ARTICLE

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Genome-wide meta-analyses of non-response to antidepressants provide insights into underlying molecular genetics and suggest potential pharmacotherapies

Elise Koch[1]✉, Tuuli Puusepp[2], Guðmundur Einarsson[3], Brittany L. Mitchell[4,5], Arvid Harder[6], Yuhao Lin[7], Luis M. García-Marín[4,5], Kristi Krebs[2], Alexey A. Shadrin[1,8], Ying Xiong[6], Estonian Biobank Research Team*, Oleksandr Frei[1,9], Yi Lu[6], Sara Hägg[6], Miguel E. Rentería[4], Sarah E. Medland[4], Naomi R. Wray[10,11], Nicholas G. Martin[4], Christopher Hübel[7,12], Gerome Breen[7], Thorgeir Thorgeirsson[3], Hreinn Stefánsson[3], Kári Stefánsson[3,13], Kelli Lehto[2], Lili Milani[2], Ole A. Andreassen[1,8]✉ and Kevin S. O'Connell[1]✉

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 one novel locus (rs1106260) associated with non-response to selective serotonin reuptake inhibitors (SSRIs), and one novel locus (rs60847828) associated with non-response to SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) 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.

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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 antidepressants [3–5], 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 outcomes [7]. Although antidepressants are linked to a reduction in depressive symptoms [8], they are often ineffective, with only approximately 35% achieving remission after their primary antidepressant treatment [6], and approximately 50% achieving remission after completing two treatments of antidepressants [7]. 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

[1]Centre for Precision Psychiatry, Division of Mental Health and Addiction, Oslo University Hospital, and Institute of Clinical Medicine, University of Oslo, Oslo, Norway. [2]Estonian Genome Centre, Institute of Genomics, University of Tartu, Tartu, Estonia. [3]deCODE Genetics/Amgen, Reykjavík, Iceland. [4]Brain & Mental Health Program, QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia. [5]School of Biomedical Sciences, Faculty of Medicine, The University of Queensland, Brisbane, QLD, Australia. [6]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Solna, Sweden. [7]Institute of Psychiatry, Psychology & Neuroscience; Social, Genetic & Developmental Psychiatry Centre; King's College London, London, UK. [8]KG Jebsen Centre for Neurodevelopmental Disorders, University of Oslo and Oslo University Hospital, Oslo, Norway. [9]Center for Bioinformatics, Department of Informatics, University of Oslo, 0316 Oslo, Norway. [10]Queensland Brain Institute, The University of Queensland, Brisbane, QLD, Australia. [11]Department of Psychiatry, The University of Oxford, Oxford, UK. [12]National Centre for Register-based Research, Aarhus Business and Social Sciences, Aarhus University, Aarhus, Denmark. [13]Faculty of Medicine, School of Health Sciences, University of Iceland, Reykjavik, Iceland. *A list of authors and their affiliations appears at the end of the paper. ✉email: e.m.koch@medisin.uio.no; ole.andreassen@medisin.uio.no; k.s.oconnell@medisin.uio.no

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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	Anti-depressant class	N total (Neff total)	Responders N (%)	Non-responders N (%)	Treatment response measure	Setting
PGC [13]	SSRIs	5151 (4479)	1852 (36)	3299 (64)	Depression symptom scores	Specialist healthcare
23andMe [20, 27]	SSRIs	19,740 (17,586)	13,130 (67)	6610 (33)	Antidepressant efficacy survey	Commercial genotyping service
	SNRIs	7079 (6943)	4030 (57)	3049 (43)		
EstBB	SSRIs	7168 (4272)	5862 (82)	1306 (18)	Antidepressant efficacy survey	Population cohort
	SNRIs	968 (584)	789 (82)	179 (18)		
AGDS	SSRIs	9208 (6902)	6908 (75)	2300 (25)	Antidepressant efficacy survey	Population cohort
	SNRIs	4426 (4304)	2580 (58)	1846 (42)		
GLAD	SSRIs	4184 (2416)	3452 (83)	732 (17)	Antidepressant efficacy survey	Population cohort
UKB	SSRIs	19,811 (10,632)	16,648 (84)	3163 (16)	Antidepressant efficacy survey	Population cohort
deCODE	SSRIs	49,062 (8391)	46,866 (96)	2196 (4)	Antidepressant switching	Public healthcare
	SNRIs	8674 (2148)	8099 (93)	575 (7)		
Total	SSRIs	114,324 (64,975)	94,718 (83)	19,606 (17)		
	SNRIs	21,147 (16,560)	15,498 (73)	5649 (27)		
	SSRIs/SNRIs	135,471 (82,187)	110,216 (81)	25,255 (19)		

