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SHORT COMMUNICATION

# Genome-wide analysis of emotional lability in adult attention deficit hyperactivity disorder (ADHD)

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**Abstract**
Emotional lability is strongly associated with Attention Deficit Hyperactivity Disorder (ADHD), represents a major source of impairment and predicts poor clinical outcome in ADHD. Given that no specific genes with a role in the co-occurrence of both conditions have been described, we conducted a GWAS of emotional lability in 563 adults with ADHD. Despite not reaching genome-wide significance, the results highlighted genes related with neurotransmission, cognitive function and a wide range of psychiatric disorders that have emotional lability as common clinical feature. By constructing polygenic risk scores on mood instability in the UK Biobank sample and assessing their association with emotional lability in our clinical dataset, we found

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suggestive evidence of common genetic variation contributing to emotional lability in general population and in clinically diagnosed ADHD. Although not conclusive, these tentative results are in agreement with previous studies that suggest emotion dysregulation as a transdiagnostic construct and highlight the need for further investigation to disentangle the genetic basis of mood instability in ADHD and co-occurring psychiatric disorders.


## 1. Introduction

Emotional lability, also known as mood instability, emotional impulsivity, emotional dysregulation, emotional impulsiveness, affective lability, mood lability and deficient emotional self-regulation, is a common clinical feature of a range of psychiatric disorders including major depressive disorder, bipolar disorder, borderline personality disorder or Attention Deficit Hyperactivity Disorder (ADHD) (Childress and Sallee, 2015). Particularly, ADHD diagnostic criteria currently recognizes symptoms of emotional lability as an associated feature of ADHD (Merwood et al., 2014), although the extent of the phenotypic and etiologic associations between emotional lability and symptoms of hyperactivity-impulsivity or inattention remains unclear.

The prevalence of emotional lability symptoms is about 25–45% in children and between 30% and 70% in adults with ADHD (Childress and Sallee, 2015). Moreover, emotional lability has been highlighted as a contributor to the functional impairment in youth and adults with ADHD, it may increase the severity of ADHD symptomatology as well as comorbid disorders and is associated with ADHD persistence and lower quality of life (Shaw et al., 2014).

The nature of the relationship between emotional lability and ADHD is still unclear. Converging evidence in twin and family studies support significant genetic overlap between emotional dysregulation and ADHD symptoms and higher risk of emotional lability in family members of ADHD subjects (Merwood et al., 2014; Riglin et al., 2017). These results are in line with the association between ADHD polygenic risk scores and early-life irritability found in a population-based cohort and in an ADHD clinical sample (Riglin et al., 2017). Pharmacological studies also document a concomitant decline in symptoms of hyperactivity-impulsivity, inattention, and emotional lability in response to methylphenidate and atomoxetine in adults (Marchant et al., 2011). All this evidence suggests that emotional lability and ADHD may arise as a result of a common etiology, point to emotional lability as etiologically relevant to the core ADHD phenotype and support that it may be targeted in clinical intervention (Merwood et al., 2014).

Although ADHD has been the focus of considerable genetic research, to date there is little work focused on the genetic underpinnings of emotional lability or on the genetic basis of the link between them. Both conditions have a complex genetic architecture, with heritability estimates of 74% (Faraone and Larsson, 2018) and 25% (Coccaro et al., 2012) for ADHD and emotional lability, respectively, but the role of specific genes remains still unclear. Although each of the associated variants appears to account for a relatively small proportion of the variance in both traits, SNPs were estimated to account for 10—28% of the heritability of ADHD (Demontis et al., 2019) and 8% of the heritability of mood instability (Ward et al., 2017).

Genetic research on ADHD or emotional lability has mainly focused on common variants through candidate gene or genome-wide association studies. A very recent GWAS meta-analysis in 20,183 ADHD cases and 35,191 controls reported 12 genome-wide significant loci including genes involved in neurodevelopmental processes and evolutionarily conserved genomic regions. Two GWAS on emotional lability have been run so far. The first one identified a genome-wide significant association between the interleukin receptor 2A gene, *IL2RA*, and emotion dysregulation in males, as well as enrichment for genes involved in different psychiatric disorders and in the calcium signaling pathway (Powers et al., 2016). Furthemore, Ward et al. (2017) conducted a GWAS on mood instability in 53,525 cases and 60,443 controls from the UK biobank which revealed four genome-wide significant loci and genetic correlation between mood instability and different psychiatric disorders.

