

Genome-wide meta-analyses of non-response to antidepressants identify novel loci and potential drugs

Elise Koch

e.m.koch@medisin.uio.no

Centre for Precision Psychiatry, University of Oslo <https://orcid.org/0000-0003-3727-4470>

Tuuli Jürgenson

Guðmundur Einarsson

Brittany Mitchell

QIMR Berghofer Medical Research Institute <https://orcid.org/0000-0002-9050-1516>

Arvid Harder

Luis M. García-Marín

Kristi Krebs

Estonian Genome Center, Institute of Genomics, University of Tartu <https://orcid.org/0000-0003-0494-2751>

Yuhao Lin

Alexey Shadrin

University of Oslo

Ying Xiong

Karolinska Institute

Oleksandr Frei

University of Oslo <https://orcid.org/0000-0002-6427-2625>

Yi Lu

Karolinska Institutet <https://orcid.org/0000-0001-9933-3654>

Sara Hägg

Karolinska Institutet <https://orcid.org/0000-0002-2452-1500>

Miguel Renteria

QIMR Berghofer Medical Research Institute <https://orcid.org/0000-0003-4626-7248>

Sarah Medland

QIMR Berghofer Medical Research Institute <https://orcid.org/0000-0003-1382-380X>

Naomi Wray

University of Oxford <https://orcid.org/0000-0001-7421-3357>

Nicholas Martin

QIMR Berghofer Medical Research Institute <https://orcid.org/0000-0003-4069-8020>

Christopher Hübel

Gerome Breen

King's College London <https://orcid.org/0000-0003-2053-1792>

Thorgeir Thorgeirsson

deCODE genetics / Amgen Inc <https://orcid.org/0000-0002-5149-7040>

Hreinn Stefansson

deCODE genetics <https://orcid.org/0000-0002-9331-6666>

Kari Stefansson

deCODE Genetics/Amgen, Inc <https://orcid.org/0000-0003-1676-864X>

Kelli Lehto

Lili Milani

University of Tartu <https://orcid.org/0000-0002-5323-3102>

Ole Andreassen

Oslo University Hospital & Institute of Clinical Medicine, University of Oslo <https://orcid.org/0000-0002-4461-3568>

Kevin O`Connell

Article

Keywords: Antidepressants, genome-wide association study, pharmacogenomics, precision medicine, real-world data, genetics-informed drug repurposing

Posted Date: December 23rd, 2024

DOI: <https://doi.org/10.21203/rs.3.rs-5418279/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Additional Declarations: Yes Dr. Andreassen reported grants from Stiftelsen Kristian Gerhard Jebsen, South-East Regional Health Authority, Research Council of Norway, and European Union's Horizon 2020 during the conduct of the study; personal fees from cortechs.ai (stock options), Lundbeck (speaker's honorarium), and Sunovion (speaker's honorarium) and Janssen (speaker's honorarium) outside the submitted work.

Abstract

Antidepressants exhibit a considerable variation in efficacy, and increasing evidence suggests that individual genetics contribute to antidepressant treatment response. Here, we combined data on antidepressant non-response measured using rating scales for depressive symptoms, questionnaires of treatment effect, and data from electronic health records, to increase statistical power to detect genomic loci associated with non-response to antidepressants in a total sample of 135,471 individuals prescribed antidepressants (25,255 non-responders and 110,216 responders). We performed genome-wide association meta-analyses, genetic correlation analyses, leave-one-out polygenic prediction, and bioinformatics analyses for genetically informed drug prioritization. We identified two novel loci (rs1106260 and rs60847828) associated with non-response to antidepressants and showed significant polygenic prediction in independent samples. Genetic correlation analyses show positive associations between non-response to antidepressants and most psychiatric traits, and negative associations with cognitive traits and subjective well-being. In addition, we investigated drugs that target proteins likely involved in mechanisms underlying antidepressant non-response, and shortlisted drugs that warrant further replication and validation of their potential to reduce depressive symptoms in individuals who do not respond to first-line antidepressant medications. These results suggest that meta-analyses of GWAS utilizing real-world measures of treatment outcomes can increase sample sizes to improve the discovery of variants associated with non-response to antidepressants.

Introduction

Antidepressants are the first-line pharmacological treatment for depression. Over 10% of the adolescent population uses antidepressant medication, and the rate of antidepressant prescriptions is increasing^{1, 2}. Selective serotonin reuptake inhibitors (SSRIs) are the most used antidepressants³⁻⁵, because they are generally better tolerated compared to other antidepressant classes^{4, 5}. However, treatment response to SSRIs and other antidepressants varies considerably between treated individuals, and less than half of individuals with major depression achieve remission of symptoms after initial antidepressant treatment^{6, 7}. It has been shown that individuals who require several antidepressant treatment steps show worse longer-term treatment outcomes⁷. Although antidepressants are linked to a reduction in depressive symptoms⁸, they are often ineffective, with only approximately 35% achieving remission after their primary antidepressant treatment⁶, and approximately 50% achieving remission after completing two treatments of antidepressants⁷. Antidepressant non-response has been associated with illness severity, more comorbidities, higher antidepressant dose requirements, and higher suicide risk as well as suicide attempts^{9, 10}. Thus, non-response to antidepressants is a major clinical problem, and early identification remains a critical priority in psychiatry research¹¹.

Increasing evidence suggests that genetic variation contributes to antidepressant treatment outcomes¹¹. Discovering genomic variants associated with antidepressant treatment outcomes could facilitate the early identification of individuals who do not respond to first-line treatments to avoid delay

in reaching recovery and advance personal treatment. However, although common single nucleotide polymorphisms (SNPs) are reported to explain a portion of the variance of antidepressant response^{12, 13}, no robustly replicated associations have been detected to date^{14–18}. Moreover, the largest genome-wide association study (GWAS) of antidepressant response, measured using depression symptom scores (N = 5,218), did not identify any genome-wide significant loci¹³. Antidepressant response is a polygenic phenotype, requiring larger sample sizes to elucidate the genetic architecture of antidepressant response¹³. Use of alternative outcome phenotypes such as antidepressant response information obtained from electronic health records (eHR)¹⁹ or self-reported questionnaires²⁰ have been used to increase sample sizes. Combining these real-world data sources could provide the sample sizes needed for discovering genetic factors associated with antidepressant treatment outcomes²¹. In the current study, we integrated GWAS data on antidepressant non-response measured using rating scales for depressive symptoms, questionnaires of treatment effect, and outcome data from eHR, to increase statistical power to detect genomic loci associated with non-response to SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs).

Methods

GWAS sample description

Using questionnaire data about the effectiveness of prescribed antidepressant drugs, we performed GWASs on non-response to SSRIs in the Estonian Biobank (EstBB)^{22, 23}, the Australian Genetics of Depression Study (AGDS)²⁴, the Genetic Links to Anxiety & Depression (GLAD) Study²⁵, and the UK Biobank (UKB)²⁶. Additionally, we performed GWASs on non-response to SNRIs in the EstBB and AGDS cohorts. Utilizing prescription registry data, we defined treatment response and non-response to antidepressants based on antidepressant switching and performed GWASs on non-response to SSRIs and SNRIs in an Icelandic cohort from deCODE Genetics. In all cohorts, treatment response and non-response was defined as a binary measure, see **Supplementary Materials** for more details about phenotype definitions, antidepressant drugs included, and description of cohorts including genotype information.

Publicly available GWAS summary statistics were obtained from a GWAS on treatment response to antidepressants performed by the Psychiatric Genomics Consortium (PGC)¹³. We used summary statistics from the European sample of the genome-wide analysis of remission after antidepressant treatment (predominantly SSRIs) in individuals diagnosed with major depressive disorder (MDD). Summary statistics from two GWASs on antidepressant treatment response performed by the 23andMe Research Team from 23andMe, Inc.^{20, 27} were obtained upon request, to meta-analyze these two GWASs. In the GWASs from the 23andMe Research Team^{20, 27}, treatment response and non-response to antidepressants was defined according to an antidepressant efficacy survey. We used separate summary statistics for treatment response to SSRIs and SNRIs. All GWAS samples and corresponding

numbers of responders and non-responders are summarized in Table 1. All subjects provided written informed consent after receiving a complete description of the respective study.