Neff = 4/(1/Ncases + 1/Ncontrols). Specialist healthcare: Clinical samples recruited from inpatient and outpatient care, including clinical studies (open label, naturalistic, randomized controlled trials); Commercial genotyping service: Customers recruited from population, self-assessment; Population cohort: Recruited from general population, self-assessment and/or health registries; Public healthcare: Recruited from public healthcare services, outcome defined by drug dispensations at pharmacies.
PGC psychiatric genomics consortium, *EstBB* Estonian Biobank, *AGDS* Australian genetics of depression study, *GLAD* genetic links to anxiety & depression, *UKB* UK biobank.

clinical problem, and early identification remains a critical priority in psychiatry research [11].

Increasing evidence suggests that genetic variation contributes to antidepressant treatment outcomes [11]. 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 loci [13]. Antidepressant response is a polygenic phenotype, requiring larger sample sizes to elucidate the genetic architecture of antidepressant response [13]. Use of alternative outcome phenotypes such as antidepressant response information obtained from electronic health records (eHRs) [19] or self-reported questionnaires [20] 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 outcomes [21]. 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 eHRs, 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) Study [25], 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. Using questionnaire data, individuals were defined as non-responders if they answered that the prescribed antidepressant (SSRI or SNRI) was not effective. When using switching between antidepressants as a proxy phenotype from prescription registry data, non-responders included individuals who switched from a prescription of an antidepressant (SSRI or SNRI) to another antidepressant (Table S1). 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.

Genome-wide meta-analyses

Meta-analyses of GWAS summary statistics were conducted using inverse-variance-weighted fixed effects models in METAL [28]. Separate meta-

analyses were performed for non-response to SSRIs and non-response to SNRIs. These were meta-analyzed to produce summary statistics for non-response to either SSRIs or SNRIs, correcting for potential sample overlap in METAL using the approach as described by Lin and Sullivan [29]. We used the standard p value thresholds for genome-wide significance, p-value < $5e^{-8}$. 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 cohorts [28]. 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 METAL [28], we used Functional Mapping and Annotation of GWAS (FUMA) [30] 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 catalogue [31]. SNPs were also queried for known expression quantitative trait loci (eQTLs) across multiple tissues using the GTEx portal (GTEx v8) [32], and in different brain tissues using the BRAINEAC portal [33]. SNPs were annotated with Combined Annotation Dependent Depletion (CADD) [34] scores and RegulomeDB [35] scores. The Open Targets Genetics platform [36] 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) [37]. We conditioned the effect of SNPs estimated for non-response to antidepressants on those of depression, using summary statistics of a GWAS on depression phenotypes [38] 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) [39] 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 traits [40], LDSC [39] 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 disease [41], attention deficiency hyperactivity disorder (ADHD) [42], autism spectrum disorder [43], anxiety disorder [44], bipolar disorder [45], general cognitive performance [46], educational attainment [47], intelligence [48], insomnia [49], depression phenotypes [38], mood instability [50], neuroticism [51], posttraumatic stress disorder (PTSD) [52], schizophrenia [53], subjective well-being [54]. We used the Benjamini-Hochberg correction (FDR < 0.05) across all genetic correlation analyses.

