intronic	T/C	0.01	4.8E-05	9.2E-03	4	7.46	Druggable genome	Memantine, philantotoxin 343, dizocilpine, dextromethorphan polistirex, tenocyclidine, felbamate, dextromethorphan hydrobromide, glycine, selfotel, phencyclidine		BD, ADHD
rs12927162	16:52684916	*CASC16*	ncRNA	A/G	-0.01	1.9E-06	4.9E-03	5	21.80	-	-	Yes	BD
rs12926961	16:71374211	*AC106736.1* (9.0)	intergenic	A/G	-0.01	4.4E-07	8.8E-03	5	0.02	-		19	BD, SZ, ADHD
rs4790082	17:1278700	*YWHAE*	intronic	A/G	-0.01	1.2E-05	8.8E-03	4	3.93	-	Insulin, phenethylisothiocyanate, CHEMBL4244843	Yes	BD, SZ
rs8071515	17:16245333	*PIGL*	intronic	A/G	-0.01	2.9E-08	5.9E-03	5	3.67	-	-	19	BD, SZ, ADHD
rs72841389	17:61437939	*TANC2*	intronic	A/G	0.01	5.4E-06	4.7E-03	7	4.83	-	-	Yes	BD
rs7240986	18:53195249	*TCF4*	intronic	A/G	0.01	1.1E-08	5.4E-05	7	6.45	-	-	19	BD, SZ, ADHD
rs6017733	20:44712815	*NCOA5*	intronic	A/G	-0.01	2.2E-06	5.7E-03	6	6.25	-	CHEMBL1232445	Yes	BD
rs28520003	22:46411969	*CITF22-92A6.1* (0.6)	downstream	A/G	-0.01	4.0E-08	6.1E-03	3a	1.15	-	-	19	BD, SZ

The table reports functional characterization for the 79 linkage disequilibrium independent genomic loci associated with risk-taking propensity conditioning on bipolar disorder at a condFDR < 0.01. Nearest gene and functional category have been annotated using FUMA (for SNPs located in intergenic regions, distance in Kb from the nearest gene is also reported). Beta risk shows the direction of effect of the A1 allele in the original risk-taking propensity GWAS dataset. The RegBD rank and the RegBD score were calculated using RegulomeDB based on known and predicted regulatory elements including regions of DNase hypersensitivity, binding sites of transcription factors and promoter regions that regulate transcription. RegulomeDB attributes to each SNP a rank (from 1 to 7, with 1 being associated with highest evidence of functional effects) as well as a probability score (from 0 to 1, with 1 being most likely to be a regulatory variant). The CADD score, which predicts how deleterious a variant is on protein structure/function was computed in FUMA, based on 63 annotations. Higher scores indicate more deleterious SNP, with a suggested threshold of 12.37 for a SNP to be considered deleterious. Nearest genes were located were searched in DGIdb in order to assess whether they are part of the druggable

genome (druggable categories) or known targets of drugs (drug-gene interactions). In case more than 10 drug-gene interactions were found, the top 10 based on their interaction score in DGIdb are reported. The Novel column indicates whether the genomic loci are novel or have been found to be associated with risk-taking propensity by previous studies indicated in supplementary references, while the Specific column indicates whether the locus was only identified conditioning risk-taking propensity on BD or also conditioning on other traits.
Abbreviations: ADHD, attention deficit hyperactivity disorder; BD, bipolar disorder; SNP, single nucleotide polymorphism; RegBD, Regulome DB; SZ, schizophrenia

Appendix Table 4. eQTL-informed gene-based analysis on variants associated with bipolar disorder

Brain region	Gene	Chr	Start	Stop	NSNPs	NPARAM	Z	p	adj p
Amygdala	*ZNF501*	3	44771098	44778575	58	3	4.72	1.2E-06	2.3E-02
	ITIH4	3	52847006	52864717	298	6	6.80	5.2E-12	1.0E-07
	TMEM110	3	52870772	52931597	2	1	4.71	1.2E-06	2.4E-02
	PLEC	8	144989321	145050913	33	1	5.25	7.7E-08	1.5E-03
	C15orf40	15	83657715	83681050	223	7	4.67	1.5E-06	2.9E-02
	TSSK6	19	19625028	19626469	7	1	4.66	1.6E-06	3.1E-02
Anterior cingulate	*KCNN3*	1	154669938	154842754	31	2	4.91	4.5E-07	8.7E-03
	GLYCTK	3	52321836	52329272	55	3	6.93	2.2E-12	4.2E-08
	GNL3	3	52719936	52728513	15	1	7.19	3.1E-13	6.1E-09
	ITIH4	3	52847006	52864717	151	6	5.40	3.3E-08	6.4E-04
	PCDHA7	5	140213969	140391929	47	1	4.69	1.4E-06	2.7E-02
	PCDHA13	5	140261854	140391929	175	7	4.84	6.5E-07	1.3E-02
	PCDHB10	5	140571952	140575213	90	5	4.68	1.4E-06	2.7E-02
	FADS1	11	61567097	61584529	46	2	7.14	4.6E-13	9.0E-09
	MED24	17	38175350	38210889	44	3	4.63	1.8E-06	3.5E-02
	CD40	20	44746899	44758384	10	1	4.81	7.7E-07	1.5E-02
Caudate	*TMEM127*	2	96915946	96931751	8	1	4.90	4.8E-07	9.2E-03
	LMAN2L	2	97371666	97405813	22	1	6.11	4.8E-10	9.4E-06
	GNL3	3	52719936	52728513	180	2	6.32	1.3E-10	2.5E-06
	ITIH4	3	52847006	52864717	423	12	6.84	4.0E-12	7.8E-08
	KIAA1109	4	123073488	123283914	50	2	5.00	2.9E-07	5.6E-03
	C4orf33	4	130014829	130034487	283	11	4.61	2.0E-06	4.0E-02
	PCDHB8	5	140557371	140560081	84	5	4.61	2.0E-06	3.9E-02
	PCDHB10	5	140571952	140575213	49	3	4.74	1.0E-06	2.0E-02
	FTSJ2	7	2273830	2281840	256	10	5.85	2.5E-09	4.8E-05
	MRPS33	7	140705961	140714781	78	4	4.64	1.7E-06	3.4E-02
	CCDC25	8	27590833	27630170	413	11	4.69	1.4E-06	2.7E-02
	PLEC	8	144989321	145050913	31	2	5.25	7.8E-08	1.5E-03
	GPT	8	145729465	145732555	7	1	4.95	3.8E-07	7.4E-03
	MFSD3	8	145733161	145736596	2	1	5.01	2.7E-07	5.2E-03
	ADD3	10	111765627	111895323	22	1	6.51	3.8E-11	7.4E-07
	FADS1	11	61567097	61584529	29	2	6.44	6.0E-11	1.2E-06
	PPP1R13B	14	104200088	104315116	39	1	4.62	1.9E-06	3.8E-02
	LRRC57	15	42834720	42841002	20	3	5.56	1.3E-08	2.6E-04
	GOLGA6L10	15	82632347	82641706	255	13	4.65	1.7E-06	3.3E-02
	C15orf40	15	83657715	83681050	303	15	5.00	2.8E-07	5.5E-03
	WDR73	15	85185607	85197521	122	4	5.57	1.2E-08	2.4E-04
	NMB	15	85198360	85201802	273	5	6.31	1.4E-10	2.7E-06
	SPG7	16	89574802	89624174	6	1	4.73	1.1E-06	2.1E-02
	SLC12A5	20	44650329	44688789	13	1	4.84	6.6E-07	1.3E-02
	ARFGAP3	22	43192530	43253408	284	4	4.94	4.0E-07	7.7E-03
	TTLL1	22	43435522	43485434	71	4	4.72	1.2E-06	2.3E-02
Cerebellar hemisphere	*VPS45*	1	150039350	150117505	146	1	4.82	7.3E-07	1.4E-02
	PLEKHO1	1	150122170	150131825	7	1	4.71	1.3E-06	2.4E-02
	DCST2	1	154991003	155006257	93	5	4.81	7.5E-07	1.5E-02
	TMEM127	2	96915946	96931751	7	1	4.82	7.2E-07	1.4E-02