Table 1

GWAS samples included in the GWAS meta-analysis of non-response to SSRIs, non-response to SNRIs, and non-response to SSRIs/SNRIs

GWAS sample	Antidepressant class	N total (Neff total)	N responders	N non-responders	Treatment response measure
Pain et al. 2022 ¹³	SSRIs	5,151 (4,479)	1,852	3,299	Depression symptom scores
Li et al. 2016 ²⁷ + Li et al. 2020 ²⁰	SSRIs	19,740 (17,586)	13,130	6,610	Antidepressant efficacy survey
	SNRIs	7,079 (6,943)	4,030	3,049	
EstBB	SSRIs	7,168 (4,272)	5,862	1,306	Antidepressant efficacy survey
	SNRIs	968 (584)	789	179	
AGDS	SSRIs	9,208 (6,902)	6,908	2,300	Antidepressant efficacy survey
	SNRIs	4,426 (4,304)	2,580	1,846	
GLAD	SSRIs	4,184 (2,416)	3,452	732	Antidepressant efficacy survey
UKB	SSRIs	19,811 (10,632)	16,648	3,163	Antidepressant efficacy survey
deCODE	SSRIs	49,062 (8,391)	46,866	2,196	Antidepressant switching
	SNRIs	8,674 (2,148)	8,099	575	
Total	SSRIs	114,324 (64,975)	94,718	19,606	
	SNRIs	21,147 (16,560)	15,498	5,649	
	SSRIs/SNRIs	135,471 (82,187)	110,216	25,255	

Neff = $4/(1/N_{cases} + 1/N_{controls})$. EstBB = Estonian Biobank, AGDS = Australian Genetics of Depression Study, GLAD = Genetic Links to Anxiety & Depression, UKB = UK Biobank

Genome-wide meta-analyses

Meta-analyses of GWAS summary statistics were conducted using inverse-variance-weighted fixed effects models in METAL²⁸. Separate meta-analyses were performed for non-response to SSRIs, non-response to SNRIs, and non-response to either SSRIs or SNRIs. We used the standard p value thresholds for GW significance, p -value $< 5e-8$, and nominal p -value $< 7e-8$. We assessed the heterogeneity across studies using the Cochran Q-test (Hetpval < 0.05) and I^2 statistics ($I^2 > 50\%$), to estimate the heterogeneity of effect sizes across cohorts²⁸. Due to differences in the definition of antidepressant treatment response across GWASs, we also performed sensitivity meta-analyses restricted to samples where treatment response was measured using only questionnaires (EstBB, AGDS, GLAD, UKB, and the GWASs from the 23andMe Research Team^{20, 27}).

Locus definition, variant annotation, and gene mapping

To define genetic loci based on the association summary statistics produced with METAL²⁸, we used Functional Mapping and Annotation of GWAS (FUMA)²⁹ with default settings. Genetic variants with a p -value $< 5e^{-8}$ and with a linkage disequilibrium (LD) $r^2 < 0.6$ with each other were defined as independent significant variants. Of these, variants with an LD $r^2 < 0.1$ were selected as lead variants. Loci that were separated by less than 250 kb were then merged. To investigate previous phenotype associations, we queried the identified loci in the GWAS catalogue³⁰. SNPs were also queried for known expression quantitative trait loci (eQTLs) across multiple tissues using the GTEx portal (GTEx v8)³¹, and in different brain tissues using the BRAINEAC portal³². SNPs were annotated with Combined Annotation Dependent Depletion (CADD)³³ scores and RegulomeDB³⁴ scores. The Open Targets Genetics platform³⁵ was used to map the identified loci to genes. For each locus, we considered the top 3 genes with the highest Variant to Gene (V2G) scores.

Multi-trait conditional and joint analysis, SNP-based heritability, and genetic correlation

To account for the possible effect of major depression, we used multi-trait conditional and joint analysis (mtCOJO)³⁶. We conditioned the effect of SNPs estimated for non-response to antidepressants on those of depression, using summary statistics of a GWAS on depression phenotypes³⁷ including 246,363 cases and 561,190 controls, performed by the Psychiatric Genetics Consortium (PGC), excluding a 23andMe sample. This was done for non-response to SSRIs, non-response to SNRIs, and non-response to either SSRIs or SNRIs. We utilized linkage disequilibrium score regression (LDSC)³⁸ to estimate the SNP-based heritability of our meta-analyzed GWAS as well as the GWAS summary statistics produced with mtCOJO. The SNP-based heritability was calculated on the observed scale. As non-response to antidepressants has been previously associated with genetics of other psychiatric traits as well as

cognitive traits³⁹, LDSC³⁸ was used to estimate bivariate genetic correlations between antidepressant non-response and various psychiatric and cognitive traits, using summary statistics from the following GWASs: Alzheimer's disease⁴⁰, attention deficiency hyperactivity disorder (ADHD)⁴¹, autism spectrum disorder⁴², anxiety disorder⁴³, bipolar disorder⁴⁴, general cognitive performance⁴⁵, educational attainment⁴⁶, intelligence⁴⁷, insomnia⁴⁸, depression phenotypes³⁷, mood instability⁴⁹, neuroticism⁵⁰, posttraumatic stress disorder (PTSD)⁵¹, schizophrenia⁵², subjective well-being⁵³.

Leave-One-Out Polygenic Scoring

Polygenic scores (PGSs) were constructed based on the association summary statistics produced in the GWAS meta-analysis of non-response to SSRIs, excluding each cohort in turn to create independent discovery and target datasets. The target samples were EstBB, UKB, AGDS, and deCODE. In EstBB, the PGS was calculated using the polygenic risk score continuous shrinkage (PRS-CS) approach⁵⁴ with default options. In UKB and AGDS, PGSs were calculated using SBayesR⁵⁵. In the deCODE sample, the PGS was calculated using LDpred⁵⁶. In all four samples, the European sample of the 1000 Genomes Phase III⁵⁷ was used to adjust for LD. To facilitate the interpretability of the results, PGSs were standardized within each sample (mean = 0, SD = 1) before statistical analysis. We performed logistic regression analyses to investigate if the PGS is associated with non-response to SSRIs in each of the four target samples. Age, sex, and the first ten principal components for genetic ancestry were included as covariates. Meta-analyses of results from the four cohorts were performed using the R-package *metaplan*⁵⁸ with standard normal random effect. We also weighted the samples based on effective sample size, using the *metafor*⁵⁹ R-package.

Genetically informed drug prioritization

To estimate gene associations, we used GSA-MiXeR⁶⁰ for the summary statistics produced in the GWAS meta-analysis of non-response to SSRIs, SNRIs, and SSRIs/SNRIs. From the outputs, we chose genes with a positive MiXeR Akaike information criterion (AIC) value, as positive AIC indicates evidence for enrichment of individual genes⁶⁰. To further sort by enrichment for biological relevance, we selected genes with an enrichment value of > 10. All genes identified from GSA-MiXeR⁶⁰ and Open Targets Genetics³⁵ were then studied within networks of protein-protein interactions (PPIs) of gene products, using the latest version of the human protein interactome⁶¹, consisting of 18,217 unique proteins (nodes) interconnected by 329,506 PPIs after removing self-loops.

As most approved drugs do not target disease-associated proteins but bind to proteins in their network vicinity⁶², we defined a network not only including the genes identified from GSA-MiXeR⁶⁰ and Open Targets Genetics³⁵, but also genes in their immediate network proximity. To define antidepressant non-response networks (one for non-response to SSRIs, one for non-response to SNRIs, and one for non-response to SSRIs or SNRIs), we used the method network propagation⁶³⁻⁶⁵, implemented in the

Cytoscape⁶⁶ application Diffusion⁶⁵. Genes identified from GSA-MiXeR⁶⁰ and Open Targets Genetics³⁵ were used as input query genes, and the top 1% of proteins from the diffusion output were included in the antidepressant non-response network. The Drug Gene Interaction Database (DGIdb, (<https://www.dgidb.org/>) v.5.0.6 (04/04/2024)⁶⁷ was used to identify drug-gene interactions between approved drugs and genes in the three antidepressant non-response networks. Gene-set enrichment analysis (GSEA) was performed to test for enrichment of drug-gene interactions within our networks.

For the drugs interacting with genes in our networks, we retrieved drug-induced gene expression data (drug versus no drug) from the Connectivity Map (CMap) 2020^{68,69}, extracted from the Phase 2 data release of the Library of Integrated Cellular Signatures (LINCS) using the cmapR package⁷⁰ in R version 4.3.1. As low drug concentrations in CMap have been shown to reduce the quality of the data⁷¹, we selected the highest concentration per drug.