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. As data on non-response to SNRIs was only available in three cohorts, we focused our PGS analyses on non-response to SSRIs. The target samples were EstBB, UKB, AGDS, GLAD, and deCODE. In all five cohorts, PGSs were calculated using SBayesR [55], and the European sample of the 1000 Genomes Phase III [56] 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 metafor [57] with standard normal random effect, weighting the samples based on effective sample size.

Genetically informed drug prioritization

To estimate gene associations, we used GSA-MiXeR [58] 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 genes [58]. To further sort by enrichment for biological relevance, we selected genes with an enrichment value of >10. All genes identified from GSA-MiXeR [58] and Open Targets Genetics [36] were then studied within networks of protein-protein interactions (PPIs) of gene products, using the latest version of the human protein interactome [59], 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 vicinity [60], we defined a network not only including the genes identified from GSA-MiXeR [58] and Open Targets Genetics [36], 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 propagation [61–63], implemented in the Cytoscape [64] application Diffusion [63]. Genes identified from GSA-MiXeR [58] and Open Targets Genetics [36] 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) [65] 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 each GSEA, we used the Benjamini-Hochberg correction (FDR < 0.05) to correct for the total number of drug-gene interactions (more details in Supplementary Methods).

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 [66, 67], extracted from the Phase 2 data release of the Library of Integrated Cellular Signatures (LINCS) using the cmapR package [68] in R version 4.3.1.

We performed transcriptome-wide association studies using S-PrediXcan [69] 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) [70, 71] and covariance matrices calculated from 503 individuals with European ancestry from the 1000 Genomes project [56]. For gene expression in brain, S-MultiXcan [72] 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. To correct for multiple correlation analyses (number of drugs), we used the Benjamini-Hochberg correction (FDR < 0.05).

Ethics approval and consent to participate

All methods were performed in accordance with the relevant guidelines and regulations, and informed consent has previously been obtained from all participants of the included GWAS.

RESULTS

GWAS meta-analyses

From the meta-analysis of non-response to SSRIs (N_{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