	UBE2E3	2	181845112	181928154	38	2	4.75	1.0E-06	2.0E-02
	ZNF197	3	44666511	44689963	225	6	4.78	8.9E-07	1.7E-02
	ZNF502	3	44754135	44765323	106	5	4.94	4.0E-07	7.7E-03
	ZNF501	3	44771098	44778575	261	6	4.91	4.4E-07	8.6E-03
	KIAA1143	3	44790236	44803173	367	10	5.42	3.0E-08	5.7E-04
	PPM1M	3	52279782	52284615	400	7	6.53	3.3E-11	6.5E-07
	GNL3	3	52719936	52728513	341	5	6.77	6.6E-12	1.3E-07
	NEK4	3	52744796	52804965	213	4	6.20	2.8E-10	5.4E-06
	ITIH4	3	52847006	52864717	354	15	5.45	2.5E-08	4.9E-04
	SFMBT1	3	52933221	53080089	74	2	4.73	1.1E-06	2.2E-02
	NDST3	4	118955500	119179789	84	8	4.69	1.3E-06	2.6E-02
	SSBP2	5	80713179	81047072	84	8	4.74	1.1E-06	2.1E-02
	TMCO6	5	140019012	140024989	557	11	4.58	2.3E-06	4.5E-02
	PCDHA9	5	140227357	140391929	408	9	4.64	1.8E-06	3.4E-02
	PCDHA13	5	140261854	140391929	516	10	5.04	2.4E-07	4.6E-03
	PCDHB16	5	140560980	140566710	164	9	5.27	6.9E-08	1.3E-03
	PCDHB10	5	140571952	140575213	120	8	4.84	6.4E-07	1.2E-02
	FTSJ2	7	2273830	2281840	212	11	5.16	1.2E-07	2.4E-03
	PLEKHA8	7	30067977	30157961	207	5	4.73	1.1E-06	2.2E-02
	PLEC	8	144989321	145050913	149	4	5.64	8.3E-09	1.6E-04
	CACNA1B	9	140772241	141019076	53	5	4.85	6.2E-07	1.2E-02
	CDHR1	10	85954391	85979377	30	4	4.66	1.6E-06	3.0E-02
	ADD3	10	111765627	111895323	514	12	6.45	5.5E-11	1.1E-06
	FADS1	11	61567097	61584529	97	6	6.93	2.0E-12	4.0E-08
	FADS3	11	61640998	61659006	57	3	6.97	1.5E-12	3.0E-08
	BBS1	11	66278077	66301084	23	1	5.20	9.9E-08	1.9E-03
	C11orf80	11	66512207	66613997	60	4	4.74	1.0E-06	2.0E-02
	PC	11	66615993	66725847	16	2	5.06	2.1E-07	4.2E-03
	CACNA1C	12	2079952	2807115	99	4	7.48	3.8E-14	7.4E-10
	PROZ	13	113812968	113826698	118	2	5.44	2.6E-08	5.1E-04
	STARD9	15	42867857	43013196	49	5	4.81	7.7E-07	1.5E-02
	GOLGA6L10	15	82632347	82641706	457	21	5.86	2.3E-09	4.4E-05
	C15orf40	15	83657715	83681050	337	16	5.14	1.4E-07	2.7E-03
	YJEFN3	19	19639670	19648393	141	3	4.77	9.2E-07	1.8E-02
	ACTR5	20	37376933	37401089	85	3	4.57	2.5E-06	4.8E-02
Cerebellum	*PLEKHO1*	1	150122170	150131825	203	3	4.74	1.0E-06	2.0E-02
	RPRD2	1	150336624	150449042	209	5	5.14	1.4E-07	2.7E-03
	SEMA6C	1	151104161	151119146	190	9	4.59	2.2E-06	4.4E-02
	DCST2	1	154991003	155006257	119	7	4.67	1.5E-06	2.9E-02
	DCST1	1	155006256	155023406	83	4	4.68	1.4E-06	2.8E-02
	ADRA2B	2	96778623	96782281	74	8	4.96	3.4E-07	6.7E-03
	LMAN2L	2	97371666	97405813	21	1	5.59	1.1E-08	2.2E-04
	CNNM4	2	97426639	97477628	16	2	5.50	1.9E-08	3.7E-04
	UBE2E3	2	181845112	181928154	232	3	4.84	6.6E-07	1.3E-02
	LRRFIP2	3	37094117	37217992	2	1	5.75	4.5E-09	8.7E-05
	ZNF502	3	44754135	44765323	116	5	4.91	4.4E-07	8.6E-03
	ZNF501	3	44771098	44778575	50	3	4.66	1.6E-06	3.1E-02
	KIAA1143	3	44790236	44803173	243	7	4.82	7.1E-07	1.4E-02
	PPM1M	3	52279782	52284615	382	5	6.58	2.4E-11	4.6E-07