Given that emotional lability is strongly associated with ADHD but no specific genes with a role in the co-occurrence of both conditions have been described, we conducted for the first time a GWAS of emotional lability in adults with ADHD to identify genes and biological pathways underlying this trait that represents a major source of impairment and predicts poor clinical outcome in ADHD.

## 2. Experimental procedures

### 2.1. Stage 1: GWAS of emotional lability in ADHD

#### 2.1.1. Participants

The clinical sample comprised 563 adults of European ancestry (67% males; mean age = 33 years; SD = 10.5), who met ADHD diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Exclusion criteria included mental retardation, schizophrenia or other psychotic disorders, symptoms of substance intoxication and withdrawal and neurological or systemic disorders that might explain ADHD symptoms. All subjects were evaluated at Hospital Universitari Vall d'Hebron of Barcelona (Spain) and diagnosis was blind to genotype. The study was approved by the Clinical Research Ethics Committee of our Institution, all methods were performed in accordance with the relevant guidelines and regulations, and written informed consent was obtained from all subjects before inclusion in the study.

#### 2.1.2. Clinical assessment

The evaluation of the ADHD diagnosis was carried out with the Spanish version of the Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID parts I and II). Emotional lability was evaluated using the following items from the self-reported Conners' Adult ADHD Rating Scale-long version (CAARS-S:L): "I am irritable", "I have unpredictable moods", "Many things set me off easily", "I have a hot

temper/I lose patience easily", "I still throw tantrums" and "I get frustrated easily". Each item is scored on a four-point Likert scale ranging from 0 to 3 (0= *not at all or never*; 1 = *just a little, once in a while*; 2 = *pretty much, often*; 3 = *very much, very frequently*). Mean score in the CAARS' emotional lability subscale was 8.99 ranging from 0 to 18.

#### 2.1.3. Genome-wide association study

Genomic DNA was isolated from peripheral blood leukocytes by the salting-out procedure. Subjects were genotyped in three different waves using the Illumina HumanOmni1-Quad ($n = 355$), HumanOmni 2.5 ($n = 166$) and the PsychChip ($n = 42$) arrays. Pre-imputation quality control and principal components analysis were implemented with the Ricopili pipeline (https://sites.google.com/a/broadinstitute.org/ricopili/), and ancestry outliers were excluded. Genotype imputation was performed using the European population haplotypes of the 1000 Genomes Project Phase I as the reference panel for waves 1 and 2 and the 1000 Genomes Project Phase III for wave 3 (The 1000 Genomes Project Consortium, 2015). Individuals with >2% genotype missingness were removed, as well as SNPs with low call rate (<0.99), with minor allele frequency (MAF) <0.01, INFO score bellow 0.8 or failing the Hardy–Weinberg equilibrium test ($P<1e{-}06$). Post-imputation best-guess genotype data from a total of 2,777,520 markers available in all three datasets were tested for association with emotional lability through proportional odds logistic regression using the function "polr", from the "MASS" R package with the ologit-gwas script (https://github.com/edm1/ologit-gwas). Age, sex, genotyping waves, ADHD subtype, comorbid psychiatric disorders and the first five principal components were included as covariates. The quantile–quantile and manhattan plots were drawn using the qqman R package (http://cran.r-project.org/web/packages/qqman). Index SNPs were defined based on clumping of variants using the PLINK software with default settings ($p_1 = 0.0001$, $p_2 = 0.01$, $r^2 = 0.5$, kb = 250) (https://www.cog-genomics.org/plink2/). Annotation was performed in accordance with the Human hg19 genome build considering genes within a ±10 kb distance from index SNPs. Locus Zoom interactive web-based visualization tool (http://locuszoom.org/) was used to generate regional plots of the top index SNP with a ±2 Mb flanking distance.

#### 2.1.4. Gene-based and gene-set analyses

The gene-based and gene-set association analyses were conducted using MAGMA (De Leeuw et al., 2015). Gene regions were defined as ±10 kb for each gene according to the UCSC Genome Browser GRCh37/hg19 release (https://genome.ucsc.edu/) and used the 1000 Genomes Project Phase I dataset as reference panel to estimate patterns of LD for each locus (The 1000 Genomes Project Consortium, 2015). For the gene-set analysis the Gene Ontology (GO) and canonical pathways downloaded from MSigDB (http://www.broadinstitute.org/gsea/msigdb) were considered. Correction for multiple testing was applied using false discovery rate (FDR) with a threshold of 5% and 10,000 permutations in the gene-based and gene-set analyses, respectively.