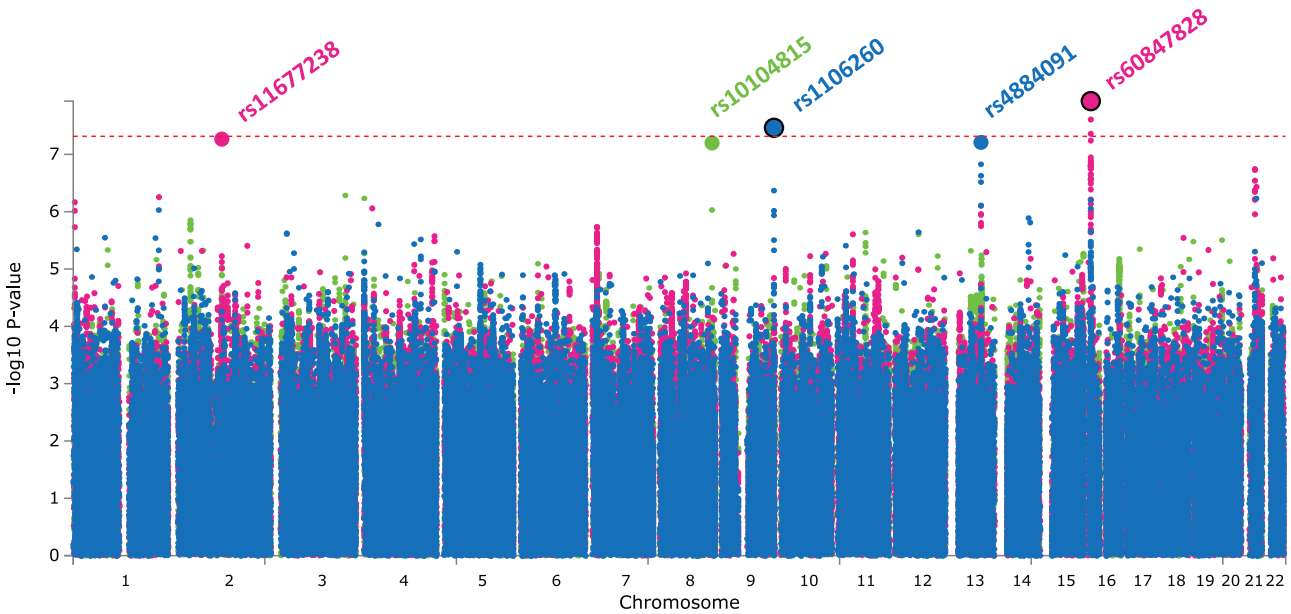

Fig. 1 Manhattan plot showing genome-wide association results of the GWAS meta-analysis on non-response to SSRIs (blue), SNRIs (green), and SSRIs or SNRIs (pink). Genome-wide significant lead SNPs are encircled in black.

be close to the genome-wide significance threshold (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_{SNPs}=8,011,440), including 21,147 individuals (5,649 non-responders and 15,498 responders). However, one locus was close to the genome-wide significance threshold (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_{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 close to the genome-wide significance threshold (rs11677238 T/G; chr2: 114,336,733-114,512,514; OR = 1.0439; SE = 0.008; p-value = 5.424 e-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 S2, Figs. 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). This might be related to reduced statistical power, with a decrease in effective sample size of 20% for non-response to SSRIs (from N = 64,975 to N = 52,105), 13% for non-response to SNRIs (from N = 16,560 to N = 14,412), and 18% for non-response to SSRIs/SNRIs (from N = 82,187 to N = 67,169). All loci achieving genome-wide significance as well as p < 1e-5 are reported in Tables S3–8.

Investigation of the genome-wide significant loci (rs1106260 and rs60847828) in the GWAS catalogue [31] showed no previous associations. Functional annotation of rs1106260 and rs60847828 using FUMA [30] 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) [32] for the lead SNP (rs1106260). Additional assessment of the lead SNP (rs1106260) and gene expression of *OLFM1, MRPS2*, and *PIERCE1* in the BRAINEAC database [33] 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) [32] nor in the BRAINEAC database [33].

The rs4884091 locus has been previously associated with SSRI non-response in the GWAS from the 23andMe Team [20] and was close to the genome-wide significance threshold for SSRI non-response in this study. 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). Similarly, the rs10104815 locus has been previously associated with non-response to SNRIs in the GWAS from the 23andMe Team [20] and was close to the genome-wide significance threshold for SNRI non-response in this study. The *KHDRBS3* gene was mapped to this locus (339,483 bp, intergenic variant). The top three genes for the locus that was close to the genome-wide significance threshold for 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 S9–11). 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 S12). Although some of the genetic correlations were non-significant after multiple testing correction (FDR > 0.05), genetic correlation analyses showed positive associations between non-response to antidepressants and most psychiatric traits, and negative associations with cognitive traits and subjective well-being (Fig. 2, Table S13–15). Similar results were obtained using the meta-analyses restricted to questionnaire data (Figure S6-8, Table S16–18) and non-response to antidepressants conditioned on depression (Figure S6-8, Table S19–21).