We performed transcriptome-wide association studies using S-PrediXcan⁷² to impute the genetically regulated gene expression using summary statistics produced in the GWAS meta-analysis of non-response to SSRIs, SNRIs, and SSRIs/SNRIs as input. Gene expression was imputed using high-performance gene expression prediction models trained on gene expression data from whole blood as well as 13 brain expression data sets from GTEx (version 8)^{73,74} and covariance matrices calculated from 503 individuals with European ancestry from the 1000 Genomes project⁵⁷. For gene expression in brain, S-MultiXcan⁷⁵ was used to combine the S-PrediXcan results across the 13 brain tissues (more details in **Supplementary Methods**).

To evaluate if the drugs interacting with genes in our networks could change the predicted expression levels associated with antidepressant non-response (whether these drugs down-regulate genes up-regulated in antidepressant non-response or vice versa), the Spearman correlation ρ between the drug-induced gene expression perturbations and the predicted expression in drug target genes within the antidepressant non-response networks was calculated for each drug (separately for non-response to SSRIs, SNRIs, and SSRIs/SNRIs), where negative correlation coefficients indicate that the drug could reverse gene expression changes associated with antidepressant non-response.

Results

GWAS meta-analyses

From the meta-analysis of non-response to SSRIs ($N_{\text{SNPs}}=8,168,467$), including a total of 114,324 individuals (19,606 non-responders and 94,718 responders), we identified one novel genome-wide significant locus (rs1106260 T/C; chr9: 138,111,032–138,136,174; OR = 1.0502; SE = 0.009; p-value = 3.55e-08). Another locus was found to be nominally significant (rs4884091 A/G; chr13: 78,971,895 – 79,003,053; OR = 1.0602, SE = 0.011, p-value = 6.38e-08). No genome-wide significant loci were identified from the meta-analysis of non-response to SNRIs ($N_{\text{SNPs}}=8,011,440$), including 21,147 individuals (5,649

non-responders and 15,498 responders). However, one locus was nominally significant (rs10104815 T/C; chr8: 136,780,782 – 136,869,414; OR = 0.9213; p-value = 6.62e-08). From the meta-analysis of non-response to SSRIs/SNRIs ($N_{\text{SNPs}}=8,416,883$), including a total of 135,471 individuals (25,255 non-responders and 110,216 responders), we identified one novel genome-wide significant locus (rs60847828 T/C; chr16: 8,460,781-8,490,789; OR = 1.0844; SE = 0.014; p-value = 1.18e-08), and one locus that was nominally significant (rs11677238 T/G; chr2: 114,336,733 – 114,512,514; OR = 1.0439; SE = 0.008; p-value = 5.424e-08). Manhattan plots from the three meta-analyses are shown in Fig. 1. Quantile-quantile plots are shown in **Figure S1**. SNPs at the two genome-wide significant loci show no evidence of heterogeneity (Hetpval > 0.05), indicating that the effect is consistent across datasets (**Table S1, Figures S2-3**). When restricting the meta-analyses to samples where treatment response was measured using only questionnaires, similar results were obtained albeit the associations were no longer significant ($p > 5e-8$) (**Figure S4-5**). All loci achieving genome-wide significance as well as $p < 1e-5$ are reported in **Tables S2-7**.

Investigation of the genome-wide significant loci (rs1106260 and rs60847828) in the GWAS catalogue³⁰ showed no previous associations. Functional annotation of rs1106260 and rs60847828 using FUMA²⁹ does not suggest these SNPs to be deleterious (CADD scores < 12.37) or likely to have regulatory functionality (RegulomeDB scores = 5–7). The top three genes with the highest V2G score for the identified locus for non-response to SSRIs (rs1106260) were *OLFM1*, *MRPS2*, and *PIERCE1*, of which the nearest gene is *OLFM1* (distance = 168,906 bp, downstream gene variant). No significant associations were found in the GTEx portal (GTEx v8)³¹ for the lead SNP (rs1106260). Additional assessment of the lead SNP (rs1106260) and gene expression of *OLFM1*, *MRPS2*, and *PIERCE1* in the BRAINEAC database³² showed significant associations between rs1106260 and gene expression of *OLFM1* in the medulla ($p = 0.015$) and temporal cortex ($p = 0.005$). The top three genes for the identified locus for non-response to SSRIs/SNRIs (rs60847828) were *TMEM114*, *METTL22*, and *ABAT*, of which the nearest gene is *TMEM114* (distance = 154,116 bp, intergenic variant). The lead SNP (rs60847828) was neither found in the GTEx portal (GTEx v8)³¹ nor in the BRAINEAC database³².

The locus that was nominally significant associated with SSRI non-response (rs4884091) has been previously associated with SSRI non-response in the GWAS from the 23andMe Team²⁰. The top three genes with the highest V2G score for this locus were *OBI1*, *POU4F1*, and *EDNRB*, of which *POU4F1* is the nearest gene (260,067 bp, intron variant). One gene was mapped to the locus that was nominally significant associated with SNRI non-response (rs10104815), *KHDRBS3* (339,483 bp, intergenic variant), and this locus has been previously associated with non-response to SNRIs in the GWAS from the 23andMe Team²⁰. The top three genes for the locus that was nominally significant associated with SSRI/SNRI non-response (rs11677238) were *SLC35F5*, *RABL2A*, and *PAX8*, of which the nearest gene is *RABL2A* (40,168 bp, upstream gene variant).

Multi-trait conditional and joint analysis, SNP-based heritability, and genetic correlations

After conditioning on depression, the identified loci were still significantly associated with non-response to antidepressants (**Table S8-10**). SNP-based heritability estimates for all meta-analyses were in the range 0.019–0.028. For non-response to SSRIs and SSRIs/SNRIs, the SNP-based heritability estimates were significantly different from zero, but not for non-response to SNRIs (**Table S11**). Genetic correlation analyses show positive associations between non-response to antidepressants and most psychiatric traits, and negative associations with cognitive traits and subjective well-being (Fig. 2, **Table S12-14**). However, some of these associations remained non-significant after multiple testing correction (FDR > 0.05). Similar results were obtained using the meta-analyses restricted to questionnaire data (**Figure S6-8, Table S15-17**) and non-response to antidepressants conditioned on depression (**Figure S6-8, Table S18-20**).

Polygenic prediction of non-response to SSRIs

Meta-analysis of leave-one-out PGS analyses using SSRI non-response GWAS results in four samples showed a significant association with non-response to SSRIs (OR = 1.016, CI = 1.005–1.039, p-value = 0.029), shown in Fig. 3. However, in two out of the four samples, the PGS was not significantly associated with SSRI non-response (**Table S21**). Similar results were obtained when the samples were weighted based on effective sample size (OR = 1.03, CI = 1.00-1.05, p-value = 0.025) (**Figure S9**).

Genetically informed drug prioritization

From GSA-MiXeR, all genes with a positive AIC value and an enrichment score > 10 can be found in **Table S22** (non-response to SSRIs, N = 65), **Table S23** (non-response to SNRIs, N = 108), and **Table S24** (non-response to SSRIs/SNRIs, N = 76). The genes included in the three networks and the corresponding diffusion output values as well as their node degrees can be found in **Table S25** (SSRIs, N = 252), **Table S26** (SNRIs, N = 287), and **Table S27** (SSRIs/SNRIs, N = 260).

Drug target genes in the SSRI non-response network were most significantly ($p < 5e-4$) enriched for targets of the synthetic cannabinoid nabilone, and the target genes in the SSRI/SNRI non-response network were most significantly ($p < 5e-4$) enriched for targets of bremelanotide, a drug developed to treat sexual dysfunction. However, after correction for the total number of drug-gene interactions (N = 2,896), the enrichments remained non-significant (FDR > 0.05). The drug target genes in the SNRI non-response network were significantly (FDR < 0.05) enriched for several GABA receptor agonists (**Table S28-30**).

In the SSRI non-response network (**Figure S10**), six drugs (letrozole, clozapine, vandetanib, decamethonium, paclitaxel, budesonide) showed significant ($p < 0.05$) opposite gene expression perturbations in drug (drug-induced expression) versus SSRI non-response-associated expression in drug target genes in brain tissue. For blood, eight drugs (temazepam, acetazolamide, chlordiazepoxide, ethionamide, amisulpride, rimonabant, clonazepam, fluorouracil) showed significant opposite gene expression (**Table S31-S34**). In the SNRI non-response network (**Figure S11**), two drugs (selegiline and norethindrone) showed significant ($p < 0.05$) opposite gene expression perturbations in brain, and 2 drugs (dexamethasone and kinetin) in blood (**Table S35-38**). In the SSRI/SNRI non-response network

(**Figure S12**), the drug simvastatin showed significant ($p < 0.05$) opposite gene expression perturbations in brain, and the drug ascorbic acid showed significant opposite gene expression in blood (**Table S39-42**). However, after correction for multiple correlation analyses (number of drugs), all correlations remained non-significant ($FDR > 0.05$). **Figure S13** summarizes the steps undertaken to identify drugs that could potentially address antidepressant non-response (more details in **Supplementary Results**), and the top drugs are shown in Fig. 4.