### 2.2. Stage 2: polygenic risk score analysis based on UK Biobank mood instability GWAS

We generated Polygenic Risk Scores (PRSs) based on the results of the GWAS on mood instability, excluding individuals with psychiatric disorders, run in the UK Biobank sample (Ward et al., 2017) using the Polygenic Risk Score software (PRSice). Quantitative CAARS-S:L scores were dichotomised using a threshold of 12. A logistic regression model was applied to test whether PRS at multiple *P*-value thresholds predicted emotional lability in our ADHD cohort ('target population'). Age, sex, genotyping waves, ADHD subtype, comorbid psychiatric disorders and the first five principal components were included as covariates and 10,000 permutations were computed at the best-fit *P*-value threshold to correct for multiple testing.

## 3. Results

In stage 1 of the study, and after individual and SNP standard quality control filtering, we conducted a GWAS of emotional lability considering 2,777,520 SNPs in a sample of 563 adults with ADHD. The quantile–quantile plot showed no departure from the null distribution of expected *P*-values, with a genomic inflation factor of $\lambda = 1.08$ (Supplementary Fig. 1).

None of the association signals at SNP or gene level exceeded the genome-wide threshold for significance, with the top hit at rs2165472 located 1.1 Mb upstream from the *LPHN3* gene on chromosome 4 ($P = 3.77e{-}06$; $B = 1.31$; SE = 0.28) (Fig. 1, Table 1). The gene-based association test showed 1016 genes associated with emotional lability ($P < 0.05$), with the top hit in *OR9A4* on chromosome 7 ($P = 1.72e{-}05$) (Table 1). No gene-set was found significant after multiple comparison correction, with a total of 262 GO terms nominally enriched in our gene set ($P<0.05$) and "*Intraciliary Transport Particle*" being the most significant one (GO:0030990, $P = 1.74e{-}04$) (Supplementary Table S1). Moreover, 64 canonical pathways were overrepresented in our gene set, with "*Terpenoid Backbone Biosyntesis*" ($P = 1.19e{-}03$) and "*p75NTR recruits signaling complexes*" ($P = 1.53e{-}03$) among the top signals (Supplementary Table S2).

In stage 2, we constructed PRSs based on mood instability data from the UK Biobank sample (Ward et al., 2017) and assessed their association with emotional lability in our ADHD clinical cohort to test whether emotional lability in a clinical sample of ADHD subjects and in the general population shares common genetic load. We found suggestive evidence of association between PRSs for emotional lability in the general population and emotional lability in clinical diagnosed ADHD, being the most predictive *P*-value threshold set at $P_T = 5e{-}05$ (corrected *P*-value = 0.078; Fig. 2), which explained 0.59% of the variation in emotional lability.

## 4. Discussion

To our knowledge, this is the first study that investigates the genetic basis of emotional lability in adults with ADHD through a GWAS perspective. Despite not reaching genome-wide significance, our findings show tentative evidence for the involvement of genes relevant in the context of emotional lability, including, cell-substrate adhesion, neurotransmission signaling, neurological diseases and psychiatric disorders.

Emotional lability is a highly prevalent clinical feature in ADHD patients across the lifespan. Although it is not part of the current definition criteria for ADHD diagnosis, emotional dysregulation is present in a subset of patients and represents a major source of functional impairment and poor clinical outcome. About 40% of children and from 35% to 70% of adults with ADHD exhibit emotional dysregulation, with low frustration tolerance, quick anger and explosive