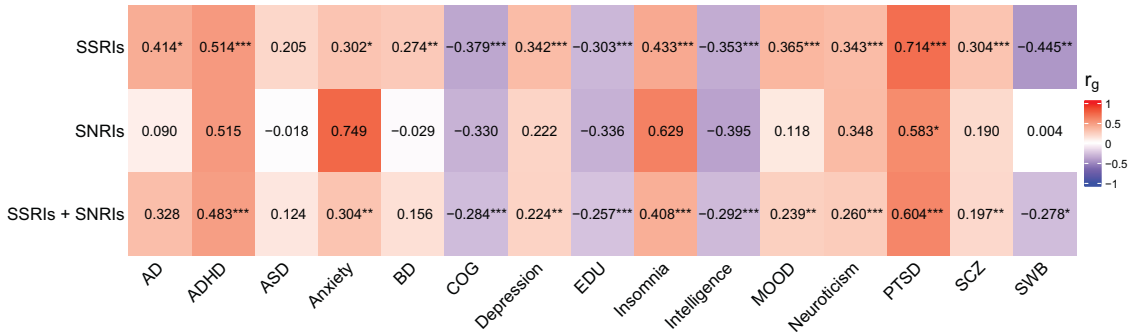

Fig. 2 Heatmap of genetic correlations. Genetic correlation between non-response to antidepressants and Alzheimer's disease (AD), attention deficiency hyperactivity disorder (ADHD), autism spectrum disorder (ASD), anxiety disorder, bipolar disorder (BD), cognitive performance (COG), educational attainment (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.

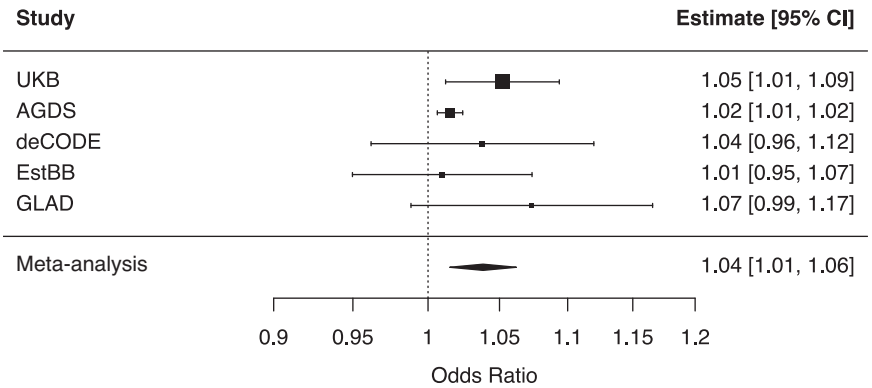

Fig. 3 Forest plots showing the results from leave-one-out polygenic prediction of non-response to SSRIs in five independent cohorts, as well as meta-analyzed across these cohorts, weighted based on effective sample size. Effects are reported as odds ratios (95% confidence interval). UKB = UK Biobank, AGDS = Australian Genetics of Depression Study, GLAD = Genetic Links to Anxiety and Depression Study, EstBB = Estonian Biobank.

Polygenic prediction of non-response to SSRIs

Meta-analysis of leave-one-out PGS analyses using SSRI non-response GWAS results in five samples showed a significant association with non-response to SSRIs (OR = 1.038, CI = 1.015–1.062, p-value = 0.0012), shown in Fig. 3. However, in three out of the five samples, the association did not reach statistical significance (Table S22).

Genetically informed drug prioritization

From GSA-MiXeR, all genes with a positive AIC value and an enrichment score >10 can be found in Table S23 (non-response to SSRIs, N = 65), Table S24 (non-response to SNRIs, N = 108), and Table S25 (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 S26 (SSRIs, N = 252), Table S27 (SNRIs, N = 287), and Table S28 (SSRIs/SNRIs, N = 260).

While the drug target genes in the SNRI non-response network were significantly (FDR < 0.05) enriched for several GABA receptor agonists, no significant (FDR < 0.05) enrichments for drug target genes in the network of SSRI non-response and SSRI/SNRI non-response network were identified after correction for the total number of drug-gene interactions (N = 21,799). At an uncorrected level, 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 (Table S29–31).