Discussion

In the present study, we identified two novel genome-wide significant loci associated with antidepressant non-response and showed that a polygenic score derived from our results predicted non-response to SSRIs in independent cohorts. By meta-analyzing real-world pharmacogenomic information on antidepressant non-response based on clinically assessed symptom scores, self-reported treatment outcomes, and data from eHR, this study represents the largest genetic investigation of non-response to antidepressants to date.

For the locus associated with non-response to SSRIs (rs1106260), the gene with the highest V2G score is *OLFM1*, which is also the nearest gene. The glycoprotein olfactomedin 1 (*OLFM1*) is highly expressed in the brain and participates in neural progenitor maintenance, cell death in brain, optic nerve arborization, and axonal growth^{76, 77}. As *OLFM1* plays a role in neuronal development, it has previously been suggested as a candidate gene for neuropsychiatric disorders⁷⁸. In a study aiming to identify biomarkers for mood disorders, *OLFM1* showed strong evidence for predicting both depression and mania and was suggested as a target gene to treat depression⁷⁹. One of the genes mapped to the identified locus for non-response to SSRIs/SNRIs (rs60847828) was *ABAT*. Variants within the GABA transaminase (*ABAT*) gene region have been associated with altered processing of somatosensory stimuli, indicating *ABAT* as a potential vulnerability marker for affective disorders⁸⁰. Furthermore, it has been suggested that variants within *ABAT* affect valproic acid response⁸¹. Increasing evidence indicates that dysfunction of GABA, as well as glutamate systems contributes to depression-related behavior, and that ketamine's antidepressant effects are related to its effect on glutamatergic and GABAergic neurons^{82, 83}. Interestingly, our SNRI non-response network includes several GABA receptor genes, and we shortlist several drugs acting on the GABA system. These GABA receptor agonists may counteract the GABAergic deficits in depression⁸⁴. We also shortlist several drugs with anti-inflammatory actions. A growing body of evidence supports an association between depression and inflammatory processes, and clinical trials have indicated antidepressant treatment effects for anti-inflammatory agents, both as add-on treatment and as monotherapy⁸⁵. Our SSRI network includes *CNR1* and *CNR2*, the genes encoding the two main cannabinoid receptors, which are the primary targets for endogenous and exogenous cannabinoids. Studies suggest that the endocannabinoid system may be involved in the aetiology of depression and that targeting this system has the potential to relieve depressive symptoms⁸⁶. However, the evidence that cannabinoids improve depressive disorders is weak and studies examining the effects of cannabinoids on mental disorders are needed^{86, 87}.

Individual differences in pharmacological treatment response can often be attributed to genetic variability in cytochrome P450 genes (*CYP450*). In our antidepressant non-response GWASs as well as previous GWASs on antidepressant non-response, no association with CYP450 genes was detected. However, our SNRI network includes *CYP17A1* and *CYP2B6*, both identified from network propagation that prioritizes genes with biological and functional similarity to the input genes. Genetic variation in *CYP2B6* influences the metabolism of several SSRIs and SNRIs⁸⁸. Guidelines from the Clinical Pharmacogenetics Implementation Consortium (CPIC) highlight the impact of *CYP2B6*, and *HTR2A* genotypes, among others, on antidepressant dosing, efficacy, and tolerability⁸⁸. The pharmacodynamic gene *HTR2A* (serotonin-2A receptor) is included in our SSRI non-response network, also identified from network propagation.

We show an association between genetic liability of psychiatric disorders and non-response to antidepressants, which is in line with clinical studies⁸⁹. We also identified a significant association between genetic propensity for cognitive phenotypes and improved antidepressant response. Similar genetic correlations have been shown in the previous GWAS on antidepressant response from the PGC¹³ as well as in a study investigating the genetic and clinical characteristics of treatment-resistant depression³⁹. The strongest negative genetic correlations with non-response to antidepressants were observed for ADHD. This may indicate that phenotypic misspecification could underlie non-response to antidepressants. In fact, undetected ADHD has been associated with lack of response to SSRIs in MDD cases⁹⁰. In adults, ADHD may be undiagnosed, and ADHD symptoms are often mistaken for those of their psychiatric comorbidities⁹¹.

Some limitations of the present study should be acknowledged. We combine various samples with differences in the assessment of treatment non-response, which introduces heterogeneity. Moreover, our study could potentially include individuals who were treated with antidepressants for conditions other than depression, especially in the sample where eHR were used to define non-response based on switching as proxy phenotype. Heterogeneity could also be introduced by differences in dosing, treatment duration, and co-treatment with other drugs. However, we performed heterogeneity tests and restricted our meta-analyses to samples where non-response was measured using only similar questionnaires, and these sensitivity analyses showed that the results were consistent across samples. It should also be noted that the individuals in our samples are of European ancestry, and our results may therefore not be directly translatable to other ethnicities.

In conclusion, these results suggest that meta-analyses of GWAS utilizing real-world measures of treatment outcomes can increase sample sizes to improve the discovery of variants associated with non-response to antidepressants.

Declarations

Conflict of Interest

Dr. Andreassen reported grants from Stiftelsen Kristian Gerhard Jebsen, South-East Regional Health Authority, Research Council of Norway, and European Union's Horizon 2020 during the conduct of the study; personal fees from cortechs.ai (stock options), Lundbeck (speaker's honorarium), and Sunovion (speaker's honorarium) and Janssen (speaker's honorarium) outside the submitted work.

Author contributions

EK, OAA, and KSO conceived the study and were involved in study design. EK, TJ, GE, BM, AH, LMGM, KK, YL, AAS, YX, and KSO conducted analyses. EK drafted the initial manuscript. All authors contributed to data interpretation and editing of the manuscript.

Acknowledgements

We would like to thank the research participants and employees of 23andMe, Inc. for making this work possible. This work was partly performed on the TSD (Tjeneste for Sensitive Data) facilities, owned by the University of Oslo, operated and developed by the TSD service group at the University of Oslo, IT-Department (USIT). Computations were also performed on resources provided by UNINETT Sigma2—the National Infrastructure for High Performance Computing and Data Storage in Norway (NS9666S). Computations of the UKB data were enabled by resources in project sens2017519 provided by the National Academic Infrastructure for Supercomputing in Sweden (NAISS) at UPPMAX, funded by the Swedish Research Council through grant agreement no. 2022–06725. We gratefully acknowledge support from the Research Council of Norway (RCN) (296030, 223273, and 334920) and from the National Institutes of Health (NIH 5R01MH124839-02). This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 964874 (REALMENT), as well as from the US NIMH (grant R01 MH123724) and from the European Union's Horizon 2021 research project Psych-STRATA (EU HORIZON-HLTH-2021, grant 101057454). The AGDS was primarily funded by National Health and Medical Research Council (NHMRC) of Australia grant 1086683, with additional funding from MRFF1200644 and MRFF2024891. This work was also supported by NHMRC Investigator Grants to BLM (2017176); SEM (1172917); NRW (1173790) and NGM (1172990). YL was supported by the European Research Council grant (grant agreement No: 101042183) and the Swedish Research Council grant (2021–02615_VR). The work of TJ, KK and LM was further supported by the Swedish Research Council (grant 2021–02732). Data analysis was carried out in part in the High-Performance Computing Center of University of Tartu. MER thanks the support of the Rebecca L Cooper Medical Research Foundation through an Al & Val Rosenstraus Fellowship (F20231230). GB, TH, and YL declare that this study represents independent research part-funded by the National Institute for Health and Social Care Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the UK National Health Service, the NIHR or the Department of Health. We gratefully acknowledge the participation of all South London and Maudsley NIHR BioResource volunteers within

the National NIHR BioResource and thank the South London and Maudsley BioResource staff for their help with volunteer recruitment.