	GLYCTK	3	52321836	52329272	495	11	7.15	4.2E-13	8.2E-09
	SEMA3G	3	52467268	52479112	5	2	5.36	4.1E-08	8.0E-04
	GNL3	3	52719936	52728513	507	7	7.22	2.5E-13	4.9E-09
	NEK4	3	52744796	52804965	275	3	6.43	6.3E-11	1.2E-06
	ITIH4	3	52847006	52864717	294	12	5.55	1.4E-08	2.7E-04
	SFMBT1	3	52933221	53080089	273	7	5.75	4.5E-09	8.7E-05
	RFT1	3	53122499	53164480	299	11	4.72	1.2E-06	2.3E-02
	NDST3	4	118955500	119179789	98	8	4.91	4.5E-07	8.7E-03
	SSBP2	5	80713179	81047072	88	7	5.17	1.1E-07	2.2E-03
	PCDHA9	5	140227357	140391929	202	16	5.01	2.7E-07	5.2E-03
	PCDHB16	5	140560980	140566710	94	5	4.72	1.2E-06	2.2E-02
	PCDHB10	5	140571952	140575213	98	6	4.68	1.4E-06	2.8E-02
	PCDHB14	5	140603078	140605860	97	5	4.73	1.1E-06	2.2E-02
	FTSJ2	7	2273830	2281840	248	9	5.29	6.0E-08	1.2E-03
	PLEKHA8	7	30067977	30157961	215	5	4.75	1.0E-06	2.0E-02
	CCDC25	8	27590833	27630170	399	11	4.71	1.2E-06	2.4E-02
	PLEC	8	144989321	145050913	152	4	5.65	7.8E-09	1.5E-04
	CDHR1	10	85954391	85979377	9	3	4.58	2.4E-06	4.6E-02
	BLOC1S2	10	102033035	102046469	131	6	4.58	2.3E-06	4.5E-02
	ADD3	10	111765627	111895323	303	11	6.71	1.0E-11	2.0E-07
	FADS1	11	61567097	61584529	126	10	7.11	5.8E-13	1.1E-08
	FADS3	11	61640998	61659006	54	3	7.14	4.7E-13	9.2E-09
	SF3B2	11	65819264	65836382	130	13	4.72	1.2E-06	2.3E-02
	C11orf80	11	66512207	66613997	94	8	5.02	2.5E-07	4.9E-03
	PC	11	66615993	66725847	80	6	5.75	4.6E-09	8.9E-05
	LRFN4	11	66624558	66627946	45	4	5.48	2.2E-08	4.2E-04
	CACNA1C	12	2079952	2807115	97	4	7.57	1.8E-14	3.5E-10
	PROZ	13	113812968	113826698	135	3	5.44	2.7E-08	5.3E-04
	CUL4A	13	113862507	113919392	47	1	5.01	2.7E-07	5.3E-03
	CDAN1	15	43015760	43029417	316	12	4.95	3.8E-07	7.3E-03
	GOLGA6L10	15	82632347	82641706	492	23	5.73	5.0E-09	9.7E-05
	C15orf40	15	83657715	83681050	352	18	5.09	1.8E-07	3.5E-03
	ALPK3	15	85359911	85416713	61	2	5.96	1.2E-09	2.4E-05
Cortex	*DCST2*	1	154991003	155006257	103	5	4.74	1.1E-06	2.1E-02
	PBX1	1	164528597	164821067	73	2	4.56	2.5E-06	4.9E-02
	FAHD2B	2	97749320	97760603	513	19	5.01	2.7E-07	5.2E-03
	TRANK1	3	36868308	36986548	16	2	6.25	2.1E-10	4.0E-06
	GLYCTK	3	52321836	52329272	37	3	6.86	3.5E-12	6.7E-08
	NT5DC2	3	52558385	52569093	40	5	5.34	4.6E-08	8.9E-04
	GNL3	3	52719936	52728513	66	2	7.08	7.4E-13	1.4E-08
	SPCS1	3	52739792	52742198	2	1	6.11	5.0E-10	9.7E-06
	NEK4	3	52744796	52804965	9	1	6.57	2.6E-11	5.1E-07
	ITIH4	3	52847006	52864717	567	12	7.20	3.0E-13	5.8E-09
	KIAA1109	4	123073488	123283914	55	2	4.83	6.7E-07	1.3E-02
	C4orf33	4	130014829	130034487	257	9	4.67	1.5E-06	2.9E-02
	PCDHB10	5	140571952	140575213	112	7	4.83	6.7E-07	1.3E-02
	FTSJ2	7	2273830	2281840	126	8	4.88	5.2E-07	1.0E-02
	WIPF3	7	29846170	29956682	54	6	5.22	8.9E-08	1.7E-03
	PLEC	8	144989321	145050913	141	3	5.65	7.9E-09	1.5E-04

