Genome-wide analysis of 113,968 individuals in UK Biobank identifies four loci associated with mood instability.

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Running title: GWAS of mood instability in UK Biobank

Abstract

Mood instability is a core clinical feature of affective disorders, particularly major depressive disorder (MDD) and bipolar disorder (BD). It may be a useful construct in line with the Research Domain Criteria (RDoC) approach, which proposes studying dimensional psychopathological traits that cut across diagnostic categories as a more effective strategy for identifying the underlying biology of psychiatric disorders. Here we report a genome-wide association study (GWAS) of mood instability in a very large study of 53,525 cases and 60,443 controls from the UK Biobank cohort, the only such GWAS reported to date. We identified four independent loci (on chromosomes eight, nine, 14 and 18) significantly associated with mood instability, with a common SNP-based heritability estimate for mood instability of approximately 8%. We also found a strong genetic correlation between mood instability and MDD (0.60, SE=0.07, $p=8.95 \times 10^{-17}$), a small but statistically significant genetic correlation with schizophrenia (0.11, SE=0.04, p=0.01), but no genetic correlation with BD. Several candidate genes harbouring variants in linkage disequilibrium with the associated loci may have a role in the pathophysiology of mood disorders, including the *DCC netrin 1 receptor (DCC)*, *eukaryotic initiation factor 2B (EIF2B2)*, *placental growth factor (PGF)* and *protein tyrosine phosphatase, receptor type D (PTPRD)* genes. Strengths of this study include the large sample size; however, our measure of mood instability may be limited by the use of a single self-reported question. Overall, this work suggests a polygenic basis for mood instability and opens up the field for the further biological investigation of this important cross-diagnostic psychopathological trait.

Introduction

Mood instability is a common clinical feature of affective disorders, particularly major depressive disorder (MDD) and bipolar disorder (BD)[1]. It is also relatively common in the general population, estimated to affect around 13% of individuals[2]. As a dimensional psychopathological trait, it is 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 recurrent MDD and BD, as well as conditions such as borderline personality disorder and psychosis[4]. This trait is reported by 40-60% of individuals with MDD [5] and is recognised as part of the bipolar prodrome[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 and clinical studies have made use of rating scales[4]. However, there is a lack of consensus about how best to measure and classify mood instability, with none of the currently available instruments able to adequately capture complexities such as intensity, speed and frequency of affective change, as well as physiological and behavioural correlates. A recent systematic review proposed that mood instability could be defined as "rapid oscillations of intense affect, with difficulty regulating these oscillations or their behavioural consequences"[8]. As such, this definition will necessitate the future development and validation of a multidimensional assessment of mood instability, which is currently not available.

Within the UK Biobank cohort of over 0.5 million individuals[9], the baseline assessment contained a question which can be considered a useful measure of mood instability within the constraints of a large general population sample: *"Does your mood often go up and down?"* This is similar to the questions for mood instability used within the APMS (*"Do you have a lot of sudden mood changes, suffered over the last several years").* As such, we hypothesised that this brief, single-item measure of mood instability within UK Biobank would be more common among individuals in the cohort with BD and MDD than for individuals with no psychiatric disorder. We also hypothesised that a genome-wide association study (GWAS) would identify loci associated with this measure of mood instability and, further, that there would be a genetic correlation between mood instability and the psychiatric disorders MDD, BD and schizophrenia.

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 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 United Kingdom (UK) ancestry and for whom information on the mood instability phenotype measure was available.

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 self-reported psychiatric disorder (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, array, assessment centre and the first 8 PCs (Biobank Data Dictionary items #22009.01 to #22009.08) as covariates. 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).

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 and schizophrenia were also evaluated using LDSR[17], a process that corrects for potential sample overlap without relying on the availability of individual genotypes[16]. For the MDD, BD and schizophrenia 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 (as well as controls) those participants who reported being on psychotropic medication, and those who self-reported psychiatric disorder (MDD, BD, anxiety/panic attacks, 'nervous breakdown', schizophrenia and deliberate self-harm/suicide attempt). This 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.