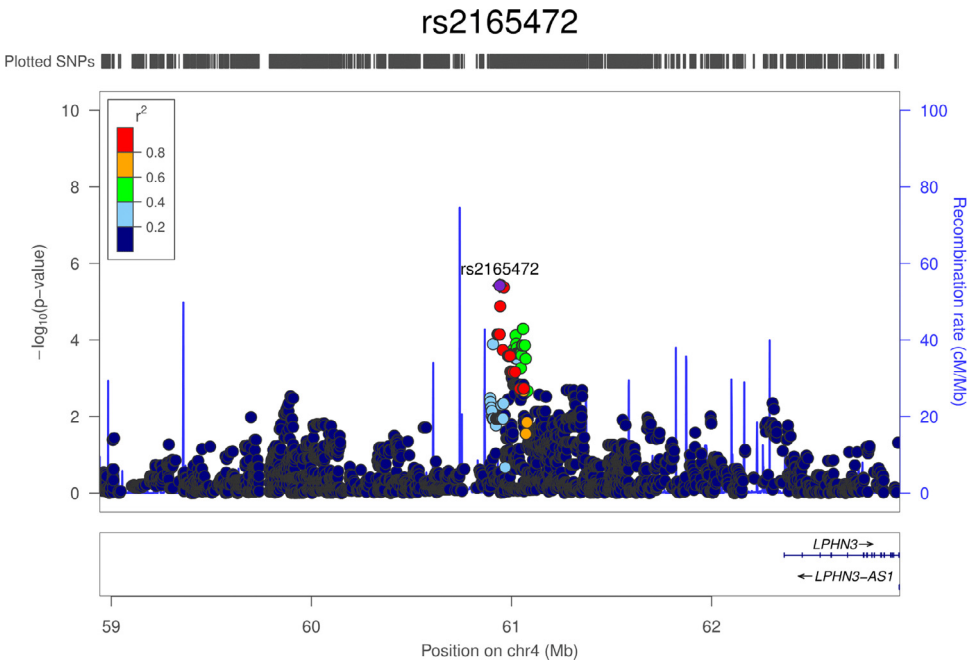


**Fig. 1** Regional association plot of top index SNP identified in genome-wide association study and nearby genes.

behavior, regardless of other comorbidities (Shaw et al., 2014). Although the results of the present study suggest potential and interesting genes for emotional lability in ADHD subjects, whether ADHD with emotional dysregulation represents a distinct genetic group or both share a common genetic load remains unknown. The largest GWAS on mood instability performed so far using the UK Biobank sample showed no genetic correlation between both symptom domains that commonly co-exist (Ward et al., 2017), but findings based on twin and familiar co-segregation studies as well as a PRS analysis on early irritability support moderate genetic overlap between ADHD and emotional dysregulation (Riglin et al., 2017; Shaw et al., 2014). Although no statistically significant, the tentative evidence of association between the PRS based on mood instability from the UK Biobank sample and emotional lability in our ADHD clinical cohort, also suggest common genetic background underlying emotional lability in general population and in clinical diagnosed ADHD. These suggestive results emphasize the need for further studies in additional samples to confirm these findings and to understand the genetic underpinnings of mood instability and its link with ADHD.

The top hit from our GWAS, rs2165472, is located 1.1 Mb upstream from the *LPNH3*, which encodes a neuronal adhesion-GPC receptor from the LPHN family that is almost exclusively expressed in brain (Acosta et al., 2016). It plays a role in the development of glutamatergic synapses (O'Sullivan et al., 2014) and has been extensively associated with ADHD, and its severity, long-term outcome, response to treatment and comorbid conditions such as disruptive behaviors and substance use disorder (SUD) (Acosta et al., 2016; Arcos-Burgos et al., 2019). Among the top hits, we also identified SNPs located within, or nearby, other genes of interest for emotional lability including *FOXK1*, expressed in key brain areas for cognitive function (Wijchers et al., 2006); *GABRG3*, which encodes a gamma-aminobutyric acid receptor subunit, or *GRM5*, a glutamate receptor. They are highly involved in neurotransmission and normal brain function and have been widely associated with a variety of psychiatric disorders including anxiety, bipolar mood disorder, SUD, autism or major depressive disorder (Fatemi and Folsom, 2015).

The gene-based and gene-set competitive analyses also highlighted genes and pathways potentially relevant for emotional lability, including genes such as *OR9A4*, previously associated with anorexia nervosa (Wade et al., 2013), *CTBP1*, which is involved in the regulation of gene expression during development and exhibited aberrant blood expression in schizophrenia and bipolar disorder subjects (Tsuang et al., 2005), or *ASS1* which was downregulated in urine samples of subjects with major depressive disorder (Wu et al., 2015). The present study points to a wide range of pathways and cellular processes involved in several psychiatric disorders and neuronal functions. Of particular interest are the "*p75NTR recruits signaling complexes*", involved in survival and formation of neurons (Dechant and Barde, 2002), the "*calcineurin pathway*", essential for synaptic plasticity processes (Xia and Storm, 2005) or "*p38MAPK events*", associated with neuronal death, development and differentiation (Ibrahim et al., 2017).