	FADS1	11	61567097	61584529	58	3	7.11	5.8E-13	1.1E-08
	HRASLS2	11	63320242	63330855	7	1	4.91	4.6E-07	8.9E-03
	PACS1	11	65837747	66012218	170	5	5.12	1.5E-07	2.9E-03
	LRRC57	15	42834720	42841002	16	1	5.58	1.2E-08	2.4E-04
	GOLGA6L10	15	82632347	82641706	352	18	5.65	8.2E-09	1.6E-04
	C15orf40	15	83657715	83681050	316	16	5.07	2.0E-07	3.8E-03
	WDR73	15	85185607	85197521	134	5	5.91	1.7E-09	3.4E-05
	DUS2	16	68056847	68113226	342	9	4.76	9.6E-07	1.9E-02
	MED24	17	38175350	38210889	67	4	4.71	1.3E-06	2.5E-02
	ARFGAP3	22	43192530	43253408	289	3	4.92	4.3E-07	8.4E-03
	PACSIN2	22	43265772	43411184	118	4	4.97	3.3E-07	6.4E-03
	TTLL1	22	43435522	43485434	167	5	4.97	3.3E-07	6.3E-03
Frontal cortex	*HTR6*	1	19991780	20006055	8	2	4.68	1.5E-06	2.8E-02
	VPS45	1	150039350	150117505	206	3	4.75	1.0E-06	2.0E-02
	DCST2	1	154991003	155006257	97	4	4.73	1.1E-06	2.1E-02
	ZNF502	3	44754135	44765323	232	6	4.80	7.9E-07	1.5E-02
	ZNF501	3	44771098	44778575	153	5	4.71	1.3E-06	2.4E-02
	GNL3	3	52719936	52728513	54	3	7.21	2.8E-13	5.4E-09
	SPCS1	3	52739792	52742198	80	2	6.18	3.1E-10	6.1E-06
	ITIH4	3	52847006	52864717	254	9	5.60	1.1E-08	2.1E-04
	SFMBT1	3	52933221	53080089	1	1	4.61	2.1E-06	4.0E-02
	PCDHA13	5	140261854	140391929	177	7	4.85	6.1E-07	1.2E-02
	CCDC25	8	27590833	27630170	337	10	4.62	1.9E-06	3.7E-02
	PLEC	8	144989321	145050913	131	3	5.66	7.6E-09	1.5E-04
	CACNA1B	9	140772241	141019076	32	3	4.79	8.4E-07	1.6E-02
	ADD3	10	111765627	111895323	145	3	6.36	9.9E-11	1.9E-06
	TMEM258	11	61556602	61560085	34	3	7.01	1.2E-12	2.3E-08
	FADS1	11	61567097	61584529	47	2	7.13	5.1E-13	9.9E-09
	PACS1	11	65837747	66012218	131	5	5.22	9.2E-08	1.8E-03
	GOLGA6L10	15	82632347	82641706	254	12	4.80	7.9E-07	1.5E-02
	C15orf40	15	83657715	83681050	293	12	4.88	5.3E-07	1.0E-02
	BTBD1	15	83685175	83736106	202	10	4.69	1.3E-06	2.6E-02
	CD40	20	44746899	44758384	10	1	4.81	7.7E-07	1.5E-02
	PACSIN2	22	43265772	43411184	144	2	5.01	2.7E-07	5.2E-03
	TTLL1	22	43435522	43485434	171	5	4.97	3.3E-07	6.4E-03
Hippocampus	*GLYCTK*	3	52321836	52329272	43	3	6.32	1.3E-10	2.5E-06
	GNL3	3	52719936	52728513	18	1	6.79	5.7E-12	1.1E-07
	ITIH4	3	52847006	52864717	329	15	5.59	1.1E-08	2.2E-04
	C4orf33	4	130014829	130034487	270	10	4.70	1.3E-06	2.5E-02
	PCDHA13	5	140261854	140391929	50	2	4.74	1.1E-06	2.1E-02
	PCDHB8	5	140557371	140560081	45	2	4.58	2.4E-06	4.6E-02
	PCDHB10	5	140571952	140575213	4	1	4.70	1.3E-06	2.5E-02
	PCDHB12	5	140587914	140592143	81	4	4.57	2.4E-06	4.7E-02
	DFNA5	7	24737974	24797639	205	13	5.24	8.0E-08	1.6E-03
	CCDC25	8	27590833	27630170	288	6	4.78	8.9E-07	1.7E-02
	FADS1	11	61567097	61584529	58	3	7.18	3.4E-13	6.6E-09
	PACS1	11	65837747	66012218	6	1	5.61	1.0E-08	2.0E-04
	PROZ	13	113812968	113826698	109	2	5.45	2.6E-08	5.0E-04
	WDR73	15	85185607	85197521	74	1	6.17	3.5E-10	6.7E-06

