Genome-wide analysis in UK Biobank identifies four loci associated with mood instability and genetic correlation with major depressive disorder and schizophrenia.

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Running title: Genome-wide analysis study of mood instability.

Abstract

Mood instability is a core clinical feature of affective and psychotic disorders. In keeping with the Research Domain Criteria (RDoC) approach, it may be a useful construct for identifying biology that cuts across psychiatric categories. We aimed to investigate the biological validity of a simple measure of mood instability and evaluate its genetic relationship with major depressive disorder (MDD), bipolar disorder (BD), schizophrenia and attention deficit hyperactivity disorder (ADHD). We conducted a genome-wide association study (GWAS) of mood instability in 53,525 cases and 60,443 controls from UK Biobank, identifying four independently-associated loci (on chromosomes eight, nine, 14 and 18), and a common single nucleotide polymorphism (SNP)-based heritability estimate of approximately 8%. We found a strong genetic correlation between mood instability and MDD (r_g=0.60, SE=0.07, p=8.95x10^{-17}) and a small but significant genetic correlation with schizophrenia (r_g=0.11, SE=0.04, p=0.01), but no genetic correlation with BD or ADHD. Several genes at the associated loci may have a role in mood instability, including the *deleted in colorectal cancer (DCC)* gene, *eukaryotic initiation factor 2B (eIF2B2)*, *placental growth factor (PGF)*, and *protein tyrosine phosphatase, receptor type D (PTPRD)*. Strengths of this study include the very large sample size but our measure of mood instability may be limited by the use of a single question. Overall, this work suggests a polygenic basis for mood instability. This simple measure can be obtained in very large samples; our findings suggest that doing so may offer the opportunity to illuminate the fundamental biology of mood regulation.

Introduction

Mood instability is a common clinical feature of affective and psychotic disorders, particularly major depressive disorder (MDD), bipolar disorder (BD) and schizophrenia[1]. It may also be relatively common in the general population, estimated to affect around 13% of individuals[2]. As a dimensional psychopathological trait, it is potentially a useful construct in line with the Research Domain Criteria (RDoC) approach[3]. Mood instability may be of fundamental importance for understanding the pathophysiology of MDD and BD, as well as conditions such as borderline personality disorder, attention deficit hyperactivity disorder (ADHD) and psychosis[4]. This trait is reported by 40-60% of individuals with MDD[5] and is recognised as part of the prodromal stage of BD[6]. In established BD, it is a clinical feature which independently predicts poor functional outcome[7].

Population-based studies such as the Adult Psychiatric Morbidity Survey (APMS) have defined mood instability based on responses to a single question, while clinical studies have made use of more detailed rating scales[4]. However, there is a lack of consensus about how best to measure and classify mood instability, and none of the currently available instruments adequately capture intensity, speed and frequency of affective change, or physiological and behavioural correlates. A recent systematic review proposed that mood instability be defined as "rapid oscillations of intense affect, with a difficulty in regulating these oscillations or their behavioural consequences"[8]. Applying this definition will require the future development and validation of a multidimensional assessment of mood instability, which is currently not available.

Within the UK Biobank population cohort of over 0.5 million individuals[9], the baseline assessment interview contained a question of relevance to mood instability, specifically: *"Does your mood often go up and down?"* This is similar to the question for mood instability used within the APMS (*"Do you have a lot of sudden mood changes, suffered over the last several years").* Hypothesizing that this simple question taps into pathological mood instability, we predicted it would be more commonly endorsed by individuals within UK Biobank with MDD and BD, compared to individuals with no

psychiatric disorder. Moreover, under the hypothesis that this question taps into a trait with cross-disorder pathophysiological relevance, we predicted that a genome-wide association study (GWAS) would identify shared genetic liability to mood instability and risk for psychiatric disorders in which disordered mood is a feature, including MDD, BD, schizophrenia and ADHD. Given the size of the sample, we also aimed to identify loci associated with this measure of mood instability.

Materials and methods

Sample

UK Biobank is a large cohort of more than 502,000 United Kingdom residents, aged between 40 and 69 years[9]. The aim of UK Biobank is to study the genetic, environmental and lifestyle factors that cause or prevent disease in middle and older age. Baseline assessments occurred over a four-year period, from 2006 to 2010, across 22 United Kingdom (UK) centres. These assessments were comprehensive and included social, cognitive, lifestyle, and physical health measures. For the present study, we used the first genetic data release based on approximately one third of UK Biobank participants. Aiming to maximise homogeneity, we restricted the sample to those who reported being of white UK ancestry (around 95% of the sample).

UK Biobank obtained informed consent from all participants and this study was conducted under generic approval from the NHS National Research Ethics Service (approval letter dated 13 May 2016, Ref 16/NW/0274) and under UK Biobank approvals for application #6553 “Genome-wide association studies of mental health” (PI Daniel Smith).

Mood instability phenotype

As part of the baseline assessment, UK Biobank participants completed the 12 items of the neuroticism scale from the Eysenck Personality Questionnaire-Revised Short Form (EPQ-R-S)[10]. One of these items assesses mood instability, namely: *"Does your mood often go up and down?"*

Participants responding 'yes' to this question were considered to be cases of mood instability and those responding 'no' were considered controls. From the control sample, we excluded those who reported being on psychotropic medication, and those who reported a physician diagnosis of psychiatric disorder (including MDD, BD, anxiety/panic attacks, 'nervous breakdown', schizophrenia and deliberate self-harm/suicide attempt).

After quality control steps (detailed below) and exclusions (3,679 participants responded 'don't know' and 211 responded 'prefer not to say'), the final sample for genetic analysis comprised 53,525 cases of mood instability and 60,443 controls. Mood instability cases were younger than controls (mean age 55.8 years (SD=8.05) versus 57.7 years (SD=7.74); $p<0.0001$) and had a greater proportion of females (55.5% versus 49.6%; $p<0.0001$).