The results of this study should be viewed in light of several limitations:

- First, our modest sample size is not powered enough to identify genome-wide significant hits and has probably prevented us from detecting variants with modest effects. Despite using a proportional odds logistic regression model to make the most of the data we had, given their ordinal nature, we cannot report any conclusive findings.
- Second, it remains unknown whether the nature of the relationship between ADHD and emotional instability is

**Table 1** Top 15 hits from the (a) SNP and (b) gene-based analyses of emotional lability in adult Attention Deficit Hyperactivity Disorder.

(a)

| SNP | CHR | Gene (kb distance) | Effect Allel | OR | CI 95% | *P*-value |
|---|---|---|---|---|---|---|
| rs2165472 | 4 | *LPHN3* (−1126 kb) | C | 3.71 | 2.13-6.48 | 3.77E−06 |
| rs35872837 | 5 | *ISL1* (+300.1 kb) | G | 0.49 | 0.36-0.66 | 3.81E−06 |
| rs723840 | 14 | *CMTM* (0 kb) | C | 1.63 | 1.33-2.00 | 3.81E−06 |
| rs2109112 | 12 | *PARP11* (+4.859 kb) | T | 1.70 | 1.36-2.13 | 3.96E−06 |
| rs117358046 | 14 | *IFT43* (0 kb) | T | 4.65 | 2.42-8.94 | 3.99E−06 |
| rs3087749 | 7 | *FOXK1* (0 kb) | T | 0.61 | 0.50-0.76 | 7.58E−06 |
| rs13236432 | 7 | *PRSS37* (+9.559 kb) | C | 1.77 | 1.38-2.27 | 8.43E−06 |
| rs113365723 | 5 | *ERAP1* (0 kb) | A | 5.61 | 2.62-12.00 | 8.88E−06 |
| rs1515594 | 3 | *NLGN1* (+278.3 kb) | G | 0.55 | 0.42-0.71 | 9.69E−06 |
| rs9841241 | 3 | *RYBP* (−20.28 kb) | G | 1.63 | 1.31-2.03 | 1.13E−05 |
| rs4778109 | 15 | *GABRG3* (0 kb) | A | 0.62 | 0.50-0.77 | 1.24E−05 |
| rs566277 | 11 | *GRM5* (0 kb) | G | 0.26 | 0.14-0.48 | 1.36E−05 |
| rs9311047 | 3 | *PDCD6IP* (+335.3 kb) | A | 2.03 | 1.47-2.79 | 1.50E−05 |
| rs11694790 | 2 | *PNPT1* (+76.83 kb) | T | 1.61 | 1.30-2.00 | 1.53E−05 |
| rs74870851 | 2 | *ABCB11* (−3.225 kb) | G | 0.16 | 0.07-0.37 | 1.58E−05 |

(b)

| Gene | CHR | Start | Stop | *n* SNPs | *P*-value |
|---|---|---|---|---|---|
| *OR9A4* | 7 | 141,608,676 | 141,629,620 | 29 | 1.72E−05 |
| *PFN1* | 17 | 4,838,945 | 4,862,381 | 17 | 6.93E−05 |
| *RWDD3* | 1 | 95,689,711 | 95,722,781 | 54 | 8.63E−05 |
| *BCAS3* | 17 | 58,745,172 | 59,480,199 | 285 | 1.00E−04 |
| *RNF167* | 17 | 4,833,328 | 4,858,517 | 21 | 1.35E−04 |
| *HGFAC* | 4 | 3,433,702 | 3,461,214 | 10 | 1.36E−04 |
| *PAPSS2* | 10 | 89,409,476 | 89,517,462 | 110 | 1.49E−04 |
| *CTBP1* | 4 | 1,195,228 | 1,252,908 | 90 | 1.60E−04 |
| *CORO2B* | 15 | 68,841,614 | 69,030,145 | 107 | 1.98E−04 |
| *HLF* | 17 | 53,332,321 | 53,412,426 | 36 | 2.37E−04 |
| *ZFP42* | 4 | 188,906,925 | 188,936,199 | 16 | 2.37E−04 |
| *ASS1* | 9 | 133,310,094 | 133,386,661 | 16 | 3.35E−04 |
| *GLTSCR1* | 19 | 48,101,453 | 48,216,534 | 131 | 3.67E−04 |
| *SLC25A11* | 17 | 4,830,425 | 4,853,462 | 22 | 3.89E−04 |
| *RBM11* | 21 | 15,578,466 | 15,610,693 | 123 | 4.13E−04 |