	MED24	17	38175350	38210889	36	3	4.71	1.2E-06	2.4E-02
	SLC12A5	20	44650329	44688789	20	2	4.87	5.5E-07	1.1E-02
	CD40	20	44746899	44758384	11	1	4.90	4.7E-07	9.1E-03
	ARFGAP3	22	43192530	43253408	278	3	4.91	4.6E-07	8.9E-03
Hypothalamus	*KCNN3*	1	154669938	154842754	76	2	4.60	2.1E-06	4.1E-02
	ZNF502	3	44754135	44765323	107	3	4.67	1.5E-06	2.9E-02
	ZNF501	3	44771098	44778575	26	2	4.64	1.7E-06	3.4E-02
	GNL3	3	52719936	52728513	237	2	6.39	8.1E-11	1.6E-06
	ITIH4	3	52847006	52864717	453	10	7.11	5.7E-13	1.1E-08
	PCDHB8	5	140557371	140560081	42	2	4.57	2.5E-06	4.8E-02
	FTSJ2	7	2273830	2281840	100	6	4.65	1.7E-06	3.3E-02
	PLEC	8	144989321	145050913	144	3	5.66	7.7E-09	1.5E-04
	CACNA1B	9	140772241	141019076	8	2	5.37	4.0E-08	7.8E-04
	FADS1	11	61567097	61584529	50	2	7.15	4.2E-13	8.2E-09
	PACS1	11	65837747	66012218	25	2	5.34	4.7E-08	9.1E-04
	C15orf40	15	83657715	83681050	264	11	4.91	4.5E-07	8.7E-03
	DPEP1	16	89679716	89707216	15	3	5.26	7.4E-08	1.4E-03
	NT5C	17	73126320	73127890	23	1	4.76	9.6E-07	1.9E-02
	XPNPEP3	22	41253085	41328823	20	2	4.61	2.0E-06	3.9E-02
Nucleus accumbens	*HTR6*	1	19991780	20006055	63	6	4.80	8.1E-07	1.6E-02
	KCNN3	1	154669938	154842754	29	1	4.71	1.2E-06	2.4E-02
	DCST2	1	154991003	155006257	98	4	4.77	9.1E-07	1.8E-02
	LMAN2L	2	97371666	97405813	30	3	6.27	1.8E-10	3.5E-06
	CNNM4	2	97426639	97477628	22	1	6.11	4.8E-10	9.4E-06
	ZNF197	3	44666511	44689963	238	9	4.97	3.4E-07	6.6E-03
	GNL3	3	52719936	52728513	20	2	7.33	1.2E-13	2.2E-09
	GLT8D1	3	52728500	52740099	101	2	6.10	5.3E-10	1.0E-05
	ITIH4	3	52847006	52864717	378	14	6.11	5.0E-10	9.8E-06
	C4orf33	4	130014829	130034487	256	10	4.73	1.1E-06	2.2E-02
	PCDHA9	5	140227357	140391929	76	4	4.74	1.1E-06	2.1E-02
	PCDHB8	5	140557371	140560081	70	3	4.58	2.3E-06	4.5E-02
	FTSJ2	7	2273830	2281840	113	7	4.65	1.6E-06	3.2E-02
	SP4	7	21467689	21554440	9	1	5.11	1.6E-07	3.1E-03
	CCDC25	8	27590833	27630170	427	12	4.79	8.1E-07	1.6E-02
	PLEC	8	144989321	145050913	6	1	5.82	2.9E-09	5.6E-05
	C11orf80	11	66512207	66613997	31	4	5.13	1.4E-07	2.8E-03
	LRRC57	15	42834720	42841002	47	2	5.16	1.2E-07	2.3E-03
	GOLGA6L10	15	82632347	82641706	290	13	5.78	3.8E-09	7.5E-05
	C15orf40	15	83657715	83681050	279	12	4.65	1.7E-06	3.2E-02
	UBE2Q2L	15	84841138	84854921	16	1	4.66	1.6E-06	3.1E-02
	WDR73	15	85185607	85197521	67	1	6.13	4.3E-10	8.4E-06
	MED24	17	38175350	38210889	64	5	4.78	8.8E-07	1.7E-02
	SLPI	20	43880880	43883205	118	3	4.85	6.1E-07	1.2E-02
Putamen	*DCST2*	1	154991003	155006257	60	5	4.96	3.5E-07	6.8E-03
	LMAN2L	2	97371666	97405813	26	3	6.23	2.3E-10	4.5E-06
	ZNF501	3	44771098	44778575	71	4	4.74	1.1E-06	2.1E-02
	POC1A	3	52109249	52188720	217	2	6.13	4.5E-10	8.8E-06
	GNL3	3	52719936	52728513	313	4	6.90	2.6E-12	5.0E-08
	GLT8D1	3	52728500	52740099	6	1	5.80	3.3E-09	6.5E-05