Genotyping and imputation

In June 2015, UK Biobank released the first set of genotypic data for 152,729 UK Biobank participants. Approximately 67% of this sample was genotyped using the Affymetrix UK Biobank Axiom array (Santa Clara, CA, USA) and the remaining 33% were genotyped using the Affymetrix UK BiLEVE Axiom array. These arrays have over 95% content in common. Only autosomal data were available under the data release. Data were pre-imputed by UK Biobank as fully described in the UK Biobank interim release documentation[11]. Briefly, after removing genotyped SNPs that were outliers, or were multiallelic or of low frequency (minor allele frequency (MAF) <1%), phasing was performed using a modified version of SHAPEIT2 and imputation was carried out using IMPUTE2 algorithms, as implemented in a C++ platform for computational efficiency[12, 13]. Imputation was based upon a merged reference panel of 87,696,888 biallelic variants on 12,570 haplotypes constituted from the 1000 Genomes Phase 3 and UK10K haplotype panels[14]. Variants with MAF <0.001% were excluded from the imputed marker set. Stringent quality control before release was applied by the Wellcome Trust Centre for Human Genetics, as described in UK Biobank documentation[15].

Statistical analyses

Quality control and association analyses

Before all analyses, further quality control measures were applied. Individuals were removed based on UK Biobank genomic analysis exclusions (Biobank Data Dictionary item #22010), relatedness (#22012: genetic relatedness factor; a random member of each set of individuals with KING-estimated kinship coefficient >0.0442 was removed), gender mismatch (#22001: genetic sex), ancestry (#22006: ethnic grouping; principal component (PC) analysis identified probable Caucasians within those individuals who were self-identified as British and other individuals were removed from the analysis), and quality control failure in the UK BiLEVE study (#22050: UK BiLEVE Affymetrix quality control for samples and #22051: UK BiLEVE genotype quality control for samples). A sample of 113,968 individuals remained for further analyses. Of these, 53,525 were classed as cases and 60,443 were classified as controls. Genotype data were further filtered by removal of SNPs with Hardy–Weinberg equilibrium $P<10^{-6}$, with MAF <0.01, with imputation quality score <0.4 and with data on <90% of the sample after excluding genotype calls made with <90% posterior probability, after which 8,797,848 variants were retained.

Association analysis was conducted using logistic regression under a model of additive allelic effects with sex, age, genotyping array and the first 8 PCs (Biobank Data Dictionary items #22009.01 to #22009.08) as covariates. Sex and age were included as covariates because cases and controls differed significantly on these measures. Genetic PCs were included to control for hidden population structure within the sample, and the first 8 PCs, out of 15 available in the Biobank, were selected after visual inspection of each pair of PCs, taking forward only those that resulted in multiple clusters of individuals after excluding individuals self-reporting as being of non-white British ancestry (Biobank Data Dictionary item #22006). The threshold for genome-wide significance was $p<5.0x10^{-8}$.

Heritability and genetic correlation between mood instability and MDD, BD and schizophrenia

We applied Linkage Disequilibrium Score Regression (LDSR)[16] to the GWAS summary statistics to estimate SNP heritability (h^2_{SNP}). Genetic correlations between mood instability and MDD, BD, schizophrenia and ADHD were also evaluated using LDSR[17] (with unconstrained intercept), a process that corrects for potential sample overlap without relying on the availability of individual genotypes [16]. For the MDD, BD, schizophrenia and ADHD phenotypes, we used GWAS summary statistics provided by the Psychiatric Genomics Consortium (http://www.med.unc.edu/pgc/)[18-20]. Note that for the purposes of these genetic correlation analyses we re-ran the GWAS of mood instability excluding from the cases those 9,865 participants who reported being on psychotropic medication, or who self-reported psychiatric disorder (MDD, BD, anxiety/panic attacks, 'nervous breakdown', schizophrenia and deliberate self-harm/suicide attempt). This secondary GWAS output (rather than the primary GWAS reported below) was used for the genetic correlation calculations, the rationale being that this was a more conservative approach which would avoid genetic correlations between mood instability and MDD/BD/schizophrenia/ADHD being driven by a subset of individuals with psychiatric disorder.

Results

Mood instability in MDD and BD within UK Biobank

In previous work we have identified individuals within UK Biobank with a probable diagnosis of mood disorder, including cases of MDD (sub-divided into single episode MDD, recurrent moderate MDD and recurrent severe MDD) and BD, as well as non-mood disordered controls[21]. These classifications were independent of response to the mood instability question or other questions from the EPQ-R-S. For the group of participants who could be classified in this way, we assessed the proportion with mood instability within each mood disorder category. All mood disorder groups had a significantly greater proportion of individuals with mood instability compared with the control

group (Table 1), in which the prevalence was 35.3%. This proportion was highest in the BD group (74.0%) followed by the three MDD groups (71.7% for recurrent severe MDD, 64.2% for recurrent moderate MDD and 43.7% for single episode MDD). Note that there were too few UK Biobank participants with schizophrenia or ADHD to allow for an assessment of the prevalence of mood instability in these groups.

GWAS of mood instability

The mood instability GWAS results are summarised in Figure 1 (Manhattan plot), Figure 2 (QQ plot) and Table 2 (genome-wide significant loci associated with mood instability). Regional plots are provided in Figures 3a-3d.

Overall, the GWAS data showed modest deviation in the test statistics compared with the null (λ_{GC} =1.13); this was negligible in the context of sample size (λ_{GC} 1000=1.002). LDSR suggested that deviation from the null was due to a polygenic architecture in which h^2_{SNP} accounted for approximately 8% of the population variance in mood instability (observed scale h^2_{SNP}=0.077 (SE 0.007)), rather than inflation due to unconstrained population structure (LD regression intercept=0.998 (SE 0.009)).