*Note:* SNP: Single Nucleotide Polymorphism CHR: Chromosome OR: Odds ratio CI: confidence intervals.
*OR: the odds per effect allele of an increase in the CAARS' emotional lability subscale.

mediated by other comorbid disorders, ADHD subtypes, gender, family history of ADHD or adverse environmental factors (Ward et al., 2017), and their role in the link between ADHD and emotional instability warrants further investigation.

- Third, given the cross-sectional nature of the study, we cannot infer causality or make assertions about the temporal relationship between ADHD and emotional lability. Therefore, prospective, longitudinal studies are required to examine the temporal onset of emotion dysregulation in ADHD subjects.
- Fourth, there are several definitions of emotional lability and different scales to measure the construct. Furthermore, there are certain limitations related to self-report measures of emotion lability. We applied the Conners' definition of emotional lability as irritability, unpredictable moods, setting off easily, hot temper, low frustration tolerance and difficulties in anger management. Although this subscale of the CAARS is a good measure for emotional lability in ADHD subjects and there is evidence supporting that adults with ADHD are reliable informants about symptomatology (Vidal et al., 2014), future research using specific scales of emotional reactivity as well as more thorough and objective measures of this construct is warranted.

In conclusion, to our knowledge, this is the first attempt to assess the genetic background of emotional instability in ADHD patients. Although not conclusive, we found suggestive evidence for genes involved in central nervous system development and function and in a wide range of psychiatric disorders that have emotional lability as common clinical feature. Our results are in line with previous studies supporting a common genetic background underlying emotional lability in the general population and in clinically diagnosed ADHD individuals, suggest emotion dysregulation as a trans-diagnostic construct (Sloan et al., 2017) and highlight the need for further investigation to disentangle the genetic basis of mood instability in ADHD and its role as a source of impairment and clinical outcome.

