TITLE: A genome-wide association study of antidepressant-induced mania

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ABSTRACT

Antidepressant-induced mania (AIM) is a side effect of antidepressant treatment that is characterized by mania or hypomania after the start of medication. It is likely polygenic, but its genetic component remains largely unexplored. We aim to conduct the first genome-wide association study of AIM in 814 bipolar disorder patients of European ancestry. We report no significant findings from our single-marker or gene-based analyses. Our polygenic risk score analyses also did not yield significant results with bipolar disorder, antidepressant response, or lithium response. Our suggestive findings on the hypothalamic-pituitary-adrenal axis and the opioid system in AIM require independent replications.

1. INTRODUCTION

Antidepressant-induced mania (AIM) is a common side effect of antidepressant treatment, described as an episode of elevated mood and excitation occurring after commencement of an antidepressant treatment at a rate of 12.5-40% (Goldberg and Truman, 2003, Tondo et al., 2010, Viktorin et al., 2014). The mechanism underlying this mood switch is unclear. Literature supports the role of several clinical factors in AIM, including absence of mood stabilizing medication or antidepressant monotherapy, a diagnosis of bipolar disorder type 1 (Bond et al., 2008), use of selective serotonin reuptake inhibitors (SSRIs) and venlafaxine (Patel et al., 2015), use of tricyclic antidepressants, and the number of previous depressive episodes (reviewed in Melhuish-Beaupre et al (Melhuish Beaupre et al., 2020 8)). The alternative terms of "antidepressant-associated mania or hypomania" or "treatment-emergent affective switch", including "treatment-emergent manic switch", have been proposed to account for the heterogeneity of altered mood states and their association with antidepressant exposure (Fornaro et al., 2018a, Malhi et al., 2015). Further complicating our understanding of the underlying biology is the observation that, although less frequently reported, antidepressant withdrawal manic states have also been described (Abou Kassm and Naja, 2018). Despite the ongoing controversies and inconsistencies surrounding the definition of AIM itself, along with its possible inclusion in the bipolar spectrum (Fornaro et al., 2018a), the clinical implications for the subsequent treatment selection for individuals presenting with AIM are particularly significant (Malhi et al., 2015). Genetic factors also contribute to antidepressant response and tolerability (Voegeli et al., 2017). However, few genetic studies have been conducted in AIM. Candidate gene studies have yielded mostly negative findings for genes including the P-glycoprotein 1 coding multidrug resistance protein 1 (MDR1) or ATP-binding cassette sub-family B member 1 (*ABCB1*) gene (De Luca et al., 2003), Serotonin receptor (*HTR2A*), Tryptophan hydroxylase (*TPH1*), Monoamine oxidase A (*MAOA*), Catechol-o-methyltransferase (*COMT*), G-protein subunit beta 3 (*GNB3*), and Dopamine receptor genes (*DRD2*, *DRD4*) (Serretti et al., 2004), Brain-derived neurotrophic factor (*BDNF*) (de Aguiar Ferreira et al., 2010, Zai et al., 2007). The most studied genetic marker for AIM has been the HTTLPR polymorphism in the serotonin transporter gene (*SLC6A4*) (Biernacka et al., 2012, Daray et al., 2010, Frye et al., 2015), with odds ratio for short allele being 1.35 (95% confidence interval: 0.99-1.85; p=0.059), indicating a small effect. Therefore, it is plausible that, similar to other traits associated with drug treatment, including response (Nohr et al., 2022) or resistance (Fanelli et al., 2021), AIM is polygenic. Yet, to date there have not been investigation at genome wide level of the genetic architecture of AIM.

Here, we performed the first genome-wide association study (GWAS) of AIM in two samples from Sardinia and one from the United States of America (Systematic Treatment Enhancement Program for Bipolar Disorder, STEPBD) study (N=814) in order to identify novel genetic markers for AIM.

2. EXPERIMENTAL PROCEDURES

2.1 Samples

Our study population consists of three sample sets, the STEP-BD clinical trial (STEPBD (Sachs et al., 2003)), Centro Bini (BINI), and University of Cagliari (UNICA). The STEPBD sample set consists of 955 bipolar disorder cases. Antidepressant-induced mania was assessed using the self-reported Affective Disorders Evaluation form during baseline interview of the study, with a specific item on "Hx of Antidepressant induced (hypo)mania" within first 12 weeks of a given treatment (Truman et al., 2007). Of the 955 STEPBD participants, 620 had data collected on AIM with 249 rated as having positive history of AIM. The clinical sample recruited at the Unit of Psychiatry of the University Health Agency of Cagliari, Italy consisted of a cohort of 50 patients selected from patients attending the outpatient clinic of this community mental health center. Patients were enrolled in the genetic study if they met the following inclusion criteria: 1) diagnosis of either bipolar I or bipolar II disorder according to DSM 5 criteria validated through the Italian version of the SCID-5-CV (Structured Clinical Interview for DSM-5 Clinical Version); 2) being in euthymic phase. All patients provided a written consent form regarding the use of their biological and clinical data for research purposes. Blood samples were gathered at the beginning of the study along with the relevant demographic and biometric data. The sample recruited at the Mood Disorder Lucio Bini Center in Cagliari (Italy), a specialized outpatient clinic for the diagnosis, treatment and research of affective disorders consisted of 198 patients diagnosed BD-I/II diagnosis based on DSM5 criteria. In both samples, AIM status was defined as experiencing a manic or hypomanic episode within 2 weeks of initiating antidepressant treatment. The AIM assessment was performed retrospectively by analyzing the medical health records and direct interviewing the study participants. The study has been approved by the institutional research ethics boards and abides by the standards set out by the 1964 Declaration of Helsinki and its amendments. All research participants provided informed consent for the study.