References

1. Iacobucci G. NHS prescribed record number of antidepressants last year. *BMJ* 2019; **364**: 1508.
2. Pratt LA, Brody DJ, Gu Q. Antidepressant Use Among Persons Aged 12 and Over: United States, 2011–2014. *NCHS Data Brief* 2017; **283**: 1-8.
3. Smith AJ, Sketris I, Cooke C, Gardner D, Kisely S, Tett SE. A comparison of antidepressant use in Nova Scotia, Canada and Australia. *Pharmacoepidemiol Drug Saf* 2008; **17**(7): 697-706.
4. Jannini TB, Lorenzo GD, Bianciardi E, Niolu C, Toscano M, Ciocca G *et al.* Off-label Uses of Selective Serotonin Reuptake Inhibitors (SSRIs). *Curr Neuropharmacol* 2022; **20**(4): 693-712.
5. Anderson HD, Pace WD, Libby AM, West DR, Valuck RJ. Rates of 5 common antidepressant side effects among new adult and adolescent cases of depression: a retrospective US claims study. *Clin Ther* 2012; **34**(1): 113-123.
6. Trivedi M, Rush A, Wisniewski S, Nierenberg AA, Warden D, Ritz L *et al.* Evaluation of Outcomes With Citalopram for Depression Using Measurement-Based Care in STAR*D: Implications for Clinical Practice. *Am J Psychiatry* 2006; **163**: 28-40.
7. Rush A, Trivedi B, Wisniewski S, Nierenberg AA, Stewart J, Warden D *et al.* Acute and Longer-Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A STAR*D Report. *Am J Psychiatry* 2006; **163**: 1905-1917.
8. Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y *et al.* Comparative Efficacy and Acceptability of 21 Antidepressant Drugs for the Acute Treatment of Adults With Major Depressive Disorder: A Systematic Review and Network Meta-Analysis. *Focus (Am Psychiatr Publ)* 2018; **16**(4): 420-429.
9. Amital D, Fostick L, Silberman A, Beckman M, Spivak B. Serious life events among resistant and non-resistant MDD patients. *J Affect Disord* 2008; **110**(3): 260-264.
10. De Carlo V, Calati R, Serretti A. Socio-demographic and clinical predictors of non-response/non-remission in treatment resistant depressed patients: A systematic review. *Psychiatry Res* 2016; **240**: 421-430.
11. Fabbri C, Corponi F, Souery D, Kasper S, Montgomery S, Zohar J *et al.* The Genetics of Treatment-Resistant Depression: A Critical Review and Future Perspectives. *Int J Neuropsychopharmacol* 2019; **22**(2): 93-104.
12. Tansey KE, Guipponi M, Hu X, Domenici E, Lewis G, Malafosse A *et al.* Contribution of common genetic variants to antidepressant response. *Biol Psychiatry* 2013; **73**(7): 679-682.
13. Pain O, Hodgson K, Trubetskoy V, Ripke S, Marshe VS, Adams MJ *et al.* Identifying the Common Genetic Basis of Antidepressant Response. *Biol Psychiatry Glob Open Sci* 2022; **2**(2): 115-126.

14. GENDEP, MARS, STAR*D. Common Genetic Variation and Antidepressant Efficacy in Major Depressive Disorder: A Meta-Analysis of Three Genome-Wide Pharmacogenetic Studies. *Am J Psychiatry* 2013; **170**(2): 207–217.
15. Biernacka JM, Sangkuhl K, Jenkins G, Whaley RM, Barman P, Batzler A *et al*. The International SSRI Pharmacogenomics Consortium (ISPC): a genome-wide association study of antidepressant treatment response. *Transl Psychiatry* 2015; **5**: e553.
16. Fabbri C, Kasper S, Kautzky A, Bartova L, Dold M, Zohar J *et al*. Genome-wide association study of treatment-resistance in depression and meta-analysis of three independent samples. *Br J Psychiatry* 2019; **214**(1): 36-41.
17. Tansey KE, Guipponi M, Perroud N, Bondolfi G, Domenici E, Evans D *et al*. Genetic predictors of response to serotonergic and noradrenergic antidepressants in major depressive disorder: a genome-wide analysis of individual-level data and a meta-analysis. *PLoS Med* 2012; **9**(10): e1001326.
18. Fabbri C, Tansey KE, Perlis RH, Hauser J, Henigsberg N, Maier W *et al*. New insights into the pharmacogenomics of antidepressant response from the GENDEP and STAR*D studies: rare variant analysis and high-density imputation. *Pharmacogenomics J* 2018; **18**(3): 413-421.
19. Wigmore EM, Hafferty JD, Hall LS, Howard DM, Clarke TK, Fabbri C *et al*. Genome-wide association study of antidepressant treatment resistance in a population-based cohort using health service prescription data and meta-analysis with GENDEP. *Pharmacogenomics J* 2020; **20**(2): 329-341.
20. Li QS, Tian C, Hinds D, and Me Research T. Genome-wide association studies of antidepressant class response and treatment-resistant depression. *Transl Psychiatry* 2020; **10**(1): 360.
21. Koch E, Pardiñas AF, O’Connell KS, Selvaggi P, Collados JC, Babic A *et al*. How real-world data can facilitate the development of precision medicine treatment in psychiatry. *Biological Psychiatry* 2024.
22. Leitsalu L, Haller T, Esko T, Tammesoo ML, Alavere H, Snieder H *et al*. Cohort Profile: Estonian Biobank of the Estonian Genome Center, University of Tartu. *Int J Epidemiol* 2015; **44**(4): 1137-1147.
23. Ojalo T, Haan E, Koiv K, Kariis HM, Krebs K, Uusberg H *et al*. Cohort Profile Update: Mental Health Online Survey in the Estonian Biobank (EstBB MHoS). *Int J Epidemiol* 2024; **53**(2).
24. Byrne EM, Kirk KM, Medland SE, McGrath JJ, Colodro-Conde L, Parker R *et al*. Cohort profile: the Australian genetics of depression study. *BMJ Open* 2020; **10**(5): e032580.
25. Davies MR, Kalsi G, Armour C, Jones IR, McIntosh AM, Smith DJ *et al*. The Genetic Links to Anxiety and Depression (GLAD) Study: Online recruitment into the largest recontactable study of depression and anxiety. *Behav Res Ther* 2019; **123**: 103503.
26. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J *et al*. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med* 2015; **12**(3): e1001779.
27. Li QS, Tian C, Seabrook GR, Drevets WC, Narayan VA. Analysis of 23andMe antidepressant efficacy survey data: implication of circadian rhythm and neuroplasticity in bupropion response. *Transl Psychiatry* 2016; **6**(9): e889.

28. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics* 2010; **26**(17): 2190-2191.
29. Watanabe K, Taskesen E, van Bochoven A, Posthuma D. Functional mapping and annotation of genetic associations with FUMA. *Nature communications* 2017; **8**(1): 1826.
30. Buniello A, MacArthur JAL, Cerezo M, Harris LW, Hayhurst J, Malangone C *et al.* The NHGRI-EBI GWAS Catalog of published genome-wide association studies, targeted arrays and summary statistics 2019. *Nucleic acids research* 2019; **47**(D1): D1005-D1012.
31. Consortium G. Human genomics. The Genotype-Tissue Expression (GTEx) pilot analysis: multitissue gene regulation in humans. *Science* 2015; **348**(6235): 648-660.
32. Hernandez DG, Nalls MA, Moore M, Chong S, Dillman A, Trabzuni D *et al.* Integration of GWAS SNPs and tissue specific expression profiling reveal discrete eQTLs for human traits in blood and brain. *Neurobiology of disease* 2012; **47**(1): 20-28.
33. Kircher M, Witten DM, Jain P, O'Roak BJ, Cooper GM, Shendure J. A general framework for estimating the relative pathogenicity of human genetic variants. *Nat Genet* 2014; **46**(3): 310-315.
34. Boyle AP, Hong EL, Hariharan M, Cheng Y, Schaub MA, Kasowski M *et al.* Annotation of functional variation in personal genomes using RegulomeDB. *Genome Res* 2012; **22**(9): 1790-1797.
35. Ghousaini M, Mountjoy E, Carmona M, Peat G, Schmidt EM, Hercules A *et al.* Open Targets Genetics: systematic identification of trait-associated genes using large-scale genetics and functional genomics. *Nucleic Acids Res* 2021; **49**(D1): D1311-D1320.
36. Zhu Z, Zheng Z, Zhang F, Wu Y, Trzaskowski M, Maier R *et al.* Causal associations between risk factors and common diseases inferred from GWAS summary data. *Nat Commun* 2018; **9**(1): 224.
37. Howard DM, Adams MJ, Shirali M, Clarke TK, Marioni RE, Davies G *et al.* Genome-wide association study of depression phenotypes in UK Biobank identifies variants in excitatory synaptic pathways. *Nat Commun* 2018; **9**(1): 1470.
38. Bulik-Sullivan BK, Loh PR, Finucane HK, Ripke S, Yang J, Schizophrenia Working Group of the Psychiatric Genomics C *et al.* LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat Genet* 2015; **47**(3): 291-295.
39. Fabbri C, Hagenaars SP, John C, Williams AT, Shrine N, Moles L *et al.* Genetic and clinical characteristics of treatment-resistant depression using primary care records in two UK cohorts. *Mol Psychiatry* 2021; **26**(7): 3363-3373.
40. Wightman DP, Jansen IE, Savage JE, Shadrin AA, Bahrami S, Holland D *et al.* A genome-wide association study with 1,126,563 individuals identifies new risk loci for Alzheimer's disease. *Nat Genet* 2021; **53**(9): 1276-1282.
41. Demontis D, Walters GB, Athanasiadis G, Walters R, Therrien K, Nielsen TT *et al.* Genome-wide analyses of ADHD identify 27 risk loci, refine the genetic architecture and implicate several cognitive domains. *Nat Genet* 2023; **55**(2): 198-208.
42. Grove J, Ripke S, Als TD, Mattheisen M, Walters RK, Won H *et al.* Identification of common genetic risk variants for autism spectrum disorder. *Nat Genet* 2019; **51**(3): 431-444.