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 did not depend on responses 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).

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). 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 a total of four independent loci exhibiting genome-wide significant associations with mood instability (Figure 1, Table 2 and Figure 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.

Genetic correlation of mood instability with MDD, schizophrenia and BD

We identified strong genetic correlation between mood instability and MDD (genetic correlation 0.60, SE=0.07, p=8.95 $x10^{-17}$) and a smaller, but significant, correlation between mood instability and schizophrenia (genetic correlation 0.11, SE=0.04, p=0.01) (Table 3). We found no significant overlap between mood instability and BD (genetic correlation 0.01, SE=0.05, p=0.27).

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.

Although it is not possible to be certain which of the genes within the associated loci are likely to be most relevant to the pathophysiology of mood instability, 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[22]. 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[23,24]. Manitt and colleagues also recently identified *DCC* as the first dopamine neuron gene to regulate connectivity of the medial prefrontal cortex during adolescence and demonstrated that *DCC* expression was elevated in the brain tissue of antidepressant-free subjects who committed suicide[25]. This suggests a possible role for *DCC* variants in increasing predisposition to mood disorders and mood instability, as well as other psychopathological phenotypes such as psychosis.

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[26]. Reduced white matter integrity has been consistently associated with traits of negative emotionality (such as harm avoidance, neuroticism and trait anxiety)[27], as well as with MDD and BD[28]. It is therefore possible that common variation in *EIF2B2* may have a role in mood instability.

Similarly, also within the associated region on chromosome 14, is *placental growth factor (PGF),* a member of the angiogenic vascular endothelial growth factor (VEGF) family[29], which has high expression in the placenta and thyroid[30]. *PGF* has a wide range of functions, including embryonic thyroid development[31] and immune system function[32,33], as well as a putative role in atherosclerosis, angiogenesis in cancer, cutaneous delayed-type hypersensitivity, obesity, rheumatoid arthritis and pre-eclampsia[32,34-37]. *PGF* may be of interest because of the long-established association between thyroid dysfunction and both MDD and BD[38], as well as the recent observation that pre-eclampsia may be a marker for the subsequent development of mood disorders[39].

Also of potential 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.

Strengths and limitations

To our knowledge, this is the largest GWAS of mood instability conducted to date, 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 clinically-relevant 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 more complete and objectively-assessed measure of mood instability would have been preferable, but this was not available to us within the UK Biobank phenotype dataset.

The lack of genetic association between mood instability and BD was surprising, given that mood instability was more common in BD cases than MDD cases within the UK Biobank cohort, but this might be explained by the use in our genetic correlation analyses of a GWAS output for BD which came from a study which could be considered relatively under-powered (and which will soon be replaced by an as yet unpublished BD GWAS from the Psychiatric Genomics Consortium).

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[40] but this is an area of research which is currently under-developed. It is hoped that our findings will stimulate new biological research in the area of mood instability. In the longer-term, our work may also contribute to a revised classification of mood disorders which focuses on dimensional traits which cut across traditional diagnostic categories[41].

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Conflict of interest

JPP is a member of UK Biobank advisory committee; this had no bearing on the study.

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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)	221.0817	<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}	8548117 - 8704330	*CLDN23, MFHAS1*
rs10959826	9	11,459,410	A/G	-0.060 (0.01)	7.7×10^{-9}	11459410 - 11701596	*PTPRD*
rs397852991	14	75,268,920	CA/C	-0.053 (0.0088)	2.98×10^{-9}	75144618 - 75359229	*LTBP2, AREL1, FCF1, YLPM1, PROX2, DLST, RPS6KL1, PGF, EIF2B2, MLH3*
rs8084280	18	50,726,749	A/T	-0.05 (0.0085)	3.15×10^{-9}	50635119 - 50893647	*DCC*