2.2 Genotyping and quality control

The STEPBD sample set was genotyped on Affymetrix 500K Arrays (372,194 markers). The Sardinian sample sets were genotyped on the Illumina Infinium Global Screening array (Illumina Inc.). We performed standard quality control of the genotype data using PLINK (Purcell et al., 2007) and R based on sex concordance, missingness (<1%), relatedness (PI_HAT<=0.185), heterozygosity (within +/-5 SD of mean), and ancestry (European and within +/-6 SD of mean); as well as for genetic markers in terms of missingness (<1%), minor allele frequency (≥5%), Hardy-Weinberg Equilibrium (p≥1e-10). Ancestry of our sample was compared to the HapMap (CEU, YRI, and CHB) reference data using principal component analysis in PLINK. Whole-genome imputation was performed using the Michigan Imputation Server docker within CAMH with 1000 Genomes Phase 3 data as the reference panel (Clarke et al., 2017), with markers having info score of less than 0.7 excluded from analyses. This resulted in 4,964,112

markers and 605 (245 positive for AIM) participants in the STEPBD sample set, and 6,514,129 markers and 209 (42 positive for AIM) participants in the Sardinian sample sets available for data analyses.

The sample of 287 cases and 527 controls has over 80% power to detect an effect size of 2.16 (minor allele frequency 20%, additive model, alpha 5e-8, QUANTO; (Gauderman and Morrison, 2006)). Table 1 summarizes the characteristics of our study sample sets.

2.3 Analysis

Single-marker analyses were performed using PLINK (Purcell et al., 2007), including sex, age, site (for UNICA/BINI), and the first two principal components as covariates. Gene-based analyses were conducted using MAGMA (de Leeuw et al., 2015). We calculated polygenic risk scores with PRSice2 using default parameters (R-Squared threshold for clumping of 0.1, clumping distance of 500kb) (Choi and O'Reilly, 2019, Euesden et al., 2015), using summary statistics for bipolar disorder (PGC3 excluding STEPBD; (Mullins et al., 2021)), lithium response (Hou et al., 2016), and antidepressant response (Pain et al., 2022) with covariates mentioned above. In addition to the standard quality control steps for ambiguous alleles, strand flips and allele calls in the summary statistics in PRSice2, we included markers with imputation info scores of at least 0.9 where applicable. We also used polygenic risk scores calculated using Bayesian regression with continuous shrinkage priors implemented by PRS-CS-auto (Ge et al., 2019) to compare with results from PRSice2. We set the significance threshold for single-marker analysis at 5e-8, for gene-based analysis at 3e-6 (for 16,890 genes), and polygenic risk score analyses 0.0013 (0.004 for thresholding and for three summary statistics). We also explored leveraging hippocampal and frontal cortical (BA9) gene expression data in a transcriptome-wide association study as described previously (Gusev et al., 2016).

3. RESULTS

Our single-marker analysis did not yield genome-wide significant results (p>5e-8), nor did our gene-based analysis (p>3e-6). Manhattan plots and quantile-quantile plots are shown in Figure 1. The top 10 suggestive independent single-marker are shown in Table 2 (p<5e-5; all suggestive single-marker findings in Supplementary Table S1), and top 10 gene-based analysis findings are shown in Table S2, and their LocusZoom plots are shown in Supplementary Figures S1 and S2. We included top phenotypes from various GWASs (source: Elsworth et al, 2020 doi: 10.1101/2020.08.10.244293) that pertain to our top suggestive SNPs in Table 2. Findings for SNPs of interest and top SNPs in candidate genes are shown in Supplementary Table S3. Of the top 10 markers, three (rs11007049, rs3843587, rs11007051) are associated with MAGUK p55

scaffold protein 7 (*MPP7*) gene expression, three (rs57423449, rs61578442, rs1047584) with Receptor Transporter Protein 4 (*RTP4*) gene expression, and one (rs61823093) is associated with the expression of the genes kelch domain containing 8A (*KLHDC8A*), NUAK family kinase 2 (*NUAK2*), dual serine/threonine and tyrosine protein kinase (*DSTYK*), and LEM domain containing 1 (*LEMD1*). Of the top 10 genes from our gene-based analysis, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta (*PIK3CD*) also have a suggestive marker (rs9430574) which is associated with its expression. The top marker for the *H6PD* gene, rs12060409, is associated with H6PD expression (GTEx Consortium, 2015). Polygenic risk score analyses did not yield significant results for lithium response, antidepressant response, or bipolar disorder using polygenic risk scores from PRSice2 or PRS-CS-auto ($p>0.0013$; Supplementary Figure S3). Our exploratory TWAS did not yield significant gene findings (top genes shown in Supplementary Table S4).

4. DISCUSSION

We report here the first genome-wide association study of antidepressant-induced mania (AIM). The heterogeneous AIM prevalence between the two cohorts appears in line with previous reports (Fornaro et al., 2018b) and may indeed depend on a variety of vulnerability factors that may be difficult to account for (Lieberman et al., 2009). While our overall findings were negative, a number of suggestive findings are worthy of further investigations. For example, RTP4 is an opioid receptor chaperone protein (Fujita et al., 2022, Fujita et al., 2019) that protects mu-delta opioid receptor heterodimers from ubiquitination and degradation (Decaillot et al., 2008). Chronic morphine exposure has been shown to upregulate RTP4 expression in the hypothalamus (Fujita et al., 2019), which leads to morphine tolerance (Fujita et al., 2022). Interestingly, morphine sensitization has been proposed as a model for manic symptoms (Grappi et al., 2011). H6PD is associated with corticosteroid metabolism (Lavery et al., 2008, White et al., 2007). It is localized in the lumen of the endoplasmic reticulum and has been implicated in cortisone reductase deficiency (Draper et al., 2003). Dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis has been reported in bipolar disorder, with cortisol levels being found to be increased, especially during manic phases (Belvederi Murri et al., 2016). The cytosolic version (G6PD; X-linked gene) has been implicated in bipolar disorder and psychosis (Bocchetta, 2003). KLHDC8A has been reported to be increased in glioma-associated macrophages and it may play a role in oxidative stress (Cheng et al., 2022).