	ITIH4	3	52847006	52864717	515	9	7.48	3.9E-14	7.5E-10
	C4orf33	4	130014829	130034487	227	11	4.65	1.7E-06	3.3E-02
	PCDHA7	5	140213969	140391929	77	3	4.87	5.6E-07	1.1E-02
	PCDHA13	5	140261854	140391929	412	8	4.60	2.1E-06	4.2E-02
	PCDHB8	5	140557371	140560081	84	5	4.59	2.2E-06	4.2E-02
	FTSJ2	7	2273830	2281840	89	5	4.63	1.9E-06	3.6E-02
	CCDC25	8	27590833	27630170	318	9	4.71	1.2E-06	2.4E-02
	PLEC	8	144989321	145050913	111	2	5.61	9.9E-09	1.9E-04
	CACNA1B	9	140772241	141019076	17	3	4.95	3.6E-07	7.0E-03
	TMEM258	11	61556602	61560085	32	1	7.10	6.2E-13	1.2E-08
	FADS1	11	61567097	61584529	54	2	7.10	6.1E-13	1.2E-08
	BBS1	11	66278077	66301084	13	2	4.89	5.1E-07	1.0E-02
	PPP1R13B	14	104200088	104315116	23	2	4.58	2.3E-06	4.4E-02
	CDAN1	15	43015760	43029417	86	2	4.60	2.1E-06	4.0E-02
	GOLGA6L10	15	82632347	82641706	335	13	5.80	3.3E-09	6.4E-05
	C15orf40	15	83657715	83681050	259	11	4.79	8.3E-07	1.6E-02
	BTBD1	15	83685175	83736106	160	5	4.61	2.0E-06	4.0E-02
	NME2	17	49242796	49249105	130	8	4.61	2.0E-06	3.9E-02
	CILP2	19	19649057	19657468	140	2	4.79	8.3E-07	1.6E-02
	SLPI	20	43880880	43883205	86	2	4.59	2.2E-06	4.3E-02
	ARFGAP3	22	43192530	43253408	268	3	4.92	4.3E-07	8.4E-03
Spinal cord	*KCNN3*	1	154669938	154842754	61	1	4.57	2.4E-06	4.6E-02
	FANCD2	3	10068113	10143614	1	1	5.10	1.7E-07	3.3E-03
	PPM1M	3	52279782	52284615	28	2	5.40	3.4E-08	6.5E-04
	ITIH4	3	52847006	52864717	136	5	5.38	3.7E-08	7.1E-04
	C4orf33	4	130014829	130034487	300	11	4.62	1.9E-06	3.7E-02
	PCDHB8	5	140557371	140560081	44	2	4.58	2.3E-06	4.5E-02
	PLEC	8	144989321	145050913	71	2	5.64	8.7E-09	1.7E-04
	FADS1	11	61567097	61584529	17	1	6.95	1.9E-12	3.6E-08
	LRFN4	11	66624558	66627946	17	2	4.69	1.3E-06	2.6E-02
	C15orf40	15	83657715	83681050	180	4	4.59	2.2E-06	4.3E-02
	ARFGAP3	22	43192530	43253408	135	2	4.59	2.2E-06	4.2E-02
Substantia nigra	*LMAN2L*	2	97371666	97405813	14	1	5.09	1.8E-07	3.4E-03
	PPM1M	3	52279782	52284615	2	1	6.11	5.0E-10	9.7E-06
	ITIH4	3	52847006	52864717	91	3	5.07	2.0E-07	4.0E-03
	PCDHA13	5	140261854	140391929	41	1	4.66	1.6E-06	3.1E-02
	TTLL1	22	43435522	43485434	118	3	5.04	2.3E-07	4.5E-03
Whole blood	*HTR6*	1	19991780	20006055	114	10	5.09	1.8E-07	3.5E-03
	CIAO1	2	96931884	96939917	430	20	4.85	6.1E-07	1.2E-02
	LMAN2L	2	97371666	97405813	19	3	6.45	5.8E-11	1.1E-06
	CNNM4	2	97426639	97477628	48	5	5.36	4.2E-08	8.1E-04
	UBE2E3	2	181845112	181928154	696	18	4.96	3.5E-07	6.8E-03
	PLCL1	2	198669426	199014608	726	11	4.60	2.2E-06	4.2E-02
	ZKSCAN7	3	44596667	44624975	259	15	5.19	1.0E-07	2.0E-03
	ZNF197	3	44666511	44689963	433	13	5.25	7.7E-08	1.5E-03
	ZNF502	3	44754135	44765323	434	13	5.24	8.1E-08	1.6E-03
	ZNF501	3	44771098	44778575	129	7	4.95	3.7E-07	7.2E-03
	KIAA1143	3	44790236	44803173	632	21	5.66	7.5E-09	1.5E-04
	GLYCTK	3	52321836	52329272	613	13	7.58	1.7E-14	3.3E-10

NT5DC2	3	52558385	52569093	612	15	7.03	1.0E-12	1.9E-08
SPCS1	3	52739792	52742198	139	1	6.22	2.5E-10	4.8E-06
ITIH3	3	52828784	52843025	154	3	6.12	4.8E-10	9.3E-06
ITIH4	3	52847006	52864717	1014	23	7.78	3.7E-15	7.2E-11
MUSTN1	3	52867131	52869235	575	11	7.29	1.6E-13	3.0E-09
TMEM110	3	52870772	52931597	522	9	7.02	1.1E-12	2.1E-08
SFMBT1	3	52933221	53080089	523	7	7.33	1.1E-13	2.2E-09
CD47	3	107761941	107809935	69	5	4.64	1.8E-06	3.4E-02
KDM3B	5	137688285	137772716	7	2	4.71	1.2E-06	2.4E-02
WDR55	5	140044384	140051930	317	9	4.64	1.7E-06	3.4E-02
FTSJ2	7	2273830	2281840	157	9	5.14	1.3E-07	2.6E-03
SCRN1	7	29959719	30029905	194	4	4.67	1.5E-06	2.9E-02
PLEKHA8	7	30067977	30157961	213	7	4.61	2.0E-06	3.9E-02
ZDHHC2	8	17013836	17080241	43	6	4.85	6.3E-07	1.2E-02
NRBP2	8	144915755	144924200	27	3	5.23	8.3E-08	1.6E-03
PLEC	8	144989321	145050913	258	11	5.96	1.2E-09	2.4E-05
PARP10	8	145051320	145060635	214	10	5.59	1.1E-08	2.2E-04
GRINA	8	145064226	145067596	144	3	5.65	8.2E-09	1.6E-04
SPATC1	8	145086582	145102015	134	3	5.66	7.4E-09	1.4E-04
ALDH1A1	9	75515578	75653633	215	11	4.84	6.5E-07	1.3E-02
ANXA1	9	75766721	75785309	272	11	4.95	3.7E-07	7.1E-03
ADO	10	64564516	64568239	101	5	4.73	1.1E-06	2.2E-02
XPNPEP1	10	111624524	111683311	162	8	6.36	1.0E-10	2.0E-06
ADD3	10	111765627	111895323	222	7	6.36	1.0E-10	1.9E-06
MYRF	11	61520121	61555990	105	11	5.36	4.2E-08	8.2E-04
TMEM258	11	61556602	61560085	67	3	7.17	3.7E-13	7.2E-09
FADS1	11	61567097	61584529	66	4	7.06	8.5E-13	1.6E-08
FADS2	11	61583675	61634826	231	24	6.97	1.6E-12	3.1E-08
NAA40	11	63706442	63724799	169	5	4.66	1.6E-06	3.1E-02
COX8A	11	63742079	63744015	123	3	4.59	2.2E-06	4.3E-02
SF3B2	11	65819264	65836382	246	21	5.09	1.8E-07	3.5E-03
PACS1	11	65837747	66012218	196	8	5.13	1.4E-07	2.8E-03
KLC2	11	66024765	66035332	24	3	5.02	2.6E-07	5.1E-03
RAB1B	11	66036056	66044963	76	2	5.19	1.1E-07	2.1E-03
YIF1A	11	66052051	66056638	32	2	4.81	7.4E-07	1.4E-02
RIN1	11	66099535	66104000	296	17	5.16	1.3E-07	2.4E-03
DPP3	11	66247484	66277130	348	15	4.67	1.5E-06	2.9E-02
ACTN3	11	66314312	66330799	55	3	5.38	3.8E-08	7.3E-04
CTSF	11	66330935	66336047	436	23	7.03	1.0E-12	2.0E-08
CCS	11	66360630	66373490	275	13	4.89	5.1E-07	1.0E-02
RCE1	11	66610883	66614003	209	11	5.60	1.1E-08	2.1E-04
LRFN4	11	66624558	66627946	377	20	6.03	8.0E-10	1.6E-05
PROZ	13	113812968	113826698	134	3	5.45	2.5E-08	4.9E-04
KLC1	14	104095525	104167888	561	16	4.99	3.0E-07	5.8E-03
XRCC3	14	104163945	104181823	513	13	4.72	1.2E-06	2.3E-02
LRRC57	15	42834720	42841002	26	2	4.93	4.0E-07	7.9E-03
C15orf40	15	83657715	83681050	407	20	5.16	1.2E-07	2.4E-03
NMB	15	85198360	85201802	190	4	6.30	1.5E-10	3.0E-06
FES	15	91427665	91439006	78	12	4.57	2.5E-06	4.8E-02