43. Purves KL, Coleman JRI, Meier SM, Rayner C, Davis KAS, Cheesman R *et al.* A major role for common genetic variation in anxiety disorders. *Mol Psychiatry* 2020; **25**(12): 3292-3303.
44. Mullins N, Forstner AJ, O'Connell KS, Coombes B, Coleman JRI, Qiao Z *et al.* Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology. *Nat Genet* 2021; **53**(6): 817-829.
45. Lee JJ, Wedow R, Okbay A, Kong E, Maghzian O, Zacher M *et al.* Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. *Nat Genet* 2018; **50**(8): 1112-1121.
46. Okbay A, Wu Y, Wang N, Jayashankar H, Bennett M, Nehzati SM *et al.* Polygenic prediction of educational attainment within and between families from genome-wide association analyses in 3 million individuals. *Nat Genet* 2022; **54**(4): 437-449.
47. Savage JE, Jansen PR, Stringer S, Watanabe K, Bryois J, de Leeuw CA *et al.* Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence. *Nat Genet* 2018; **50**(7): 912-919.
48. Jansen PR, Watanabe K, Stringer S, Skene N, Bryois J, Hammerschlag AR *et al.* Genome-wide analysis of insomnia in 1,331,010 individuals identifies new risk loci and functional pathways. *Nat Genet* 2019; **51**(3): 394-403.
49. Ward J, Tunbridge EM, Sandor C, Lyall LM, Ferguson A, Strawbridge RJ *et al.* The genomic basis of mood instability: identification of 46 loci in 363,705 UK Biobank participants, genetic correlation with psychiatric disorders, and association with gene expression and function. *Mol Psychiatry* 2020; **25**(11): 3091-3099.
50. Nagel M, Jansen PR, Stringer S, Watanabe K, de Leeuw CA, Bryois J *et al.* Meta-analysis of genome-wide association studies for neuroticism in 449,484 individuals identifies novel genetic loci and pathways. *Nat Genet* 2018; **50**(7): 920-927.
51. Gelernter J, Sun N, Polimanti R, Pietrzak R, Levey DF, Bryois J *et al.* Genome-wide association study of post-traumatic stress disorder reexperiencing symptoms in >165,000 US veterans. *Nat Neurosci* 2019; **22**(9): 1394-1401.
52. Trubetskoy V, Pardinas AF, Qi T, Panagiotaropoulou G, Awasthi S, Bigdeli TB *et al.* Mapping genomic loci implicates genes and synaptic biology in schizophrenia. *Nature* 2022; **604**(7906): 502-508.
53. Okbay A, Baselmans BM, De Neve JE, Turley P, Nivard MG, Fontana MA *et al.* Genetic variants associated with subjective well-being, depressive symptoms, and neuroticism identified through genome-wide analyses. *Nat Genet* 2016; **48**(6): 624-633.
54. Ge T, Chen CY, Ni Y, Feng YA, Smoller JW. Polygenic prediction via Bayesian regression and continuous shrinkage priors. *Nat Commun* 2019; **10**(1): 1776.
55. Lloyd-Jones LR, Zeng J, Sidorenko J, Yengo L, Moser G, Kemper KE *et al.* Improved polygenic prediction by Bayesian multiple regression on summary statistics. *Nat Commun* 2019; **10**(1): 5086.
56. Vilhjalmsson BJ, Yang J, Finucane HK, Gusev A, Lindstrom S, Ripke S *et al.* Modeling Linkage Disequilibrium Increases Accuracy of Polygenic Risk Scores. *American journal of human genetics*

- 2015; **97**(4): 576-592.
57. Genomes Project C, Auton A, Brooks LD, Durbin RM, Garrison EP, Kang HM *et al.* A global reference for human genetic variation. *Nature* 2015; **526**(7571): 68-74.
58. Beath K. metaplust: An R Package for the Analysis of Robust Meta-Analysis and Meta-Regression. *R Journal* 2016; **8**: 5-16.
59. Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. *Journal of Statistical Software* 2010; **36**(3): 1 - 48.
60. Frei O, Hindley G, Shadrin AA, van der Meer D, Akdeniz BC, Hagen E *et al.* Improved functional mapping of complex trait heritability with GSA-MiXeR implicates biologically specific gene sets. *Nat Genet* 2024; **56**(6): 1310-1318.
61. Morselli Gysi D, Barabasi AL. Noncoding RNAs improve the predictive power of network medicine. *Proc Natl Acad Sci U S A* 2023; **120**(45): e2301342120.
62. Yildirim MA, Goh KI, Cusick ME, Barabasi AL, Vidal M. Drug-target network. *Nat Biotechnol* 2007; **25**(10): 1119-1126.
63. Köhler S, Bauer S, Horn D, Robinson PN. Walking the interactome for prioritization of candidate disease genes. *American journal of human genetics* 2008; **82**(4): 949-958.
64. Vanunu O, Magger O, Ruppin E, Shlomi T, Sharan R. Associating genes and protein complexes with disease via network propagation. *PLoS Comput Biol* 2010; **6**(1): e1000641.
65. Carlin DE, Demchak B, Pratt D, Sage E, Ideker T. Network propagation in the cytoscape cyberinfrastructure. *PLoS Comput Biol* 2017; **13**(10): e1005598.
66. Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D *et al.* Cytoscape: a software environment for integrated models of biomolecular interaction networks. *Genome Res* 2003; **13**(11): 2498-2504.
67. Cannon M, Stevenson J, Stahl K, Basu R, Coffman A, Kiwala S *et al.* DGIdb 5.0: rebuilding the drug-gene interaction database for precision medicine and drug discovery platforms. *Nucleic Acids Res* 2024; **52**(D1): D1227-D1235.
68. Lamb J, Crawford ED, Peck D, Modell JW, Blat IC, Wrobel MJ *et al.* The Connectivity Map: Using Gene-Expression Signatures to Connect Small Molecules, Genes, and Disease. *Science* 2006; **313**: 1929-1935.
69. Subramanian A, Narayan R, Corsello SM, Peck DD, Natoli TE, Lu X *et al.* A Next Generation Connectivity Map: L1000 Platform and the First 1,000,000 Profiles. *Cell* 2017; **171**(6): 1437-1452 e1417.
70. Enache OM, Lahr DL, Natoli TE, Litichevskiy L, Wadden D, Flynn C *et al.* The GCTx format and cmapPy, R, M, J packages: resources for optimized storage and integrated traversal of annotated dense matrices. *Bioinformatics* 2019; **35**(8): 1427-1429.
71. Lim N, Pavlidis P. Evaluation of connectivity map shows limited reproducibility in drug repositioning. *Sci Rep* 2021; **11**(1): 17624.