Previously examined AIM candidate genes, including *SLC6A4*, did not show up in our suggestive findings, indicating that these markers may not play major roles in the etiology of AIM. Our negative findings are also likely due to the limited sample sizes, especially of the source GWASs from which the polygenic risk scores were derived (lithium response, antidepressant response) and our target GWAS, available for our current analyses. Our polygenic risk score analyses did not consider sex

chromosomes, and neither our GWAS nor polygenic risk score analyses considered the mitochondrial genome, which could play a role in AIM risk (Gardea-Resendez et al., 2023). Different study designs between STEPBD and UNICA/BINI, including participant selection and different timeframes for definitions of AIM, could explain the different rates of AIM between the two studies, and could have led to lack of significant findings. We also did not have detailed information on medications and clinical data that could have influenced AIM status. Larger prospectively followed sample sizes with standardized definition of AIM cases and controls would have increased power for polygenic risk score analyses, and enable us to conduct gene-set analyses and to consider clinical factors of AIM in the analyses. Our preliminary, suggestive findings on HPA axis and opioid systems in AIM reported herein will need independent replications in larger well-characterized samples.

AUTHOR DISCLOSURES

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CONTRIBUTORS

CCZ contributed to study design and performed GWAS quality control and statistical analyses and wrote the first draft of the manuscript. MM contributed to study design and co-wrote the first draft of the manuscript. AS, CP, MP, FP, AM, PP, BC, LT, and JLK contributed to study design. AS, AKT, PP, MAF, JMB, BJC revised the manuscript draft. All authors contributed to and have approved the final manuscript.

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CONFLICT OF INTEREST

CCZ, AKT, and JLK hold patents for genetic markers related to psychotropic medication outcomes. JLK is a member of the Scientific Advisory Board of Myriad Neuroscience (unpaid). The other authors reported no conflicts of interest related to this study.

HIGHLIGHTS

- We report the first genome-wide association study of antidepressant-induced mania.
- We report no significant single-markers or genes in 814 bipolar disorder patients.
- Suggestive findings will need replications in larger well-characterized samples.

Table 1. Characteristics of our study sample sets.		
Sample sets	**UNICA/BINI (N=209)**	**STEPBD (N=605)**
AIM (%)	42 (20%)	245 (40%)
Females (%)	86 (41%)	335 (55%)
Average age (SD) years	40 (14)	41 (12)
Lifetime Bipolar I / II (%)	96 (46)	605 (100)
Age at onset (<30 years old)	134 (64)	511 (84)

Table 2. Top 10 independent SNPs from single-marker analysis of antidepressant-induced mania*.

SNP	CHR	BP	Allele1	Allele2	Pooled OR	P-value	Dir	Closest Gene	PheWAS*
rs4653202	1	37054082	T	C	0.642	2.49×10^{-5}	--	intergenic	Tyrosine, Hip circumference, Mean thickness of S-front-inf (left hemisphere), Job involves mainly walking or standing, Mean thickness of S-orbital-lateral (left hemisphere)
rs61823093	1	205304806	A	G	0.607	1.63×10^{-5}	--	*KLHDC8A*	NUAK2 gene expression^, Mean platelet (thrombocyte) volume^, Sex hormone-binding globulin levels adjusted for BMI, Hair colour (natural, before greying): Dark brown, Platelet count
rs4613462	3	88539687	T	C	0.572	1.99×10^{-5}	--	*CSNKA2IP*	Leg fat mass (left)^, Body mass index (BMI)^, Leg fat mass (right)^, Arm fat mass (right)^, Arm fat mass (left)^
rs7433834	3	107235710	T	C	2.058	1.03×10^{-5}	++	*BBX*	Worry too long after embarrassment, Neuroticism, Worrier / anxious feelings, Ankle spacing width (left), Invitation to complete online 24-hour recall dietary questionnaire (acceptance)
rs7644809	3	107564459	T	C	0.615	2.26×10^{-5}	--	*LINC00635*	Sleep duration^, Schizophrenia, Irritable mood, Snoring, Hemoglobin concentration
rs1047584	3	187088656	T	C	0.544	1.06×10^{-5}	--	*RTP4*	RTP4 gene expression^, Types of transport used (excluding work), Brain imaging NET100 0070, Asthma mixed form (mode), Number of days/week walked 10+ minutes
rs56355054	9	78465983	A	G	1.927	8.08×10^{-7}	++	*PCSK5*	PCSK5 expression, Matrix metalloproteinase-7 levels, Other and unspecified follicular disorders, Reason for not eating or drinking normally: Away, ER membrane protein complex subunit 4
rs3843587	10	28643990	A	G	1.687	1.32×10^{-5}	++	*MPP7*	MPP7 gene expression^, Heel Broadband ultrasound attenuation: direct entry, Heel bone mineral density, Macular hole, Plexin C1
rs10761853	10	66376716	A	C	1.564	2.36×10^{-5}	++	*LOC105378335; LOC124902439*	Pericarditis, Cognitive performance, Illnesses of father, Brain imaging NET100 1141, Participation in an health questionnaire (not invited vs invited)
rs2593286	15	76044074	T	C	1.613	2.51×10^{-5}	++	Intergenic; *50kb 5' of CSPG4*	MAN2C1 gene expression^, UBE2Q2 gene expression^, SNUPN gene expression^, Hematocrit^, FBXO22 gene expression