We observed four independent genomic loci exhibiting genome-wide significant associations with mood instability (Figure 1, Table 2 and Figures 3a-d), on chromosome eight (index SNP rs7829975; *CLDN23 and MFHAS1*), chromosome nine (index SNP rs10959826; *PTPRD*), chromosome 14 (index SNP rs397852991; *LTBP2, AREL1, FCF1, YLPM1, PROX2, DLST, RPS6KL1, PGF, EIF2B2* and *MLH3*) and chromosome 18 (index SNP rs8084280; *DCC*). In total, there were 111 genome-wide significant SNPs across all loci. Given the functional alleles that drive association signals in GWAS may not affect the nearest gene, we use the above gene names to provide a guide to location rather than to imply that altered function or expression of those genes are the sources of the association signals.

Genetic correlation of mood instability with MDD, schizophrenia and BD

We identified strong genetic correlation between mood instability and MDD (r_g=0.60, SE=0.07, p=8.95x10^{-17}) and a smaller, but significant, correlation between mood instability and schizophrenia (r_g=0.11, SE=0.04, p=0.01) (Table 3). We did not find significant overlap between mood instability and BD (r_g=0.01, SE=0.05, p=0.27) or ADHD (r_g=0.14, SE=0.11, p=0.18).

Discussion

We have identified four independent loci associated with mood instability within a large population cohort, in what is to date the only GWAS of this phenotype. We also identified a SNP-based heritability estimate for mood instability of approximately 8%, and a strong genetic correlation between mood instability and MDD, suggesting substantial genetic overlap between mood instability and vulnerability to MDD. There was a small but significant genetic correlation between mood instability and schizophrenia but no genetic correlation with BD or ADHD.

The strong genetic correlation between mood instability and MDD is of interest because it is consistent with the hypothesis that at least part of the pathophysiology of MDD might include a reduced capacity to effectively regulate affective states. In support of this is evidence that individuals with MDD tend to have maladaptive responses to intense emotions, responding with worry, rumination and self-criticism, which can then exacerbate negative emotional states[22].

The lack of genetic correlation between mood instability and BD was unexpected, given that mood instability is considered a core deficit in BD[4] and was more common in our BD cases than MDD cases. Similarly, a genetic correlation between mood instability and ADHD might have been anticipated. This lack of correlation between mood instability and both BD and ADHD is difficult to account for but might be explained by the relatively under-powered nature of the BD and ADHD analyses,

compared to the analyses used for MDD and schizophrenia. It is worth noting that, although not significant, the magnitude of the genetic correlation between mood instability and ADHD was 0.14.

It is not possible to be certain which of the genes within associated loci are likely to be most relevant to the pathophysiology of mood instability but several genes of interest were identified. For example, the lead SNP within the associated region on chromosome 18 lies in intron 9 of the *DCC netrin 1 receptor* (originally named *deleted in colorectal cancer; DCC)* gene, with no other protein-coding genes for >500kb on either side (Figure 3d). *DCC* is the receptor for the guidance cue *netrin-1*, which has a central role in the development of the nervous system, including (but not limited to) the organization and function of mesocorticolimbic dopamine systems[23]. Recent studies have shown a range of human phenotypes associated with loss-of-function mutations in *DCC*, including agenesis of the corpus callosum, learning disabilities and mirror movements, all associated with a large-scale disruption of the development of commissural connectivity and lateralisation[24, 25]. Manitt and colleagues have identified that *DCC* has a role in regulating the connectivity of the medial prefrontal cortex during adolescence and found that *DCC* expression was elevated in the brain tissue of antidepressant-free subjects who committed suicide[26]. This suggests a possible role for *DCC* variants in increasing predisposition to mood instability and mood disorders, as well as related psychopathological phenotypes.

The associated region on chromosome 14 contains at least 10 candidate genes (Table 2 and Figure 3c). One of these is *eukaryotic initiation factor 2B (EIF2B2),* mutations in which are known to cause a range of clinically heterogeneous leukodystrophies[27]. Reduced white matter integrity has been consistently associated with negative emotionality traits (such as harm avoidance, neuroticism and trait anxiety)[28], as well as with MDD and BD[29]. It is therefore possible that variation in *EIF2B2* may have a role in mood instability.

Another gene within the associated region on chromosome 14 is *placental growth factor (PGF),* a member of the *angiogenic vascular endothelial growth factor (VEGF)* family[30, 31], which is expressed

at high levels in the placenta and thyroid[32]. *PGF* has a wide range of functions, including embryonic thyroid development[33] and immune system function[34, 35], as well as a role in atherosclerosis, angiogenesis in cancer, cutaneous delayed-type hypersensitivity, obesity, rheumatoid arthritis and pre-eclampsia[34, 36-39]. *PGF* may be of interest because of the long-established association between thyroid dysfunction and both MDD and BD[40], along with the recent observation that pre-eclampsia may be a marker for the subsequent development of mood disorders[41].

Also of interest is the finding that the gene for *protein tyrosine phosphatase, receptor type D (PTPRD)* lies within 1Mb of the associated region on chromosome 9 (Figure 3b). *PTPRD* encodes a receptor-type protein tyrosine phosphatase known to be expressed in brain and with an organising role at a variety of synapses, including those that play a role in synaptic plasticity[42]. As such, it may have a role in a broad range of psychopathology.

Two of the genomic loci associated with mood instability (on chromosomes eight and nine) overlap with loci found to be associated with neuroticism in a recent GWAS and meta-analysis which combined data from the UK Biobank cohort, the Generation Scotland cohort, and a cohort from the Queensland Institute of Medical Research[43]. The neuroticism study made use of scores on the 12-item EPQ-R-S questionnaire, of which one of the questions was the mood instability question used in the present study. This overlap in findings suggests that mood instability is a key component of neuroticism as defined by the EPQ-R-S and that at least some of the gene variants implicated in mood instability are likely to contribute to the broader phenotype of neuroticism. We did not assess for genetic correlation between mood instability and neuroticism using LDSR because both GWAS outputs were predominantly from the same UK Biobank sample.