72. Barbeira AN, Dickinson SP, Bonazzola R, Zheng J, Wheeler HE, Torres JM *et al.* Exploring the phenotypic consequences of tissue specific gene expression variation inferred from GWAS summary statistics. *Nat Commun* 2018; **9**(1): 1825.
73. Barbeira AN, Bonazzola R, Gamazon ER, Liang Y, Park Y, Kim-Hellmuth S *et al.* Exploiting the GTEx resources to decipher the mechanisms at GWAS loci. *Genome Biol* 2021; **22**(1): 49.
74. Consortium GT. The Genotype-Tissue Expression (GTEx) project. *Nat Genet* 2013; **45**(6): 580-585.
75. Barbeira AN, Pividori M, Zheng J, Wheeler HE, Nicolae DL, Im HK. Integrating predicted transcriptome from multiple tissues improves association detection. *PLoS Genet* 2019; **15**(1): e1007889.
76. Nakaya N, Sultana A, Lee HS, Tomarev SI. Olfactomedin 1 interacts with the Nogo A receptor complex to regulate axon growth. *J Biol Chem* 2012; **287**(44): 37171-37184.
77. Nakaya N, Sultana A, Tomarev SI. Impaired AMPA receptor trafficking by a double knockout of zebrafish olfactomedin1a/b. *J Neurochem* 2017; **143**(6): 635-644.
78. Bertelsen B, Melchior L, Jensen LR, Groth C, Nazaryan L, Debes NM *et al.* A t(3;9)(q25.1;q34.3) translocation leading to OLFM1 fusion transcripts in Gilles de la Tourette syndrome, OCD and ADHD. *Psychiatry Res* 2015; **225**(3): 268-275.
79. Le-Niculescu H, Roseberry K, Gill SS, Levey DF, Phalen PL, Mullen J *et al.* Precision medicine for mood disorders: objective assessment, risk prediction, pharmacogenomics, and repurposed drugs. *Mol Psychiatry* 2021; **26**(7): 2776-2804.
80. Wegerer M, Adena S, Pfennig A, Czamara D, Sailer U, Bettecken T *et al.* Variants within the GABA transaminase (ABAT) gene region are associated with somatosensory evoked EEG potentials in families at high risk for affective disorders. *Psychol Med* 2013; **43**(6): 1207-1217.
81. Li X, Zhang J, Wu X, Yan H, Zhang Y, He RH *et al.* Polymorphisms of ABAT, SCN2A and ALDH5A1 may affect valproic acid responses in the treatment of epilepsy in Chinese. *Pharmacogenomics* 2016; **17**(18): 2007-2014.
82. Lener MS, Niciu MJ, Ballard ED, Park M, Park LT, Nugent AC *et al.* Glutamate and Gamma-Aminobutyric Acid Systems in the Pathophysiology of Major Depression and Antidepressant Response to Ketamine. *Biol Psychiatry* 2017; **81**(10): 886-897.
83. Duman RS, Sanacora G, Krystal JH. Altered Connectivity in Depression: GABA and Glutamate Neurotransmitter Deficits and Reversal by Novel Treatments. *Neuron* 2019; **102**(1): 75-90.
84. Luscher B, Shen Q, Sahir N. The GABAergic deficit hypothesis of major depressive disorder. *Mol Psychiatry* 2011; **16**(4): 383-406.
85. Marwaha S, Palmer E, Suppes T, Cons E, Young AH, Upthegrove R. Novel and emerging treatments for major depression. *Lancet* 2023; **401**(10371): 141-153.
86. Bright U, Akirav I. Modulation of Endocannabinoid System Components in Depression: Pre-Clinical and Clinical Evidence. *Int J Mol Sci* 2022; **23**(10).

87. Hasbi A, Madras BK, George SR. Endocannabinoid System and Exogenous Cannabinoids in Depression and Anxiety: A Review. *Brain Sci* 2023; **13**(2).
88. Bousman CA, Stevenson JM, Ramsey LB, Sangkuhl K, Hicks JK, Strawn JR *et al*. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6, CYP2C19, CYP2B6, SLC6A4, and HTR2A Genotypes and Serotonin Reuptake Inhibitor Antidepressants. *Clin Pharmacol Ther* 2023; **114**(1): 51-68.
89. Perlman K, Benrimoh D, Israel S, Rollins C, Brown E, Tunteng JF *et al*. A systematic meta-review of predictors of antidepressant treatment outcome in major depressive disorder. *J Affect Disord* 2019; **243**: 503-515.
90. Sternat T, Fotinos K, Fine A, Epstein I, Katzman MA. Low hedonic tone and attention-deficit hyperactivity disorder: risk factors for treatment resistance in depressed adults. *Neuropsychiatr Dis Treat* 2018; **14**: 2379-2387.
91. Ginsberg Y, Quintero J, Anand E, Casillas M, Upadhyaya HP. Underdiagnosis of attention-deficit/hyperactivity disorder in adult patients: a review of the literature. *Prim Care Companion CNS Disord* 2014; **16**(3).

Figures

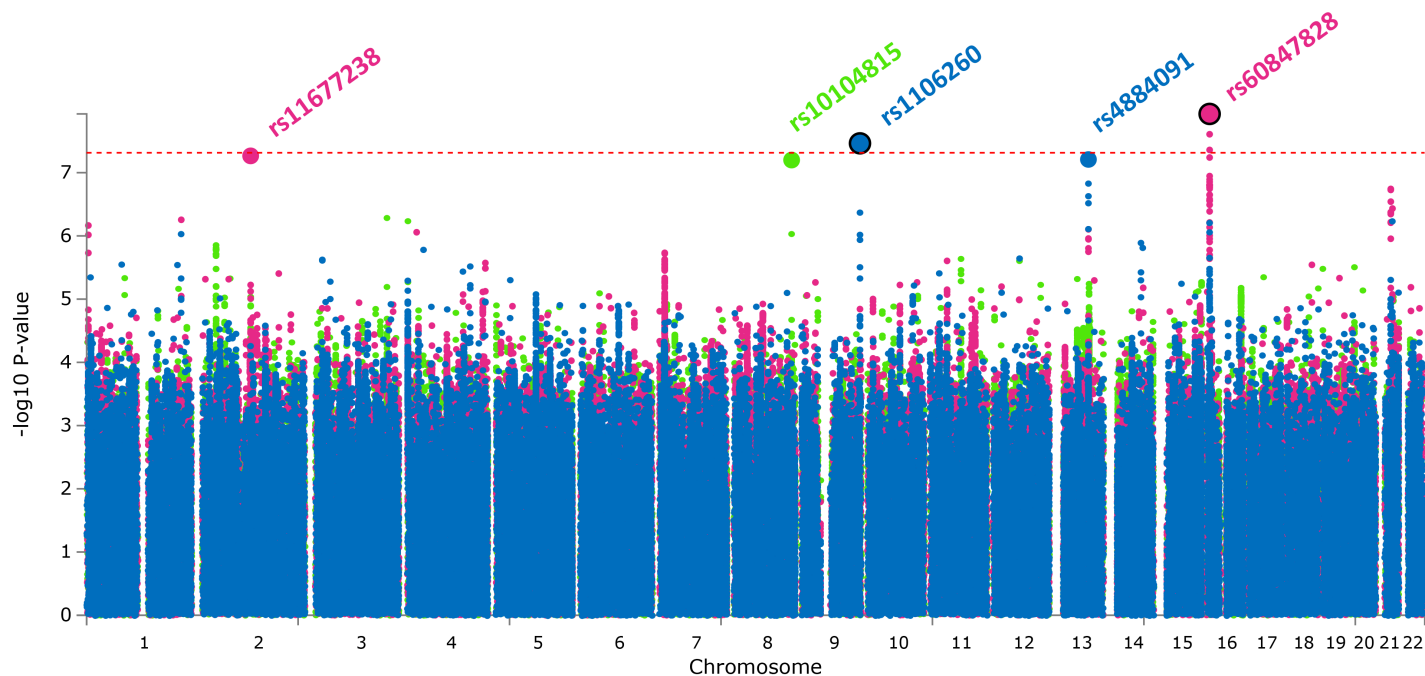


Figure 1

Manhattan plot showing genome-wide association results of the GWAS meta-analysis on non-response to SSRIs (blue), SNRIs (green), and SSRIs or SNRIs (pink). Genome-wide significant lead SNPs are encircled in black.