SNP single-nucleotide polymorphism; CHR chromosome; BP position; Dir direction of effect of Allele 1 in the two samples. Independent SNPs are based on clumping R-Squared threshold of 0.1 and clumping distance of 250kb. *Data from MRC Integrative Epidemiology Unit OpenGWAS database (IEUGWASdb; https://gwas.mrcieu.ac.uk/; doi: 10.1101/2020.08.10.244293); ^genome-wide significant association (p<5e-8)

REFERENCES

Abou Kassm, S. & Naja, W., 2018. Looking for bipolarity in antidepressant discontinuation manic states: Update and diagnostic considerations of the phenomenon. J Affect Disord 235, 551-556.

Angulo, I., Vadas, O., Garcon, F., Banham-Hall, E., Plagnol, V., Leahy, T. R., Baxendale, H., Coulter, T., Curtis, J., Wu, C., Blake-Palmer, K., Perisic, O., Smyth, D., Maes, M., Fiddler, C., Juss, J., Cilliers, D., Markelj, G., Chandra, A., Farmer, G., Kielkowska, A., Clark, J., Kracker, S., Debre, M., Picard, C., Pellier, I., Jabado, N., Morris, J. A., Barcenas-Morales, G., Fischer, A., Stephens, L., Hawkins, P., Barrett, J. C., Abinun, M., Clatworthy, M., Durandy, A., Doffinger, R., Chilvers, E. R., Cant, A. J., Kumararatne, D., Okkenhaug, K., Williams, R. L., Condliffe, A. & Nejentsev, S., 2013. Phosphoinositide 3-kinase delta gene mutation predisposes to respiratory infection and airway damage. Science 342, 866-71.

Belvederi Murri, M., Prestia, D., Mondelli, V., Pariante, C., Patti, S., Olivieri, B., Arzani, C., Masotti, M., Respino, M., Antonioli, M., Vassallo, L., Serafini, G., Perna, G., Pompili, M. & Amore, M., 2016. The HPA axis in bipolar disorder: Systematic review and meta-analysis. Psychoneuroendocrinology 63, 327-42.

Bennison, S. A., Liu, X. & Toyo-Oka, K., 2022. Nuak kinase signaling in development and disease of the central nervous system. Cell Signal 100, 110472.

Biernacka, J. M., McElroy, S. L., Crow, S., Sharp, A., Benitez, J., Veldic, M., Kung, S., Cunningham, J. M., Post, R. M., Mrazek, D. & Frye, M. A., 2012. Pharmacogenomics of antidepressant induced mania: a review and meta-analysis of the serotonin transporter gene (5HTTLPR) association. J Affect Disord 136, e21-e29.

Bocchetta, A., 2003. Psychotic mania in glucose-6-phosphate-dehydrogenase-deficient subjects. Ann Gen Hosp Psychiatry 2, 6.

Bond, D. J., Noronha, M. M., Kauer-Sant'Anna, M., Lam, R. W. & Yatham, L. N., 2008. Antidepressant-associated mood elevations in bipolar II disorder compared with bipolar I disorder and major depressive disorder: a systematic review and meta-analysis. J Clin Psychiatry 69, 1589-601.

Cheng, T., Xu, M., Zhang, H., Lu, B., Zhang, X., Wang, Z. & Huang, J., 2022. KLHDC8A Expression in Association with Macrophage Infiltration and Oxidative Stress Predicts Unfavorable Prognosis for Glioma. Oxid Med Cell Longev 2022, 2694377.

Choi, S. W. & O'Reilly, P. F., 2019. PRSice-2: Polygenic Risk Score software for biobank-scale data. Gigascience 8.

Clarke, L., Fairley, S., Zheng-Bradley, X., Streeter, I., Perry, E., Lowy, E., Tasse, A. M. & Flicek, P., 2017. The international Genome sample resource (IGSR): A worldwide collection of genome variation incorporating the 1000 Genomes Project data. Nucleic Acids Res 45, D854-D859.

Cohen, S. B., Bainter, W., Johnson, J. L., Lin, T. Y., Wong, J. C. Y., Wallace, J. G., Jones, J., Qureshi, S., Mir, F., Qamar, F., Cantley, L. C., Geha, R. S. & Chou, J., 2019. Human primary immunodeficiency caused by expression of a kinase-dead p110delta mutant. J Allergy Clin Immunol 143, 797-799 e2.

Daray, F. M., Thommi, S. B. & Ghaemi, S. N., 2010. The pharmacogenetics of antidepressant-induced mania: a systematic review and meta-analysis. Bipolar Disord 12, 702-6.

de Aguiar Ferreira, A., Neves, F. S., Pimenta, G. J., Mello, M. P., Miranda, D. M., Romano-Silva, M. A., De Marco, L. A. & Correa, H., 2010. The role of genetic variation of BDNF gene in antidepressant-induced mania in bipolar disorder. Psychiatry Res 180, 54-6.

de Leeuw, C. A., Mooij, J. M., Heskes, T. & Posthuma, D., 2015. MAGMA: generalized gene-set analysis of GWAS data. PLoS Comput Biol 11, e1004219.

De Luca, V., Mundo, E., Trakalo, J., Wong, G. W. & Kennedy, J. L., 2003. Investigation of polymorphism in the MDR1 gene and antidepressant-induced mania. Pharmacogenomics J 3, 297-9.

Decaillot, F. M., Rozenfeld, R., Gupta, A. & Devi, L. A., 2008. Cell surface targeting of mu-delta opioid receptor heterodimers by RTP4. Proc Natl Acad Sci U S A 105, 16045-50.