NFATC3	16	68118654	68263162	458	14	4.99	3.0E-07	5.8E-03
ORMDL3	17	38077294	38083884	591	14	4.82	7.3E-07	1.4E-02
NT5C	17	73126320	73127890	10	2	4.69	1.4E-06	2.6E-02
DIRAS1	19	2714565	2721390	157	10	4.61	2.0E-06	3.9E-02
YJEFN3	19	19639670	19648393	197	6	4.89	5.1E-07	1.0E-02
LPAR2	19	19734464	19739039	441	18	4.61	2.0E-06	3.9E-02
GMIP	19	19740285	19754457	159	5	4.75	1.0E-06	2.0E-02
ACTR5	20	37376933	37401089	205	10	4.90	4.9E-07	9.5E-03
PI3	20	43803540	43805185	192	3	4.76	9.9E-07	1.9E-02
SEMG1	20	43835605	43838414	199	3	4.80	8.1E-07	1.6E-02
KCNJ15	21	39601837	39675043	285	11	4.65	1.7E-06	3.2E-02
ARFGAP3	22	43192530	43253408	343	6	5.02	2.6E-07	5.1E-03
PACSIN2	22	43265772	43411184	409	9	4.84	6.3E-07	1.2E-02

Appendix Table 5. eQTL-informed gene-based analysis on variants associated with risk-taking propensity

Brain region	Gene	Chr	Start	Stop	NSNPs	NPARAM	Z	p	adj p
Amygdala	*CENPV*	17	16245831	16256812	270	3	4.81	7.4E-07	1.4E-02
Anterior cingulate	*ERICH2*	2	171627528	171655481	5	1	4.82	7.1E-07	1.4E-02
	CASP1	11	104896235	104905884	10	1	4.75	1.0E-06	2.0E-02
	MARVELD3	16	71660056	71675868	1	1	4.58	2.4E-06	4.6E-02
	ZSWIM7	17	15879874	15903006	275	3	4.79	8.5E-07	1.7E-02
	CENPV	17	16245831	16256812	300	5	4.89	5.1E-07	9.9E-03
	TRPV2	17	16318856	16340317	155	8	5.04	2.3E-07	4.5E-03
Caudate	*SDCCAG8*	1	243419307	243663393	27	1	5.92	1.6E-09	3.2E-05
	CADM2	3	85008133	86123579	107	6	5.66	7.6E-09	1.5E-04
	PPP1R13B	14	104200088	104315116	39	1	5.03	2.4E-07	4.7E-03
	KIF26A	14	104605060	104647235	36	3	4.96	3.5E-07	6.8E-03
	ADORA2B	17	15848231	15879210	9	1	4.69	1.4E-06	2.6E-02
	ZSWIM7	17	15879874	15903006	270	3	4.78	8.9E-07	1.7E-02
	CENPV	17	16245831	16256812	296	5	4.89	5.1E-07	9.9E-03
Cerebellar hemisphere	*RGS17*	6	153332026	153452389	30	3	4.60	2.1E-06	4.0E-02
	SND1	7	127292043	127732659	169	7	5.11	1.6E-07	3.1E-03
	ARHGAP19	10	98981930	99052430	12	1	4.84	6.6E-07	1.3E-02
	CARD16	11	104912053	104916051	332	7	4.56	2.5E-06	4.9E-02
	CACNA1C	12	2079952	2807115	99	4	4.65	1.7E-06	3.3E-02
	XRCC3	14	104163945	104181823	203	11	4.75	1.0E-06	2.0E-02
	ZSWIM7	17	15879874	15903006	284	3	4.76	9.6E-07	1.9E-02
	CENPV	17	16245831	16256812	270	3	4.81	7.7E-07	1.5E-02
Cerebellum	*ZNF362*	1	33721908	33766321	1	1	4.65	1.7E-06	3.2E-02
	SDCCAG8	1	243419307	243663393	144	5	5.89	1.9E-09	3.7E-05
	DPYSL5	2	27070969	27173219	316	5	4.59	2.2E-06	4.4E-02
	SIX3	2	45169037	45173216	20	4	4.77	9.4E-07	1.8E-02
	RGS17	6	153332026	153452389	106	7	4.88	5.4E-07	1.0E-02
	ARHGAP19	10	98981930	99052430	78	2	4.81	7.7E-07	1.5E-02
	CASP1	11	104896235	104905884	14	1	4.82	7.2E-07	1.4E-02
	CARD16	11	104912053	104916051	247	5	4.85	6.2E-07	1.2E-02
	CACNA1C	12	2079952	2807115	97	4	4.66	1.6E-06	3.0E-02
	XRCC3	14	104163945	104181823	142	6	5.01	2.7E-07	5.2E-03
	ZSWIM7	17	15879874	15903006	298	5	4.84	6.6E-07	1.3E-02
	CENPV	17	16245831	16256812	279	4	4.83	6.8E-07	1.3E-02
Cortex	*SDCCAG8*	1	243419307	243663393	58	2	6.15	4.0E-10	7.7E-06
	DPYSL5	2	27070969	27173219	338	6	4.63	1.8E-06	3.6E-02
	KHK	2	27309611	27323619	26	1	4.74	1.1E-06	2.1E-02
	GABRA2	4	46246470	46392056	82	4	4.92	4.4E-07	8.5E-03
	FAM184A	6	119280992	119470552	68	4	4.61	2.0E-06	3.9E-02
	LY6D	8	143866298	143868008	339	9	4.80	8.0E-07	1.6E-02
	XRCC3	14	104163945	104181823	77	3	4.90	4.7E-07	9.1E-03
	ZSWIM7	17	15879874	15903006	294	4	4.82	7.3E-07	1.4E-02
	PIGL	17	16120509	16230098	1	1	5.17	1.2E-07	2.3E-03
	CENPV	17	16245831	16256812	285	4	4.81	7.5E-07	1.5E-02
	TRPV2	17	16318856	16340317	149	8	5.09	1.8E-07	3.6E-03