Strengths and limitations

To the best of our knowledge, this is the first reported GWAS of mood instability. It has enabled objective estimates of heritability and genetic correlation with important psychiatric disorders to be

made for the first time; but some limitations are acknowledged. The mood instability phenotype used was based on response to a single-item question (*"Does your mood often go up and down?"*) which may be an imperfect measure of mood instability. Approximately 44% of the whole UK Biobank cohort answered 'yes' to this question, a much larger proportion than the 13% of participants classified as having mood instability within the UK APMS[2]. This may be because the assessment of mood instability in the APMS was based on a slightly different question *("Do you have a lot of sudden mood changes"*) and because respondents had to additionally report that they *"suffered this symptom over the last several years".* Clearly, a potential limitation of self-report is the possibility of responder bias and, further, a more complete and objectively-assessed measure of mood instability would have been preferable. However, this was not available to us in the UK Biobank phenotype dataset and is unlikely to be feasible to collect within a population cohort of this size.

Conclusions

Despite a recognition that mood instability is likely to be an important phenotype underpinning a range of psychiatric disorders - particularly mood disorders[4] - there has to date been very little work on its neural correlates. Early investigations tentatively suggest a role for altered function and/or connectivity of the amygdala[44] but this is an area which is currently under-developed. It is hoped that our findings will stimulate new research on mood instability, which may be a clinically useful and biologically valid trait that cuts across traditional diagnostic categories[45].

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Conflict of interest

All authors declare no conflicts of interest. JPP is a member of UK Biobank advisory committee; this had no bearing on the study.

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Figure legends

Figure 1. Manhattan plot of GWAS of mood instability in UK Biobank (n=113,968).

Figure 2. QQ plot for UK Biobank mood instability GWAS results.

Figures 3a-3d. Regional plots of the four genome-wide significant mood instability loci.

Figure 3a. Chromosome 8 region 8.5MB-8.8MB

Figure 3b. Chromosome 9 region 10MB – 12MB

Figure 3c. Chromosome 14 region 75MB-75.5MB

Figure 3d. Chromosome 18 region 50.5MB-51MB

Table 1. Proportion of individuals with mood instability within mood disorder groups, compared to non-mood disordered controls.

	Mood instability N (%)	Pearson Chi-squared	P-value
BD	1,180 (74.0)	$1.0x10^3$	<0.001
Recurrent MDD, severe	6,303 (71.7)	$4.5x10^3$	<0.001
Recurrent MDD, moderate	9,509 (64.2)	$4.4x10^3$	<0.001
Single episode MDD	3,403 (43.7)	221.1	<0.001
Non-mood disordered controls	30,844 (35.3)	-	-

BD bipolar disorder; MDD major depressive disorder

Table 2. Genome-wide significant loci associated with mood instability in UK Biobank.

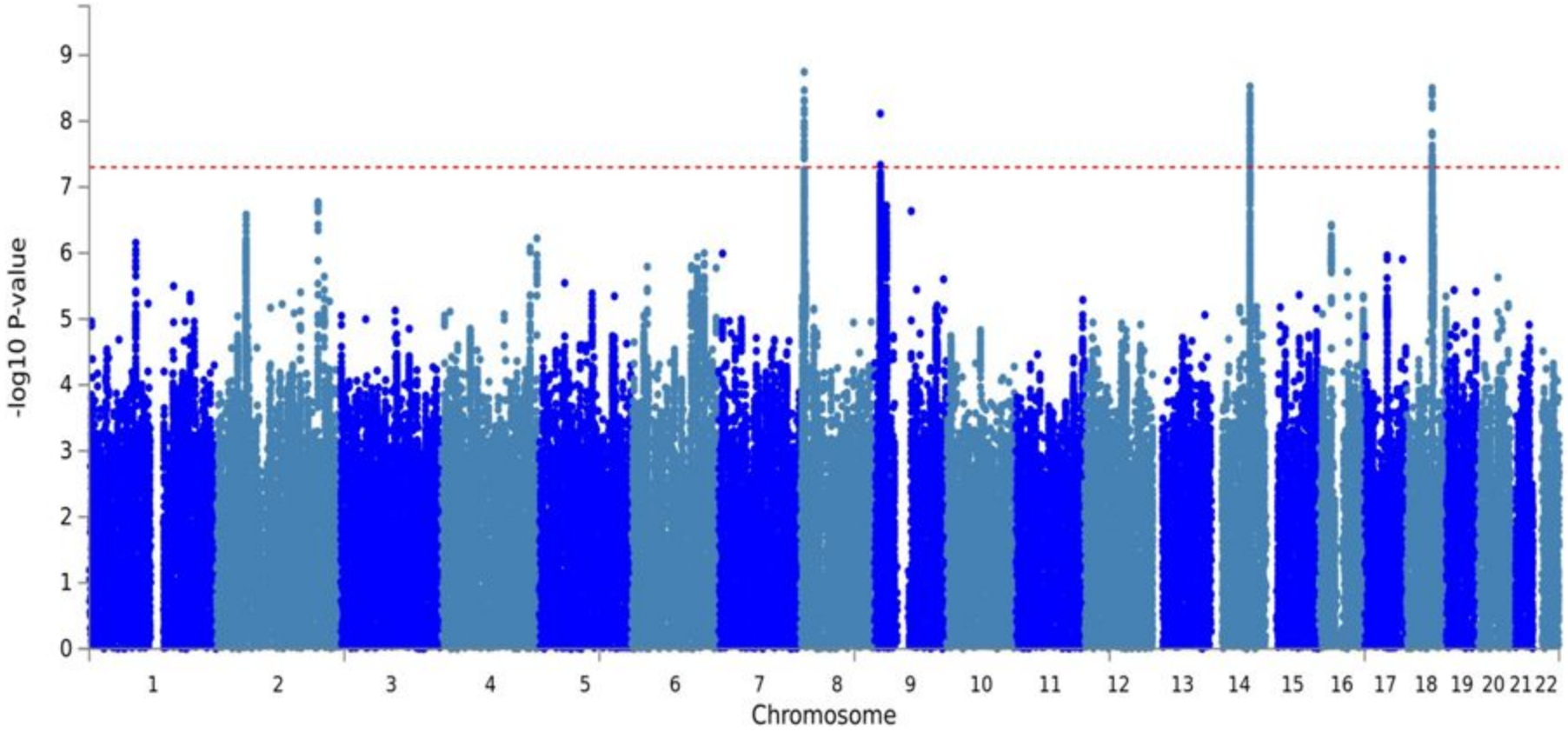
Index SNP	Chromosome	Position	A1/A2	Beta (SE)	P-value	Associated region	Genes
rs7829975	8	8,548,117	T/A	-0.051 (0.0085)	1.8×10^{-9}	8,088,230– 8,730,488	*CLDN23, MFHAS1*
rs10959826	9	11,459,410	A/G	-0.060 (0.01)	7.7×10^{-9}	11,267,514 – 11,810,796	*PTPRD*
rs397852991	14	75,268,920	CA/C	-0.053 (0.0088)	2.98×10^{-9}	75,182,937 – 75,377,008	*LTBP2, AREL1, FCF1, YLPM1, PROX2, DLST, RPS6KL1, PGF, EIF2B2, MLH3*
rs8084280	18	50,726,749	A/T	-0.050 (0.0085)	3.15×10^{-9}	50,612,329 – 50,907,127	*DCC*