Draper, N., Walker, E. A., Bujalska, I. J., Tomlinson, J. W., Chalder, S. M., Arlt, W., Lavery, G. G., Bedendo, O., Ray, D. W., Laing, I., Malunowicz, E., White, P. C., Hewison, M., Mason, P. J., Connell, J. M., Shackleton, C. H. & Stewart, P. M., 2003. Mutations in the genes encoding 11beta-hydroxysteroid dehydrogenase type 1 and hexose-6-phosphate dehydrogenase interact to cause cortisone reductase deficiency. Nat Genet 34, 434-9.
Euesden, J., Lewis, C. M. & O'Reilly, P. F., 2015. PRSice: Polygenic Risk Score software. Bioinformatics 31, 1466-8.
Fanelli, G., Benedetti, F., Kasper, S., Zohar, J., Souery, D., Montgomery, S., Albani, D., Forloni, G., Ferentinos, P., Rujescu, D., Mendlewicz, J., Serretti, A. & Fabbri, C., 2021. Higher polygenic risk scores for schizophrenia may be suggestive of treatment non-response in major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry 108, 110170.
Fornaro, M., Anastasia, A., Monaco, F., Novello, S., Fusco, A., Iasevoli, F., De Berardis, D., Veronese, N., Solmi, M. & de Bartolomeis, A., 2018a. Clinical and psychopathological features associated with treatment-emergent mania in bipolar-II depressed outpatients exposed to antidepressants. J Affect Disord 234, 131-138.
Fornaro, M., Anastasia, A., Novello, S., Fusco, A., Solmi, M., Monaco, F., Veronese, N., De Berardis, D. & de Bartolomeis, A., 2018b. Incidence, prevalence and clinical correlates of antidepressant-emergent mania in bipolar depression: a systematic review and meta-analysis. Bipolar Disord 20, 195-227.
Frye, M. A., McElroy, S. L., Prieto, M. L., Harper, K. L., Walker, D. L., Kung, S., Chauhan, M., Crow, S., Sutor, B., Galardy, C. W., Veldic, M., Palmer, B. A., Geske, J. R., Fuentes, M., Cuellar-Barboza, A. B., Seymour, L. R., Mori, N. & Biernacka, J. M., 2015. Clinical risk factors and serotonin transporter gene variants associated with antidepressant-induced mania. J Clin Psychiatry 76, 174-80.
Fujita, W., Uchida, H., Kawanishi, M., Kuroiwa, Y., Abe, M. & Sakimura, K., 2022. Receptor Transporter Protein 4 (RTP4) in the Hypothalamus Is Involved in the Development of Antinociceptive Tolerance to Morphine. Biomolecules 12.
Fujita, W., Yokote, M., Gomes, I., Gupta, A., Ueda, H. & Devi, L. A., 2019. Regulation of an Opioid Receptor Chaperone Protein, RTP4, by Morphine. Mol Pharmacol 95, 11-19.
Gardea-Resendez, M., Coombes, B. J., Veldic, M., Tye, S. J., Romo-Nava, F., Ozerdem, A., Prieto, M. L., Cuellar-Barboza, A., Nunez, N. A., Singh, B., Pendegraft, R. S., Miola, A., McElroy, S. L., Biernacka, J. M., Morava, E., Kozicz, T. & Frye, M. A., 2023. Antidepressants that increase mitochondrial energetics may elevate risk of treatment-emergent mania. Mol Psychiatry 28, 1020-1026.
Gauderman, W. J. & Morrison, J. M., 2006. QUANTO 1.1: A computer program for power and sample size calculations for genetic-epidemiology studies, http://hydra.usc.edu/gxe. .
Ge, T., Chen, C. Y., Ni, Y., Feng, Y. A. & Smoller, J. W., 2019. Polygenic prediction via Bayesian regression and continuous shrinkage priors. Nat Commun 10, 1776.
Goldberg, J. F. & Truman, C. J., 2003. Antidepressant-induced mania: an overview of current controversies. Bipolar Disord 5, 407-20.
Grappi, S., Marchese, G., Secci, M. E., De Montis, M. G., Gambarana, C. & Scheggi, S., 2011. Morphine sensitization as a model of mania: comparative study of the effects of repeated lithium or carbamazepine administration. Pharmacol Biochem Behav 99, 749-58.
GTEx Consortium, 2015. Human genomics. The Genotype-Tissue Expression (GTEx) pilot analysis: multitissue gene regulation in humans. Science 348, 648-60.
Gusev, A., Ko, A., Shi, H., Bhatia, G., Chung, W., Penninx, B. W., Jansen, R., de Geus, E. J., Boomsma, D. I., Wright, F. A., Sullivan, P. F., Nikkola, E., Alvarez, M., Civelek, M., Lusis, A. J., Lehtimaki, T., Raitoharju, E., Kahonen, M., Seppala, I., Raitakari, O. T., Kuusisto, J., Laakso, M., Price, A. L., Pajukanta, P. & Pasaniuc, B., 2016. Integrative approaches for large-scale transcriptome-wide association studies. Nat Genet 48, 245-52.