Frontal cortex	*SDCCAG8*	1	243419307	243663393	46	2	5.71	5.7E-09	1.1E-04
	FRAT2	10	99092254	99094458	139	6	4.70	1.3E-06	2.5E-02
	ZSWIM7	17	15879874	15903006	275	3	4.79	8.2E-07	1.6E-02
	CENPV	17	16245831	16256812	273	3	4.81	7.7E-07	1.5E-02
	TRPV2	17	16318856	16340317	121	7	4.93	4.0E-07	7.9E-03
Hippocampus	*SDCCAG8*	1	243419307	243663393	50	2	5.71	5.8E-09	1.1E-04
	CADM2	3	85008133	86123579	168	13	6.17	3.4E-10	6.6E-06
	APOPT1	14	104029299	104057236	122	6	4.59	2.2E-06	4.4E-02
	PIGL	17	16120509	16230098	17	1	5.33	4.8E-08	9.4E-04
	CENPV	17	16245831	16256812	274	3	4.82	7.2E-07	1.4E-02
Hypothalamus	*CADM2*	3	85008133	86123579	58	3	6.26	1.9E-10	3.8E-06
	GABRA2	4	46246470	46392056	19	1	4.85	6.3E-07	1.2E-02
	ZSWIM7	17	15879874	15903006	269	3	4.76	9.7E-07	1.9E-02
	CENPV	17	16245831	16256812	270	3	4.81	7.5E-07	1.5E-02
	TRPV2	17	16318856	16340317	128	8	4.91	4.6E-07	8.9E-03
Accumbens	*KHK*	2	27309611	27323619	55	2	4.78	8.6E-07	1.7E-02
	CADM2	3	85008133	86123579	162	11	6.11	5.0E-10	9.7E-06
	ZSWIM7	17	15879874	15903006	275	3	4.79	8.2E-07	1.6E-02
	CENPV	17	16245831	16256812	309	5	4.79	8.5E-07	1.7E-02
	TRPV2	17	16318856	16340317	88	6	4.91	4.7E-07	9.1E-03
Putamen	*SDCCAG8*	1	243419307	243663393	42	3	5.79	3.6E-09	7.0E-05
	CADM2	3	85008133	86123579	165	8	5.27	7.0E-08	1.4E-03
	APOPT1	14	104029299	104057236	312	9	4.99	3.0E-07	5.8E-03
	PPP1R13B	14	104200088	104315116	23	2	4.94	3.9E-07	7.5E-03
	ZSWIM7	17	15879874	15903006	266	3	4.77	9.0E-07	1.8E-02
	CENPV	17	16245831	16256812	277	3	4.82	7.3E-07	1.4E-02
Spinal cord	*SDCCAG8*	1	243419307	243663393	49	1	5.72	5.4E-09	1.1E-04
	CADM2	3	85008133	86123579	175	11	5.29	6.0E-08	1.2E-03
	CENPV	17	16245831	16256812	292	5	4.88	5.4E-07	1.0E-02
Substantia nigra	*DPYSL5*	2	27070969	27173219	315	5	4.60	2.1E-06	4.0E-02
	CADM2	3	85008133	86123579	65	2	5.27	6.8E-08	1.3E-03
	TTC19	17	15902694	15932723	20	1	4.86	5.9E-07	1.1E-02
	CENPV	17	16245831	16256812	272	3	4.79	8.4E-07	1.6E-02
Whole blood	*CEP170*	1	243287730	243419284	136	5	6.15	3.8E-10	7.4E-06
	SDCCAG8	1	243419307	243663393	295	15	6.27	1.9E-10	3.6E-06
	FUT10	8	33228057	33330664	732	30	5.60	1.1E-08	2.1E-04
	STK32C	10	133996038	134145377	364	26	4.81	7.5E-07	1.5E-02
	BAG5	14	104022881	104029151	109	4	5.04	2.3E-07	4.5E-03
	KLC1	14	104095525	104167888	561	16	5.91	1.7E-09	3.2E-05
	XRCC3	14	104163945	104181823	513	13	5.72	5.4E-09	1.1E-04
	TDRD9	14	104394776	104519004	394	18	4.71	1.2E-06	2.4E-02
	WWP2	16	69796187	69975644	177	4	4.65	1.6E-06	3.2E-02
	ADORA2B	17	15848231	15879210	359	9	4.75	1.0E-06	2.0E-02
	TTC19	17	15902694	15932723	345	7	4.94	3.8E-07	7.4E-03
	NCOR1	17	15933408	16118874	363	7	4.88	5.3E-07	1.0E-02
	PIGL	17	16120509	16230098	63	2	5.09	1.7E-07	3.4E-03
	CENPV	17	16245831	16256812	309	6	4.97	3.4E-07	6.6E-03

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