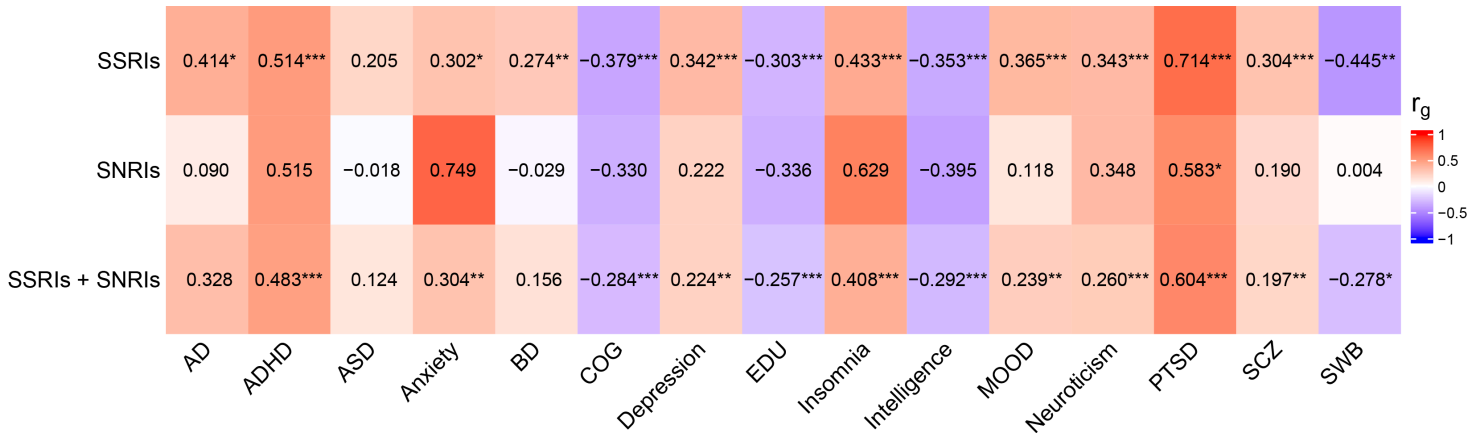


Figure 2

Genetic correlation between non-response to antidepressants and Alzheimer’s disease (AD), attention deficiency hyperactivity disorder (ADHD), autism spectrum disorder (ASD), anxiety disorder, bipolar disorder (BD), cognitive performance (COG), educational attainment (EDU), insomnia, intelligence, depression phenotypes, mood instability (MOOD), neuroticism, posttraumatic stress disorder (PTSD), schizophrenia (SCZ), subjective well-being (SWB). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

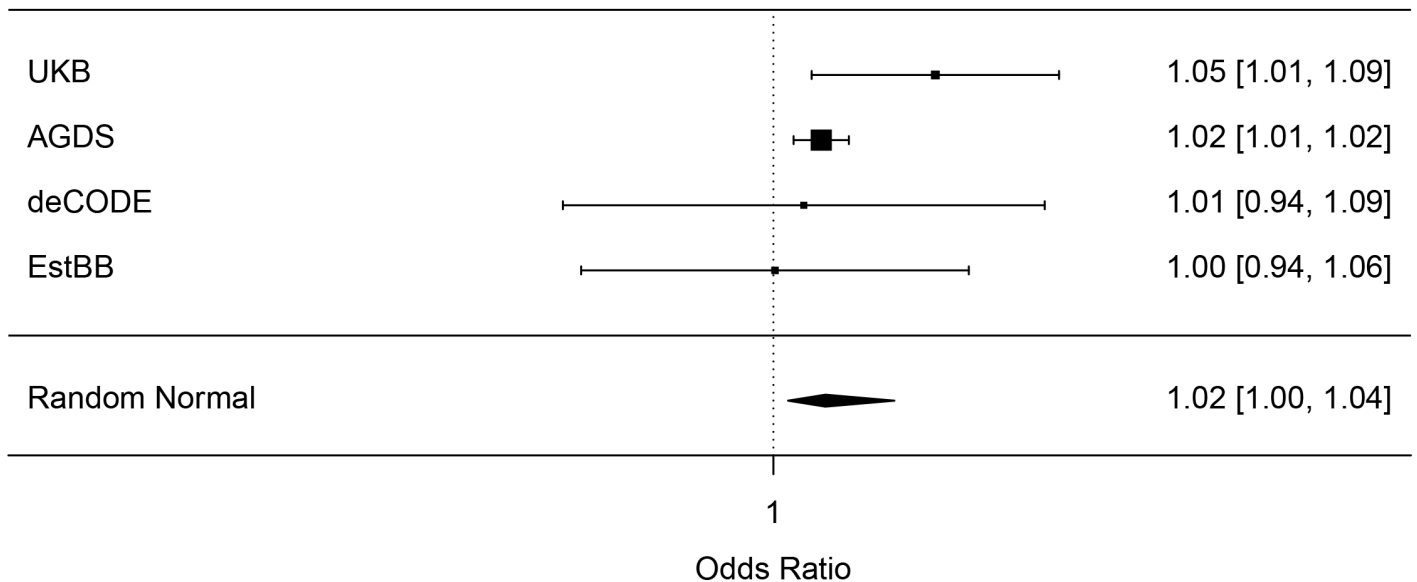


Figure 3

Forest plots showing the results from leave-one-out polygenic prediction of non-response to SSRIs in four independent cohorts, as well as meta-analyzed across these cohorts. Effects are reported as odds

ratios (95% confidence interval).

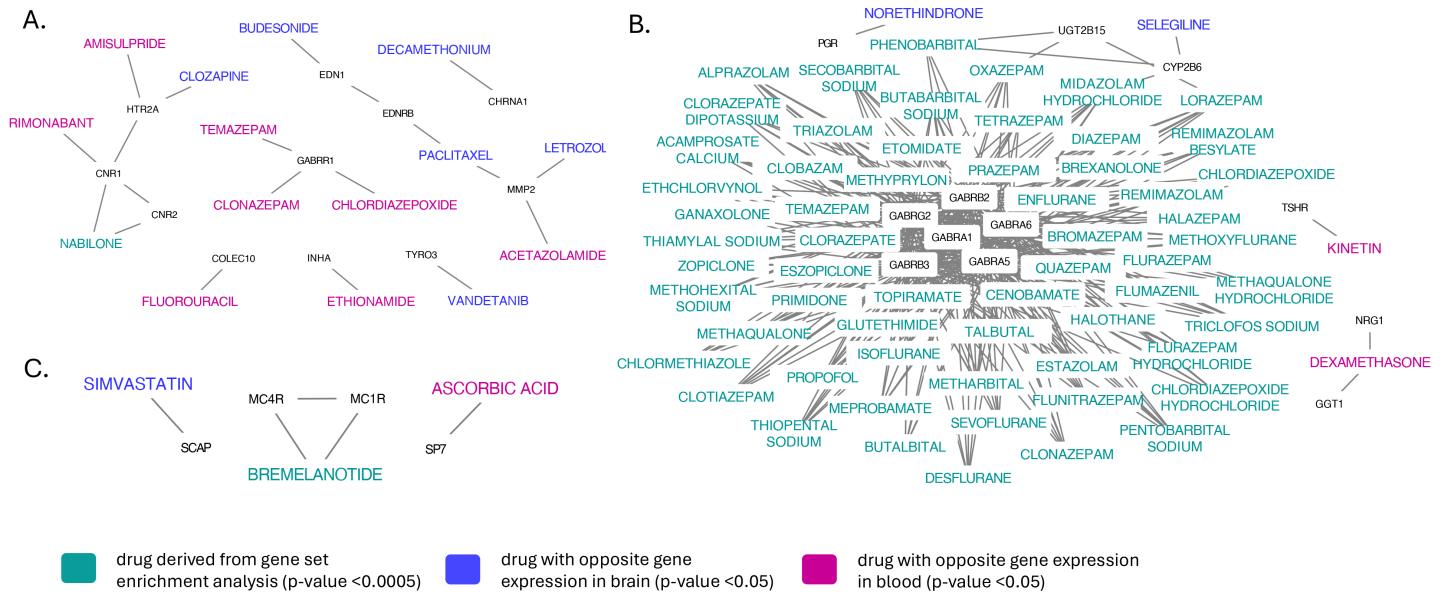


Figure 4

Top drugs identified based on gene-set enrichment analyses and drug-induced versus antidepressant non-response-associated gene expression, and their protein interaction partners in the SSRI non-response network (**A**), the SNRI non-response network (**B**), and SSRI/SNRI non-response network (**C**). Nodes refer to genes or drugs, and edges refer to gene-drug interactions or gene-gene interactions through identified protein-protein interactions between gene products (proteins).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementarymaterial.pdf](#)
- [Supplementarytables.xlsx](#)