Hou, L., Heilbronner, U., Degenhardt, F., Adli, M., Akiyama, K., Akula, N., Ardau, R., Arias, B., Backlund, L., Banzato, C. E. M., Benabarre, A., Bengesser, S., Bhattacharjee, A. K., Biernacka, J. M., Birner, A., Brichant-Petitjean, C., Bui, E. T., Cervantes, P., Chen, G. B., Chen, H. C., Chillotti, C., Cichon, S., Clark, S. R., Colom, F., Cousins, D. A., Cruceanu, C., Czerski, P. M., Dantas, C. R., Dayer, A., Etain, B., Falkai, P., Forstner, A. J., Frisen, L., Fullerton, J. M., Gard, S., Garnham, J. S., Goes, F. S., Grof, P., Gruber, O., Hashimoto, R., Hauser, J., Herms, S., Hoffmann, P., Hofmann, A., Jamain, S., Jimenez, E., Kahn, J. P., Kassem, L., Kittel-Schneider, S., Kliwicki, S., Konig, B., Kusumi, I., Lackner, N., Laje, G., Landen, M., Lavebratt, C., Leboyer, M., Leckband, S. G., Jaramillo, C. A. L., MacQueen, G., Manchia, M., Martinsson, L., Mattheisen, M., McCarthy, M. J., McElroy, S. L., Mitjans, M., Mondimore, F. M., Monteleone, P., Nievergelt, C. M., Nothen, M. M., Osby, U., Ozaki, N., Perlis, R. H., Pfennig, A., Reich-Erkelenz, D., Rouleau, G. A., Schofield, P. R., Schubert, K. O., Schweizer, B. W., Seemuller, F., Severino, G., Shekhtman, T., Shilling, P. D., Shimoda, K., Simhandl, C., Slaney, C. M., Smoller, J. W., Squassina, A., Stamm, T., Stopkova, P., Tighe, S. K., Tortorella, A., Turecki, G., Volkert, J., Witt, S., Wright, A., Young, L. T., Zandi, P. P., Potash, J. B., DePaulo, J. R., Bauer, M., Reininghaus, E. Z., Novak, T., Aubry, J. M., Maj, M., Baune, B. T., Mitchell, P. B., Vieta, E., Frye, M. A., Rybakowski, J. K., Kuo, P. H., Kato, T., Grigoroiu-Serbanescu, M., Reif, A., Del Zompo, M., Bellivier, F., Schalling, M., Wray, N. R., Kelsoe, J. R., Alda, M., Rietschel, M., McMahon, F. J. & Schulze, T. G., 2016. Genetic variants associated with response to lithium treatment in bipolar disorder: a genome-wide association study. Lancet 387, 1085-1093.

Lavery, G. G., Walker, E. A., Tiganescu, A., Ride, J. P., Shackleton, C. H., Tomlinson, J. W., Connell, J. M., Ray, D. W., Biason-Lauber, A., Malunowicz, E. M., Arlt, W. & Stewart, P. M., 2008. Steroid biomarkers and genetic studies reveal inactivating mutations in hexose-6-phosphate dehydrogenase in patients with cortisone reductase deficiency. J Clin Endocrinol Metab 93, 3827-32.

Li, L. & Fan, C. M., 2017. A CREB-MPP7-AMOT Regulatory Axis Controls Muscle Stem Cell Expansion and Self-Renewal Competence. Cell Rep 21, 1253-1266.

Lieberman, D. Z., Kolodner, G., Massey, S. H. & Williams, K. P., 2009. Antidepressant-induced mania with concomitant mood stabilizer in patients with comorbid substance abuse and bipolar disorder. J Addict Dis 28, 348-55.

Malhi, G. S., Masson, M. & Bellivier, F., 2015. Teasing apart Bipolar III: The causes and consequences of a Treatment-Emergent Affective Switch (TEAS) into mania. Aust N Z J Psychiatry 49, 866-8.

Melhuish Beaupre, L. M., Tiwari, A. K., Goncalves, V. F., Lisoway, A. J., Harripaul, R. S., Muller, D. J., Zai, C. C. & Kennedy, J. L., 2020. Antidepressant-Associated Mania in Bipolar Disorder: A Review and Meta-analysis of Potential Clinical and Genetic Risk Factors. J Clin Psychopharmacol 40, 180-185.

Mullins, N., Forstner, A. J., O'Connell, K. S., Coombes, B., Coleman, J. R. I., Qiao, Z., Als, T. D., Bigdeli, T. B., Borte, S., Bryois, J., Charney, A. W., Drange, O. K., Gandal, M. J., Hagenaars, S. P., Ikeda, M., Kamitaki, N., Kim, M., Krebs, K., Panagiotaropoulou, G., Schilder, B. M., Sloofman, L. G., Steinberg, S., Trubetskoy, V., Winsvold, B. S., Won, H. H., Abramova, L., Adorjan, K., Agerbo, E., Al Eissa, M., Albani, D., Alliey-Rodriguez, N., Anjorin, A., Antilla, V., Antoniou, A., Awasthi, S., Baek, J. H., Baekvad-Hansen, M., Bass, N., Bauer, M., Beins, E. C., Bergen, S. E., Birner, A., Bocker Pedersen, C., Boen, E., Boks, M. P., Bosch, R., Brum, M., Brumpton, B. M., Brunkhorst-Kanaan, N., Budde, M., Bybjerg-Grauholm, J., Byerley, W., Cairns, M., Casas, M., Cervantes, P., Clarke, T. K., Cruceanu, C., Cuellar-Barboza, A., Cunningham, J., Curtis, D., Czerski, P. M., Dale, A. M., Dalkner, N., David, F. S., Degenhardt, F., Djurovic, S., Dobbyn, A. L., Douzenis, A., Elvsashagen, T., Escott-Price, V., Ferrier, I. N., Fiorentino, A., Foroud, T. M., Forty, L., Frank, J., Frei, O., Freimer, N. B., Frisen, L., Gade, K., Garnham, J., Gelernter, J., Giortz Pedersen, M., Gizer, I. R., Gordon, S. D., Gordon-Smith, K., Greenwood, T. A., Grove, J., Guzman-Parra, J., Ha, K., Haraldsson, M., Hautzinger, M., Heilbronner, U., Hellgren, D., Herms, S., Hoffmann, P., Holmans, P. A., Huckins, L., Jamain, S., Johnson, J. S., Kalman, J. L., Kamatani, Y., Kennedy, J. L., Kittel-Schneider, S., Knowles, J. A., Kogevinas, M., Koromina, M., Kranz, T. M., Kranzler, H. R., Kubo, M., Kupka, R., Kushner, S. A., Lavebratt, C., Lawrence, J., Leber, M., Lee, H. J., Lee, P. H., Levy, S. E., Lewis, C., Liao, C., Lucae, S., Lundberg, M.,