We identified opposite gene expression perturbations in drug (drug-induced expression) versus non-response associated gene expression. However, after correction for multiple correlation analyses (number of drugs), all correlations became non-significant (FDR > 0.05). In the SSRI non-response network (Figure S9), six drugs (letrozole, clozapine, vandetanib, decamethonium, paclitaxel, budesonide) showed opposite gene expression perturbations in drug versus SSRI non-response-associated expression in drug target genes in brain tissue (p < 0.05, uncorrected). For blood, eight drugs (temazepam, acetazolamide, chlordiazepoxide, ethionamide, amisulpride, rimonabant, clonazepam, fluorouracil) showed opposite gene expression at an uncorrected level of p < 0.05 (Table S32–S35). In the SNRI non-response network (Figure S10), two drugs (selegiline and norethindrone) showed opposite gene expression perturbations (p < 0.05, uncorrected) in brain, and 2 drugs (dexamethasone and kinetin) in blood (Table S36–39). In the SSRI/SNRI non-response network (Figure S11), the drug simvastatin showed opposite gene expression perturbations (p < 0.05, uncorrected) in brain, and the drug ascorbic acid in blood (Table S40–43). Figure S12 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-

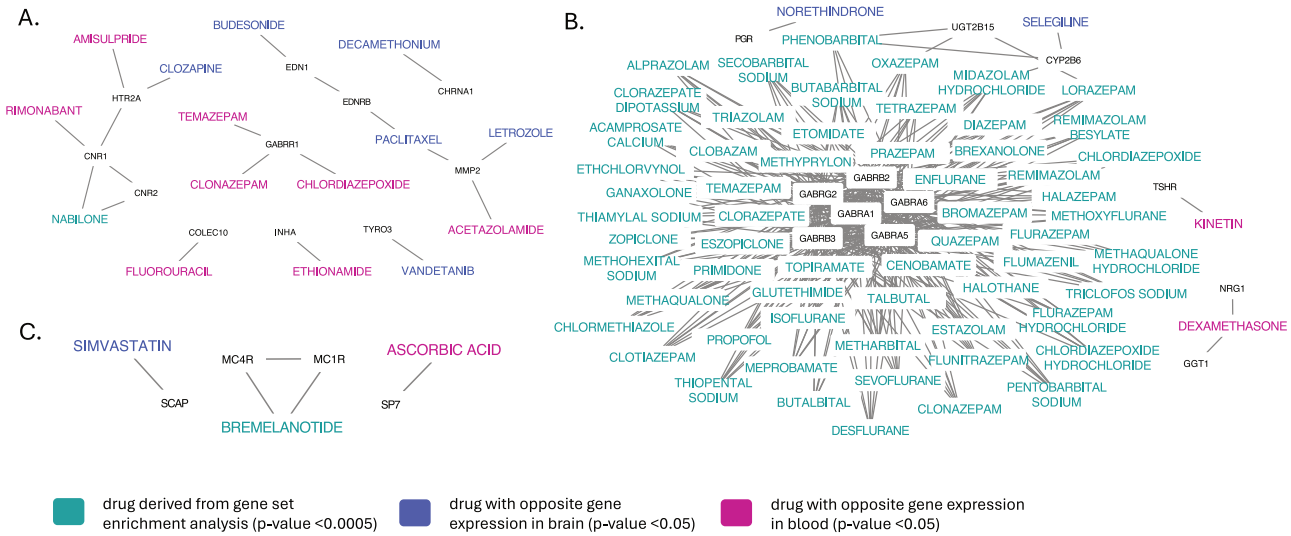

Fig. 4 Genetically informed drug prioritization. Top drugs identified based on gene-set enrichment analyses and drug-induced versus antidepressant non-response-associated gene expression, and their protein interaction partners in the SSRI non-response network (**A**), the SNRI non-response network (**B**), 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).

response based on clinically assessed symptom scores, self-reported treatment outcomes, and data from eHRs, 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 [73, 74]. As OLFM1 plays a role in neuronal development, it has previously been suggested as a candidate gene for neuropsychiatric disorders [75]. 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 depression [76]. 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 disorders [77]. Furthermore, it has been suggested that variants within *ABAT* affect valproic acid response [78]. 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 [79, 80]. 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 depression [81]. 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 monotherapy [82]. 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 symptoms [83]. However, the evidence that cannabinoids improve depressive disorders is weak and studies examining the effects of cannabinoids on mental disorders are needed [83, 84].