Shown are LD-independent genome-wide significant SNP associations for mood instability (sorted by genomic position according to NCBI Build 37). Chromosome and Position denote the location of the index SNP. A1/A2 denote the reference and other allele. Beta = logistic regression coefficient for allele1, SE = standard error for Beta. P-value = the probability of getting the derived test statistic under the null hypothesis. The final column indicates protein-coding genes at the associated loci (see regional plots in supplementary information) or, where there are no genes at the associated locus, the nearest gene if less than 1 MB from the locus.

Table 3. Genetic correlation between mood instability and MDD, schizophrenia, BD and ADHD.

	r_g	SE	Z	P	h^2 obs	h^2 obs SE	h^2 int	h^2 int se	Gcov int	Gcov int SE
MDD	0.60	0.07	8.32	8.95×10^{-17}	0.11	0.01	0.99	0.008	-0.0019	0.006
Schizophrenia	0.11	0.04	2.48	0.01	0.25	0.01	1.03	0.01	0.0008	0.007
BD	0.01	0.05	0.27	0.27	0.12	0.01	1.02	0.008	0.0069	0.005
ADHD	0.14	0.11	1.35	0.18	0.397	0.15	1.01	0.007	0.0046	0.0044

r_g = genetic correlation with mood instability; SE = standard error of the genetic correlation; Z = the test statistic; P= p-value. h^2 obs = heritability on the observed scale; h^2 obs SE = the standard error of the heritability; h^2 int = intercept of the heritability; h^2 int SE = standard error of the heritability intercept; Gcov int = intercept of the genetic covariance; Gcov int SE = standard error of the genetic covariance intercept. MDD = major depressive disorder; BD = bipolar disorder; ADHD = attention deficit hyperactivity disorder.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3
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5
6
7
8
9
1
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3
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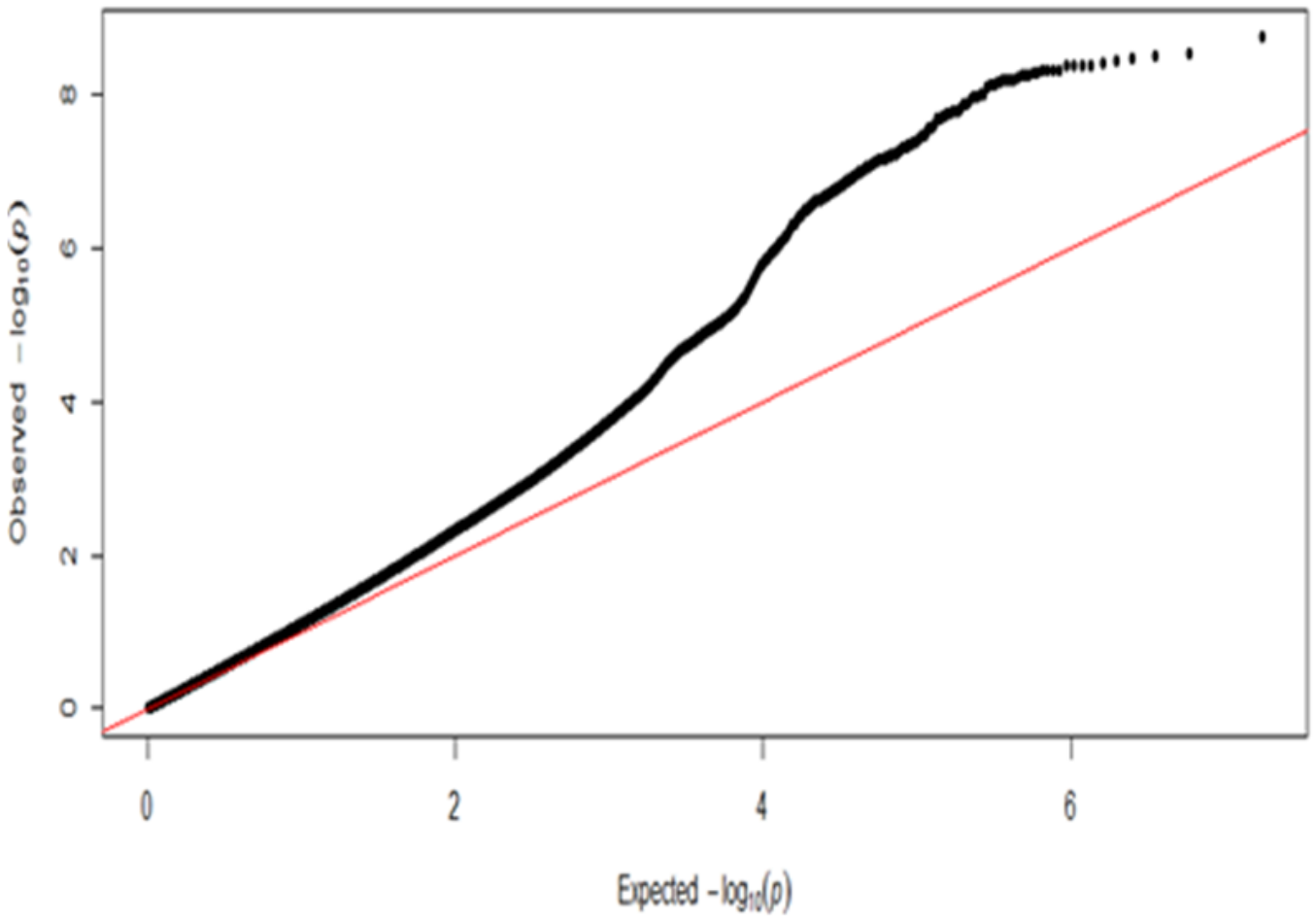
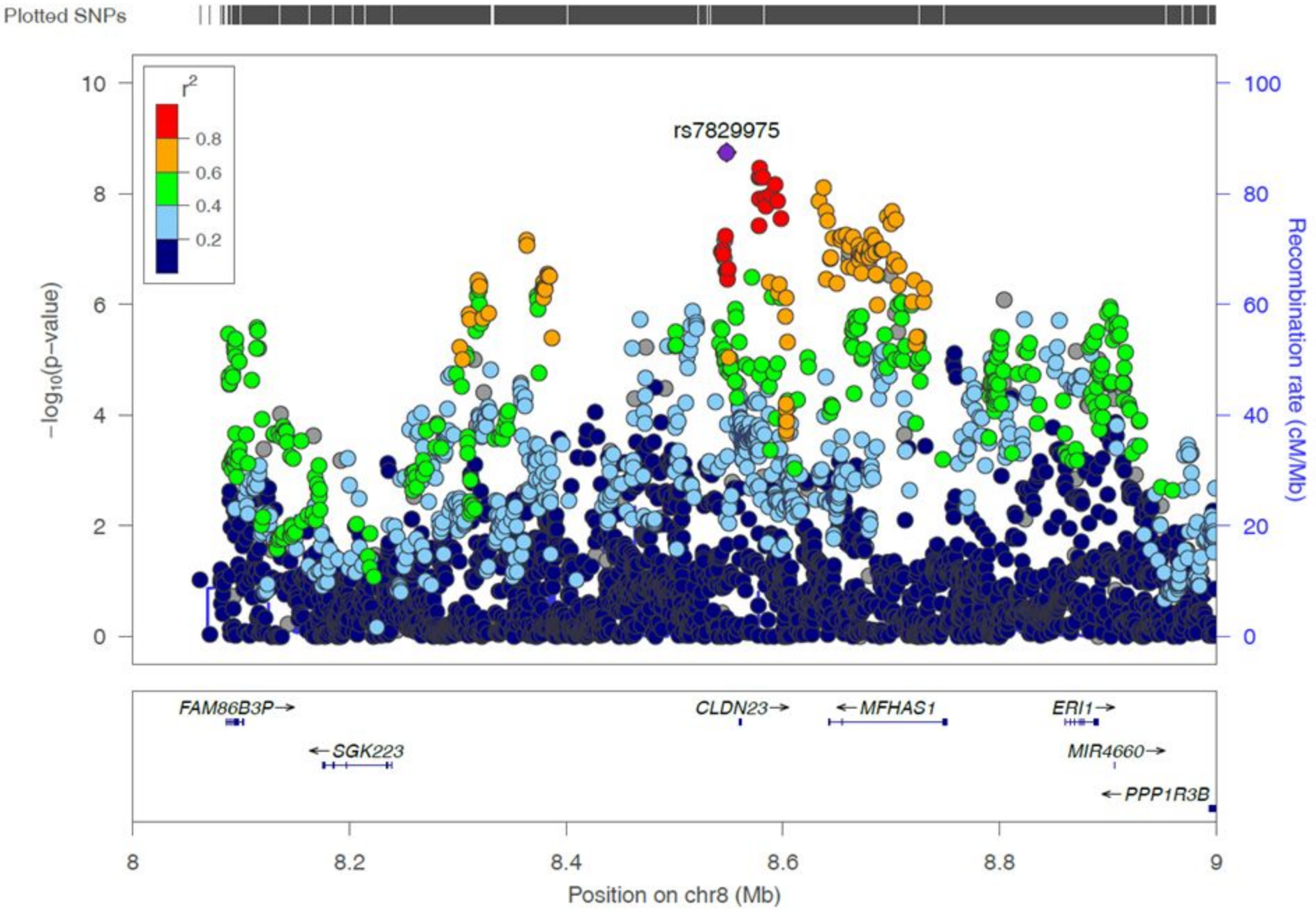
15
16
17
18
19
20
21
22
Chromosome