MacIntyre, D. J., Magnusson, S. H., Maier, W., Maihofer, A., Malaspina, D., Maratou, E., Martinsson, L., Mattheisen, M., McCarroll, S. A., McGregor, N. W., McGuffin, P., McKay, J. D., Medeiros, H., Medland, S. E., Millischer, V., Montgomery, G. W., Moran, J. L., Morris, D. W., Muhleisen, T. W., O'Brien, N., O'Donovan, C., Olde Loohuis, L. M., Oruc, L., Papiol, S., Pardinas, A. F., Perry, A., Pfennig, A., Porichi, E., Potash, J. B., Quested, D., Raj, T., Rapaport, M. H., DePaulo, J. R., Regeer, E. J., Rice, J. P., Rivas, F., Rivera, M., Roth, J., Roussos, P., Ruderfer, D. M., Sanchez-Mora, C., Schulte, E. C., Senner, F., Sharp, S., Shilling, P. D., Sigurdsson, E., Sirignano, L., Slaney, C., Smeland, O. B., Smith, D. J., Sobell, J. L., Soholm Hansen, C., Soler Artigas, M., Spijker, A. T., Stein, D. J., Strauss, J. S., Swiatkowska, B., Terao, C., Thorgeirsson, T. E., Toma, C., Tooney, P., Tsermpini, E. E., Vawter, M. P., Vedder, H., Walters, J. T. R., Witt, S. H., Xi, S., Xu, W., Yang, J. M. K., Young, A. H., Young, H., Zandi, P. P., Zhou, H., Zillich, L., Psychiatry, H. A.-I., Adolfsson, R., Agartz, I., Alda, M., Alfredsson, L., Babadjanova, G., Backlund, L., Baune, B. T., Bellivier, F., Bengesser, S., Berrettini, W. H., Blackwood, D. H. R., Boehnke, M., Borglum, A. D., Breen, G., Carr, V. J., Catts, S., Corvin, A., Craddock, N., Dannlowski, U., Dikeos, D., Esko, T., Etain, B., Ferentinos, P., Frye, M., Fullerton, J. M., Gawlik, M., Gershon, E. S., Goes, F. S., Green, M. J., Grigoroiu-Serbanescu, M., Hauser, J., Henskens, F., Hillert, J., Hong, K. S., Hougaard, D. M., Hultman, C. M., Hveem, K., Iwata, N., Jablensky, A. V., Jones, I., Jones, L. A., Kahn, R. S., Kelsoe, J. R., Kirov, G., Landen, M., Leboyer, M., Lewis, C. M., Li, Q. S., Lissowska, J., Lochner, C., Loughland, C., Martin, N. G., Mathews, C. A., Mayoral, F., McElroy, S. L., McIntosh, A. M., McMahon, F. J., Melle, I., Michie, P., Milani, L., Mitchell, P. B., Morken, G., Mors, O., Mortensen, P. B., Mowry, B., Muller-Myhsok, B., Myers, R. M., Neale, B. M., Nievergelt, C. M., Nordentoft, M., Nothen, M. M., O'Donovan, M. C., Oedegaard, K. J., Olsson, T., Owen, M. J., Paciga, S. A., Pantelis, C., Pato, C., Pato, M. T., Patrinos, G. P., Perlis, R. H., Posthuma, D., Ramos-Quiroga, J. A., Reif, A., Reininghaus, E. Z., Ribases, M., Rietschel, M., Ripke, S., Rouleau, G. A., Saito, T., Schall, U., Schalling, M., Schofield, P. R., Schulze, T. G., Scott, L. J., Scott, R. J., Serretti, A., Shannon Weickert, C., Smoller, J. W., Stefansson, H., Stefansson, K., Stordal, E., Streit, F., Sullivan, P. F., Turecki, G., Vaaler, A. E., Vieta, E., Vincent, J. B., Waldman, I. D., Weickert, T. W., Werge, T., Wray, N. R., Zwart, J. A., Biernacka, J. M., Nurnberger, J. I., Cichon, S., Edenberg, H. J., Stahl, E. A., McQuillin, A., Di Florio, A., Ophoff, R. A. & Andreassen, O. A., 2021. Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology. Nat Genet 53, 817-829.

Nohr, A. K., Forsingdal, A., Moltke, I., Howes, O. D., Vitezic, M., Albrechtsen, A. & Dalby, M., 2022. Polygenic heterogeneity in antidepressant treatment and placebo response. Transl Psychiatry 12, 456.