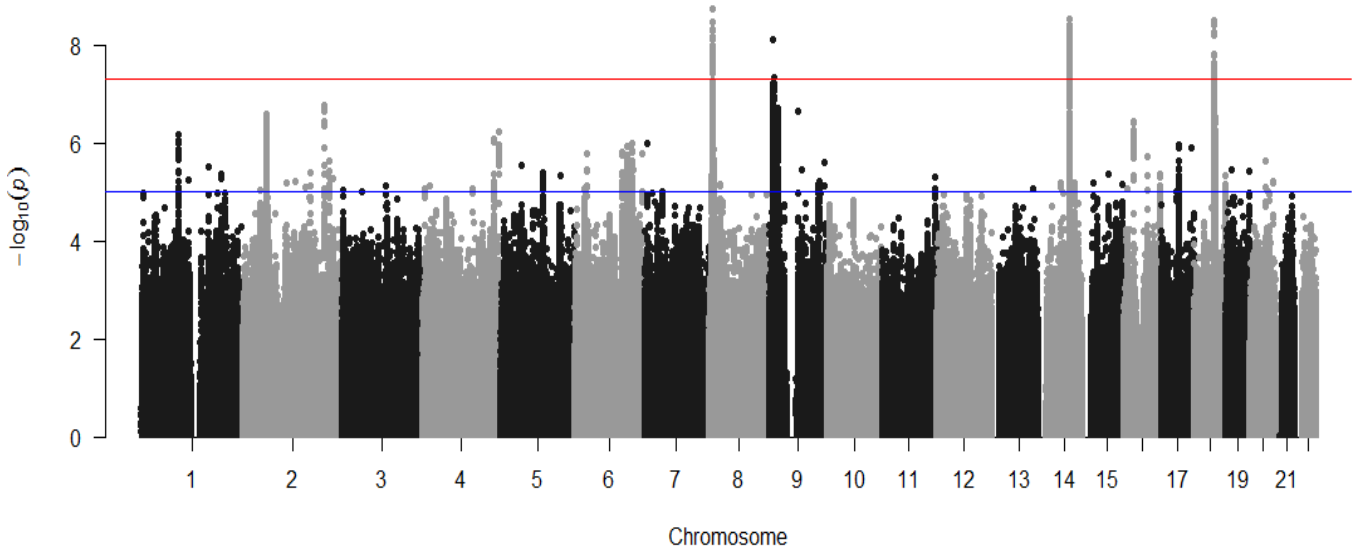
Shown are LD-independent genome-wide significant SNP associations for mood instability (sorted by genomic position according to UCSC hg19/NCBI Build 37). Chromosome and Position denote the location of the index SNP. A1/A2 denote the reference and other allele. Beta = logistic regression coefficient for 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 reference sequence genes at the associated loci (see region 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 and BD.

	Rg	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

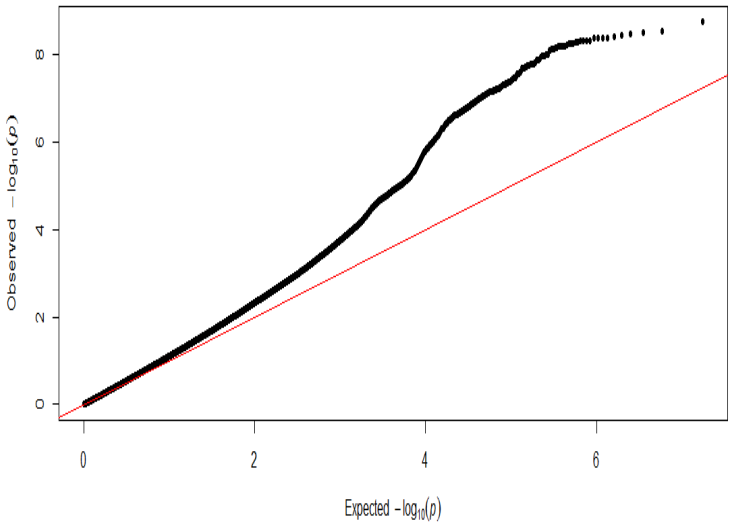
Rg = genetic correlation with mood instability; SE = standard error of the genetic correlation; Z = the test statistic; P= p-value. h^2 obs = heritability on the observed scale; h^2 obs SE = the standard error of the heritability; h^2 int = intercept of the heritability; h^2 int SE = standard error of the heritability intercept; Gcov int = intercept of the genetic covariance; Gcov int SE = standard error of the genetic covariance intercept.