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r²
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0.6
0.4
0.2
rs7829975
−log10(p−value)
Recombination rate (cM/Mb)
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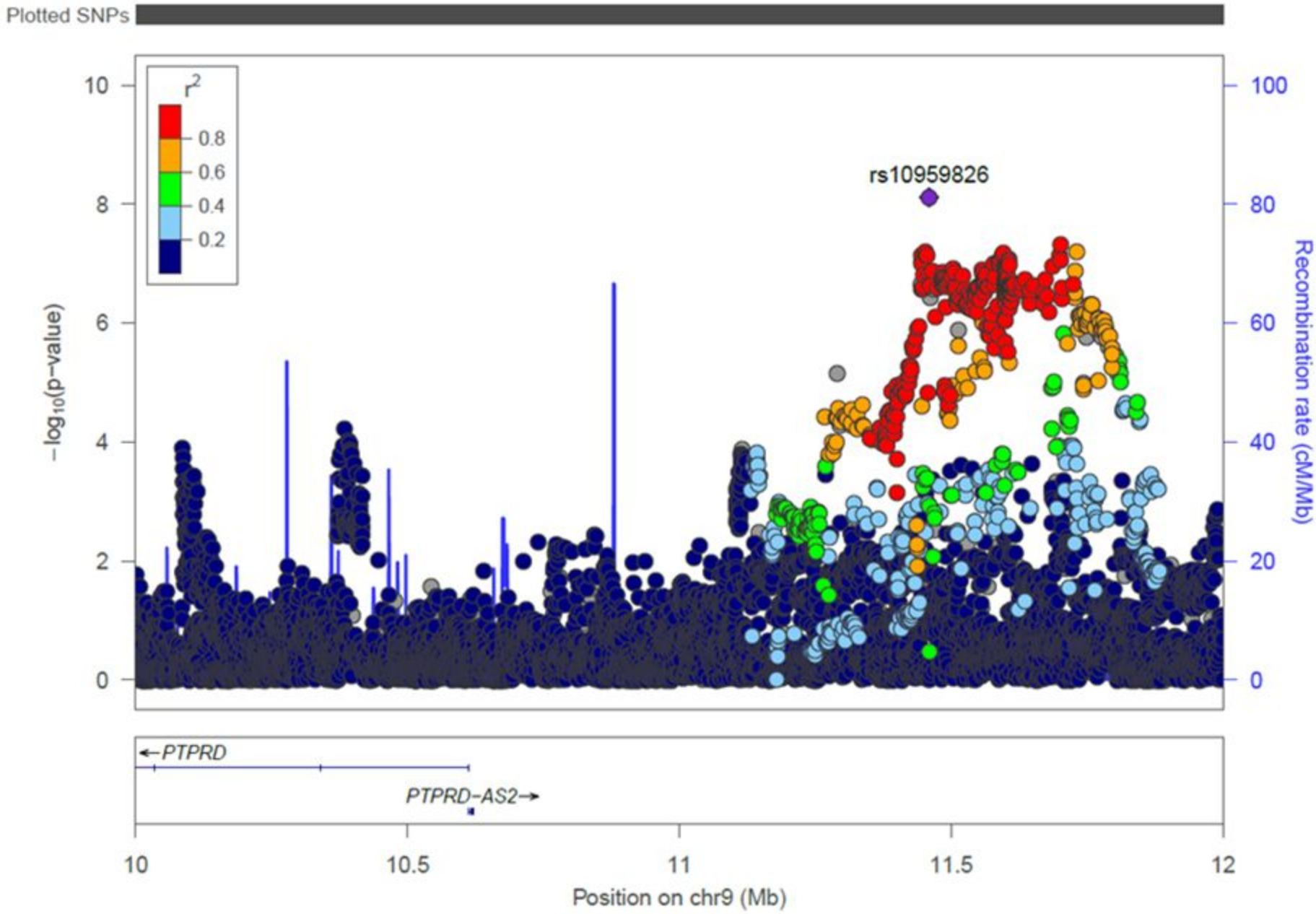
←SGK223
CLDN23→
←MFHAS1
ERI1→
MIR4660→
←PPP1R3B
Position on chr8 (Mb)


Plotted SNPs
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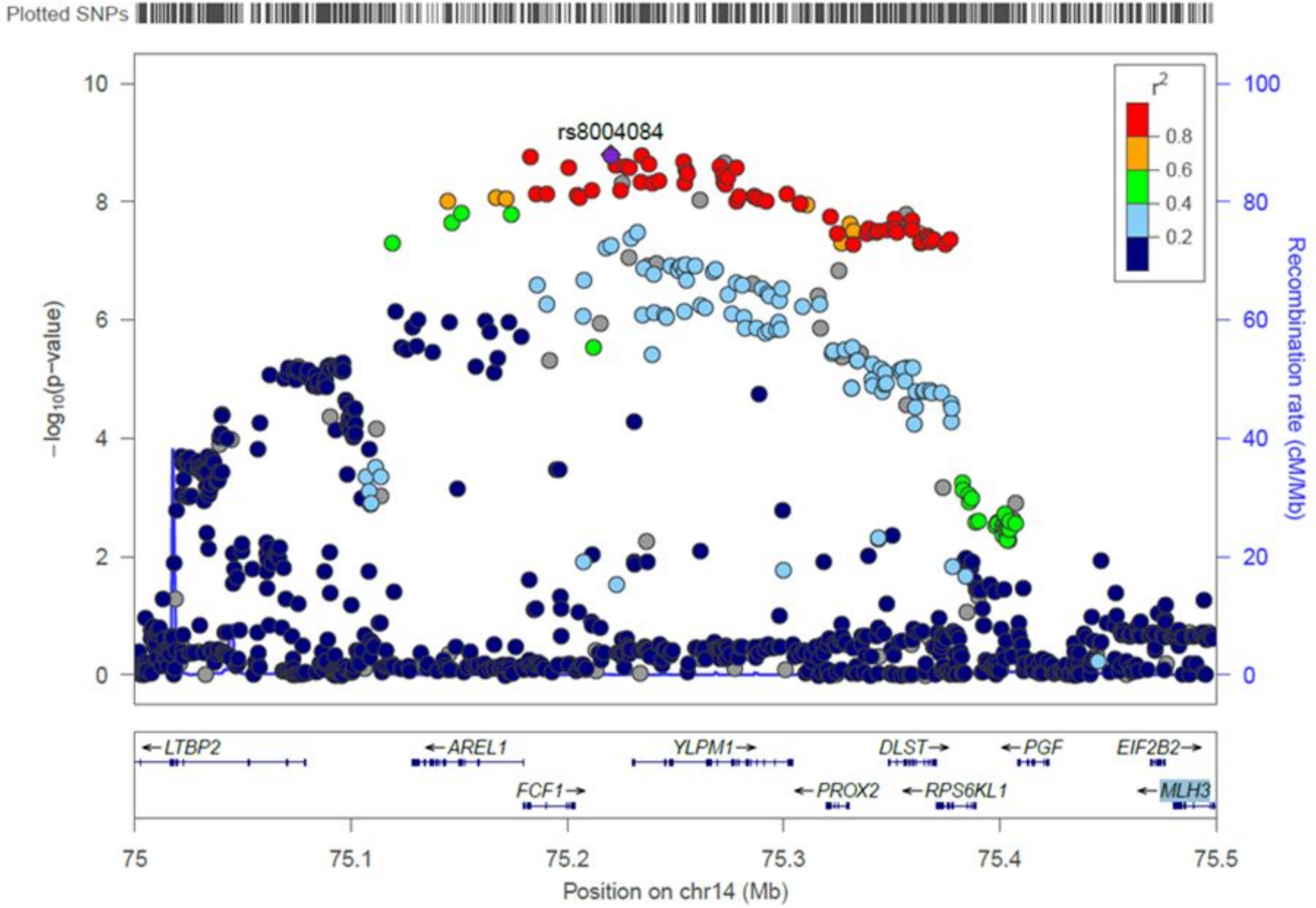
0.4
0.2
rs10959826
−log10(p−value)
Recombination rate (cM/Mb)
PTPRD
PTPRD−AS2
Position on chr9 (Mb)