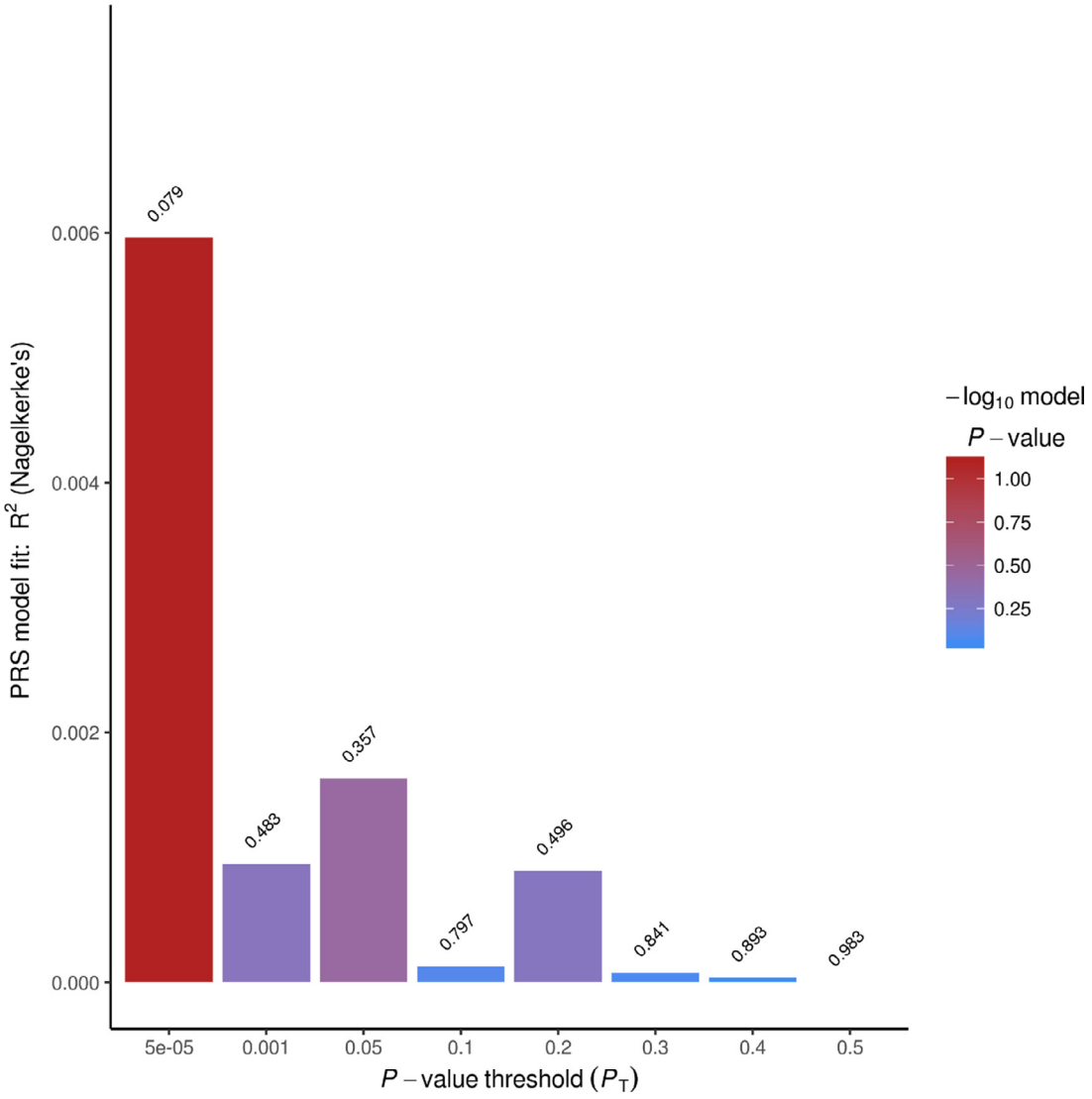


**Fig. 2** Bar plot showing results from the PRS analysis based on mood instability data from UK Biobank at broad *P*-value thresholds ($P_T = 0.001$, $P_T = 0.05$, $P_T = 0.1$, $P_T = 0.2$, $P_T = 0.3$, $P_T = 0.4$, $P_T = 0.5$) and at the best-fit PRS ($P_T = 5e{-}05$).

## Contributors

P.R., C.S.M., I.G., and M.P. participated in the DNA isolation and preparation of samples. L.G., L.V., P.R., C.S.M., I.G., M.P., M.S.A and M.R., undertook the statistical analyses. L.G., V. R., and M. C., contributed to the clinical assessment and recruitment of patients. M. C. and J. A. R. Q. participated in the study design, clinical assessment and coordination of the clinical research. M. R. conceived the project, wrote the protocol and coordinated the study design and the statistical analyses. J.A.R.Q., M.S.A and M. R. supervised the project and the manuscript preparation. All authors contributed to and have approved the final version.

## Conflict of interest

The author L.G. received travel awards for taking part in psychiatric meetings from Shire in the last 3 years.

The author V.R. received travel awards for taking part in psychiatric meetings from Shire in the last 3 years.

The author M.C has received fees to give talks for Janssen-Cilag, Bristol-Mayers Squibb, Ferrer-Brainfarma, Pfizer, Reckitt-Benckiser, Lundbeck, Otsuka, Servier, Lilly, Shire, GSK, Rovi and Adamed. He has received financial compensation for his participation as a member of the Janssen-Cilag, Lilly, Shire, Lundbeck, Otsuka, Ferrer and Rovi board.

The author J.A.R.Q was on the speakers' bureau and/or acted as consultant for Eli-Lilly, Novartis, Shire, Lundbeck, Almirall, BGaze and Rubió in the last 3 years. He also received travel awards (air tickets + hotel) for taking part in psychiatric meetings from Rubió, Shire, and Eli-Lilly. The ADHD Program chaired by him received unrestricted educational and research support from the following pharmaceutical companies in the last 3 years: Eli-Lilly, Lundbeck, Janssen-Cilag, Actelion, Shire, and Rubió.

All other authors declare that they have no conflicts of interest.

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## Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2019.04.004.

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