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



Red line = genome-wide significance threshold; blue line = suggestive genome wide significance threshold.

Figure 2. QQ plot for genome-wide association with mood instability in UK Biobank.



Red line = theoretical distribution under the null hypothesis of no association.

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

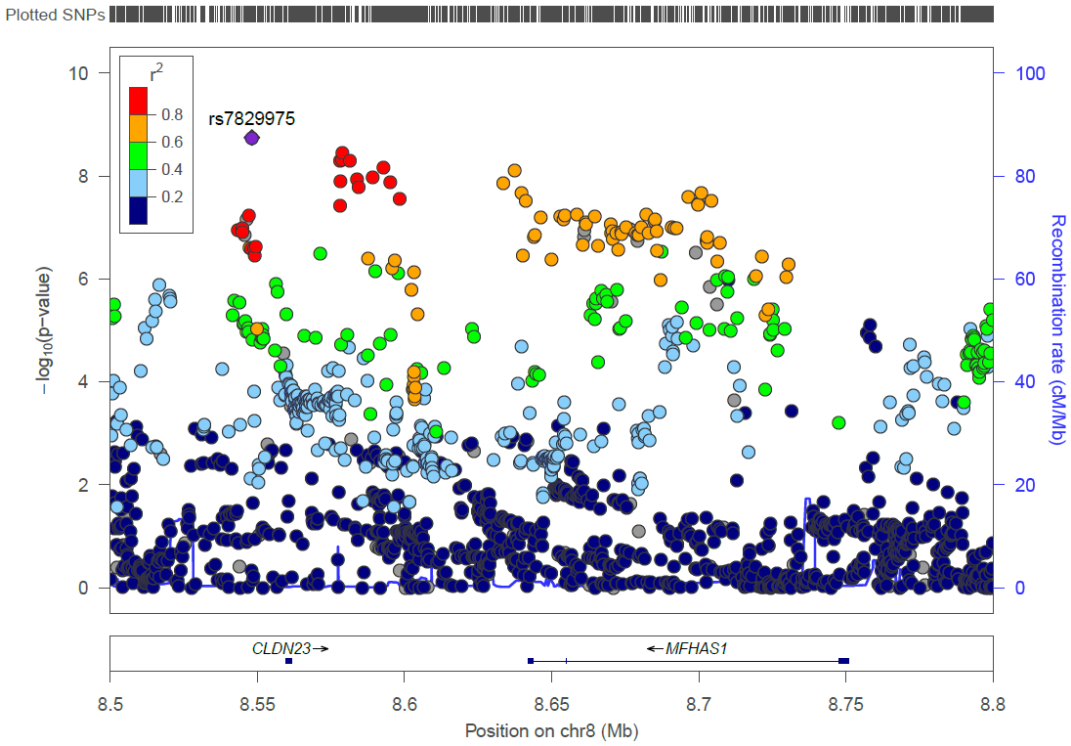


Figure 3a. Chromosome 8 region 8.5MB-8.8MB