Plotted SNPs
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0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
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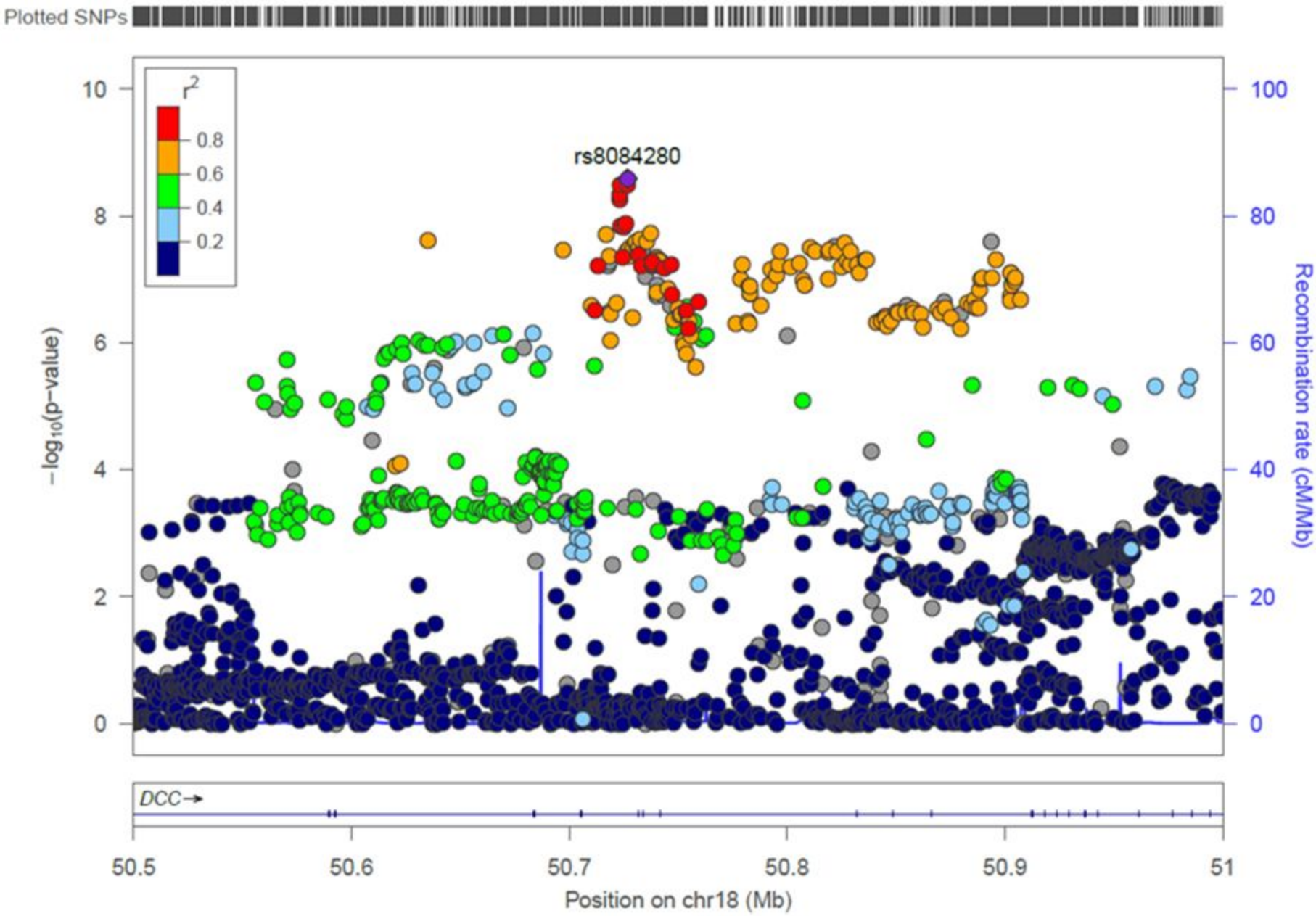
6
4
2
0
100
80
60
40
20
0
←LTBP2
←AREL1
YLPM1→
DLST→
←PGF
EIF2B2→
FCF1→
←PROX2
←RPS6KL1
←MLH3
75
75.1
75.2
75.3
75.4
75.5
Position on chr14 (Mb)


Plotted SNPs
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0.6
0.4
0.2
rs8084280
10
8
6
4
2
0
−log10(p−value)
100
80
60
40
20
0
Recombination rate (cM/Mb)
DCC→
50.5
50.6
50.7
50.8
50.9
51
Position on chr18 (Mb)