Pain, O., Hodgson, K., Trubetskoy, V., Ripke, S., Marshe, V. S., Adams, M. J., Byrne, E. M., Campos, A. I., Carrillo-Roa, T., Cattaneo, A., Als, T. D., Souery, D., Dernovsek, M. Z., Fabbri, C., Hayward, C., Henigsberg, N., Hauser, J., Kennedy, J. L., Lenze, E. J., Lewis, G., Muller, D. J., Martin, N. G., Mulsant, B. H., Mors, O., Perroud, N., Porteous, D. J., Renteria, M. E., Reynolds, C. F., 3rd, Rietschel, M., Uher, R., Wigmore, E. M., Maier, W., Wray, N. R., Aitchison, K. J., Arolt, V., Baune, B. T., Biernacka, J. M., Bondolfi, G., Domschke, K., Kato, M., Li, Q. S., Liu, Y. L., Serretti, A., Tsai, S. J., Turecki, G., Weinshilboum, R., Consortium, G., Major Depressive Disorder Working Group of the Psychiatric Genomics, C., McIntosh, A. M. & Lewis, C. M., 2022. Identifying the Common Genetic Basis of Antidepressant Response. Biol Psychiatry Glob Open Sci 2, 115-126.

Patel, R., Reiss, P., Shetty, H., Broadbent, M., Stewart, R., McGuire, P. & Taylor, M., 2015. Do antidepressants increase the risk of mania and bipolar disorder in people with depression? A retrospective electronic case register cohort study. BMJ Open 5, e008341.

Purcell, S., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M. A., Bender, D., Maller, J., Sklar, P., de Bakker, P. I., Daly, M. J. & Sham, P. C., 2007. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet 81, 559-75.

Roberts, N. A., Hilton, E. N., Lopes, F. M., Singh, S., Randles, M. J., Gardiner, N. J., Chopra, K., Coletta, R., Bajwa, Z., Hall, R. J., Yue, W. W., Schaefer, F., Weber, S., Henriksson, R., Stuart, H. M., Hedman, H.,

Newman, W. G. & Woolf, A. S., 2019. Lrig2 and Hpse2, mutated in urofacial syndrome, pattern nerves in the urinary bladder. Kidney Int 95, 1138-1152.
Sachs, G. S., Thase, M. E., Otto, M. W., Bauer, M., Miklowitz, D., Wisniewski, S. R., Lavori, P., Lebowitz, B., Rudorfer, M., Frank, E., Nierenberg, A. A., Fava, M., Bowden, C., Ketter, T., Marangell, L., Calabrese, J., Kupfer, D. & Rosenbaum, J. F., 2003. Rationale, design, and methods of the systematic treatment enhancement program for bipolar disorder (STEP-BD). Biol Psychiatry 53, 1028-42.
Sanna-Cherchi, S., Sampogna, R. V., Papeta, N., Burgess, K. E., Nees, S. N., Perry, B. J., Choi, M., Bodria, M., Liu, Y., Weng, P. L., Lozanovski, V. J., Verbitsky, M., Lugani, F., Sterken, R., Paragas, N., Caridi, G., Carrea, A., Dagnino, M., Materna-Kiryluk, A., Santamaria, G., Murtas, C., Ristoska-Bojkovska, N., Izzi, C., Kacak, N., Bianco, B., Giberti, S., Gigante, M., Piaggio, G., Gesualdo, L., Vukic, D. K., Vukojevic, K., Saraga-Babic, M., Saraga, M., Gucev, Z., Allegri, L., Latos-Bielenska, A., Casu, D., State, M., Scolari, F., Ravazzolo, R., Kiryluk, K., Al-Awqati, Q., D'Agati, V. D., Drummond, I. A., Tasic, V., Lifton, R. P., Ghiggeri, G. M. & Gharavi, A. G., 2013. Mutations in DSTYK and dominant urinary tract malformations. N Engl J Med 369, 621-9.
Serretti, A., Artioli, P., Zanardi, R., Lorenzi, C., Rossini, D., Cusin, C., Arnoldi, A. & Catalano, M., 2004. Genetic features of antidepressant induced mania and hypo-mania in bipolar disorder. Psychopharmacology (Berl) 174, 504-11.
Tondo, L., Vazquez, G. & Baldessarini, R. J., 2010. Mania associated with antidepressant treatment: comprehensive meta-analytic review. Acta Psychiatr Scand 121, 404-14.
Truman, C. J., Goldberg, J. F., Ghaemi, S. N., Baldassano, C. F., Wisniewski, S. R., Dennehy, E. B., Thase, M. E. & Sachs, G. S., 2007. Self-reported history of manic/hypomanic switch associated with antidepressant use: data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). J Clin Psychiatry 68, 1472-9.
Viktorin, A., Lichtenstein, P., Thase, M. E., Larsson, H., Lundholm, C., Magnusson, P. K. & Landen, M., 2014. The risk of switch to mania in patients with bipolar disorder during treatment with an antidepressant alone and in combination with a mood stabilizer. Am J Psychiatry 171, 1067-73.
Voegeli, G., Clery-Melin, M. L., Ramoz, N. & Gorwood, P., 2017. Progress in Elucidating Biomarkers of Antidepressant Pharmacological Treatment Response: A Systematic Review and Meta-analysis of the Last 15 Years. Drugs 77, 1967-1986.
White, P. C., Rogoff, D., McMillan, D. R. & Lavery, G. G., 2007. Hexose 6-phosphate dehydrogenase (H6PD) and corticosteroid metabolism. Mol Cell Endocrinol 265-266, 89-92.
Woolf, A. S., Stuart, H. M. & Newman, W. G., 2014. Genetics of human congenital urinary bladder disease. Pediatr Nephrol 29, 353-60.
Yuki, D., Lin, Y. M., Fujii, Y., Nakamura, Y. & Furukawa, Y., 2004. Isolation of LEM domain-containing 1, a novel testis-specific gene expressed in colorectal cancers. Oncol Rep 12, 275-80.
Zai, G., Mundo, E., Strauss, J., Wong, G. W. & Kennedy, J. L., 2007. Brain-derived neurotrophic factor (BDNF) gene not associated with antidepressant-induced mania. Bipolar Disord 9, 521-5.