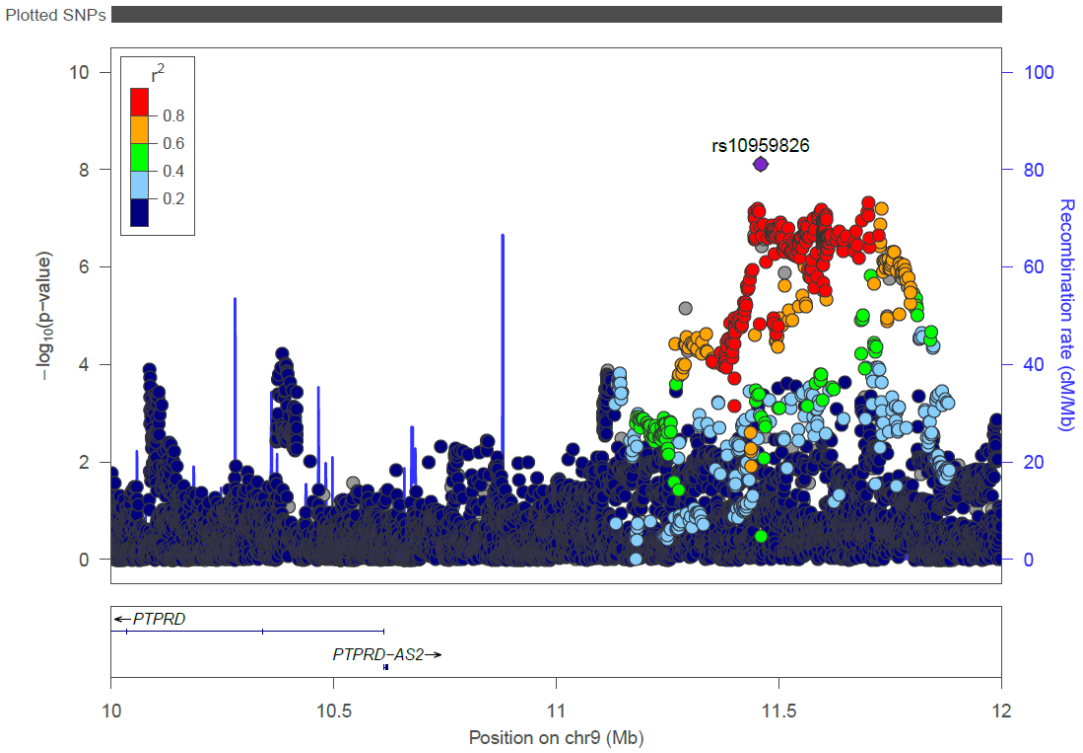


Figure 3b. Chromosome 9 region 10MB – 12MB

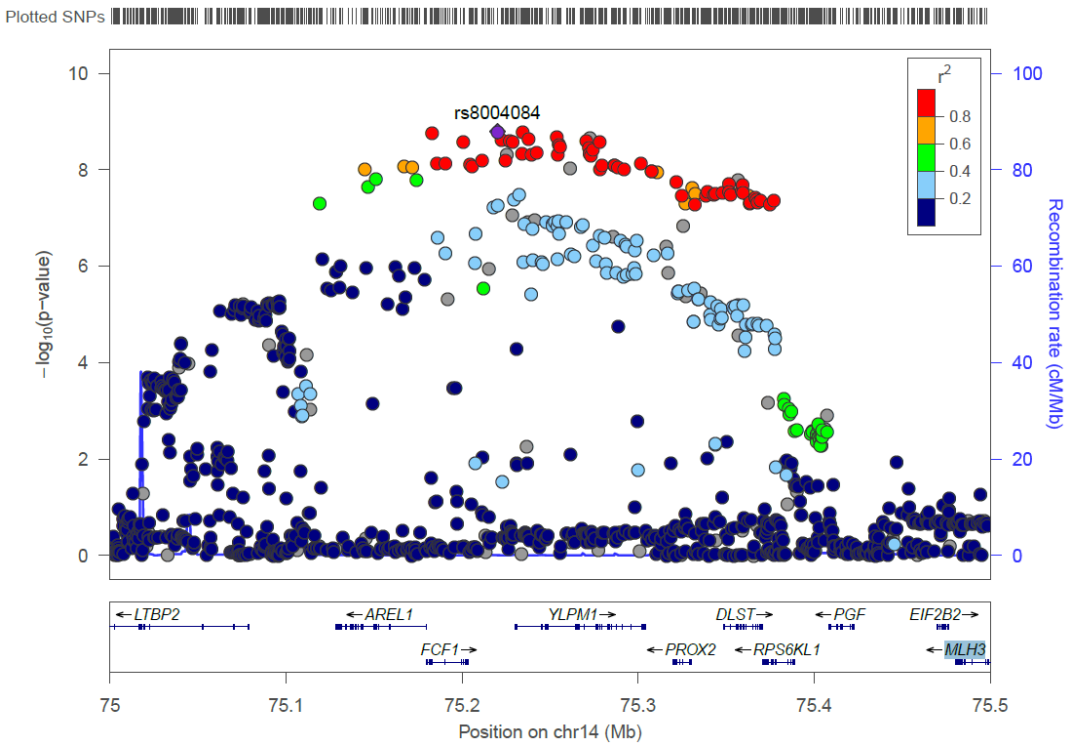


Figure 3c. Chromosome 14 region 75MB-75.5MB

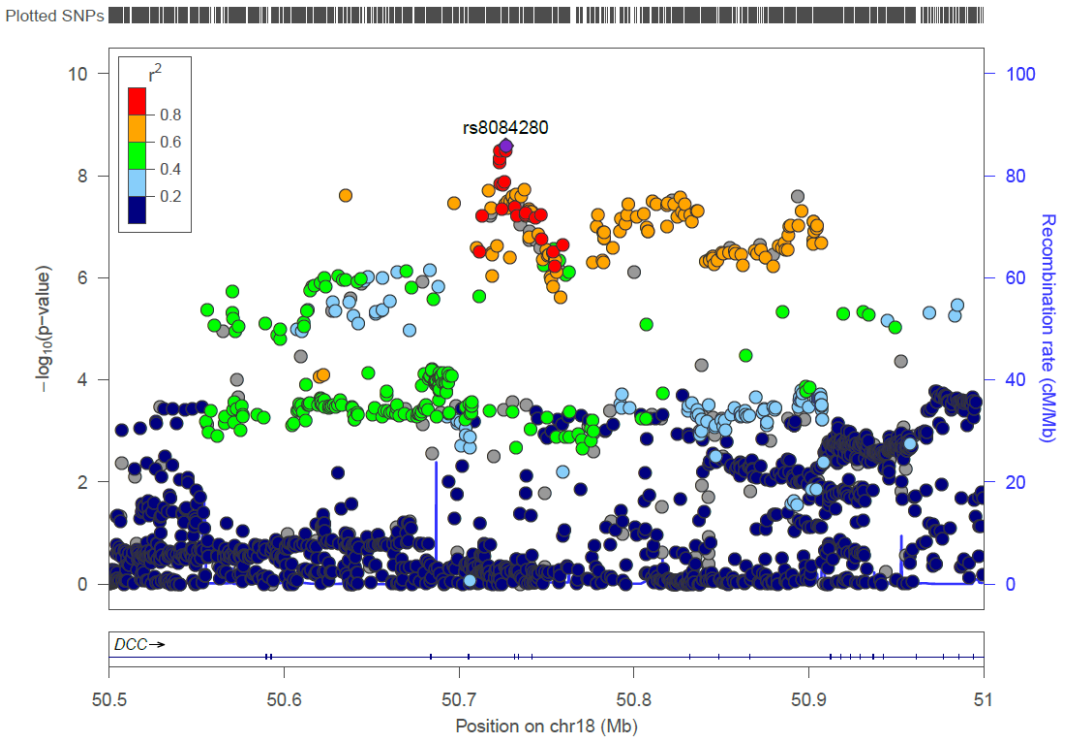


Figure 3d. Chromosome 18 region 50.5MB-51MB