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 SNRIs [85]. Guidelines from the Clinical Pharmacogenetics Implementation Consortium (CPIC) highlight the impact of *CYP2B6*, and *HTR2A* genotypes, among others, on antidepressant dosing, efficacy, and tolerability [85]. 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 studies [86]. 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 PGC [13] as well as in a study investigating the genetic and clinical characteristics of treatment-resistant depression [40]. 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 cases [87]. In adults, ADHD may be undiagnosed, and ADHD symptoms are often mistaken for those of their psychiatric comorbidities [88]. Of note, most of the genetic correlations were still significant when the analyses were conditioned on depression using mtCOJO, indicating that the genetics captured in our GWAS meta-analyses are to a large degree independent of the genetic contribution of depression.

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. The heterogeneity in the outcome measures across the included studies is a limitation, as it may cause spurious results. However, in the current scenario the heterogeneity across samples seems more likely to result in type II errors than type I errors [89]. Still,

significant discoveries in GWAS always warrant replication as there can be unknown sources of bias. Unfortunately, no established standards for outcome measures in real-world data (RWD) sources exist, leading to variability in treatment outcome definitions, which makes it difficult to perform replication [90]. However, there are emerging initiatives to standardize real-world outcome measures [90], which can help the field to obtain more robust findings. In randomized controlled trials (RCTs), treatment response is assessed with disease specific rating scales in selected participants and treatment adherence is monitored. In real-world settings, self-reports and clinical evaluations are used to measure treatment response. While the RWD samples are more representative, the measures have a higher variability [21]. This is reflected in the varying non-response rate across our datasets, with highest rate in the PGC GWAS (symptom rating scales, clinical hospital setting), and lowest in the deCODE dataset (public healthcare setting), and the datasets using questionnaires in between (self-reports, population biobanks). However, large-scale studies are essential for the discovery of genetic variants affecting pharmacological treatment outcomes in psychiatry. To obtain datasets with sufficient statistical power, RWD from different sources can power gene discovery to facilitate the development of prediction and stratification tools for precision treatment in psychiatry [21]. While RWD from health registries, eHRs, and self-reports on medication response could provide clinically useful treatment outcome measures, they have to be tested, validated, and standardized [90]. Moreover, our study could potentially include individuals who were treated with antidepressants for conditions other than depression, especially in the deCODE sample where eHRs were used to define non-response based on switching as proxy phenotype. For example, it is common to use low doses of some antidepressants for sleep [91], so these prescriptions should not be considered as treatment of depression. In a recent study from the EstBB [92], it was shown that about 80% of individuals who use antidepressants have a depression diagnosis recorded in their eHRs. In the UKB, a recent study [93] investigating SSRI switching using prescription records reported that only about 60% of individuals who use SSRIs had a depression diagnosis. However, the depression diagnoses were only based on primary care records [93]. Among SSRI users in the AGDS, about 95% reported a diagnosis of major depressive disorder [94]. All participants included in the GWAS from the 23andMe Team self-reported taking antidepressants for depression indication [20, 27]. The GLAD study only includes individuals with depression or anxiety [25], and all individuals in the PGC GWAS [13] have a depression diagnosis. 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. These sensitivity analyses showed that the results were consistent across samples. However, the genome-wide significant findings became non-significant when the analyses were restricted to samples with similar questionnaires, which might be related to the reduced sample size and thus statistical power. 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. To identify drugs targeting genes associated with antidepressant non-response, we used strict thresholds for gene selection (enrichment score >10 from GSA-MiXeR and top 1% of proteins from network propagation output) to prioritize biologically relevant genes. It should be noted that the choice of these thresholds may increase the risk for false negatives, i.e. some relevant drug target genes may not be included in our analyses to identify potential drugs for repurposing.

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.

DATA AVAILABILITY

The GWAS summary statistics produced in this study (excluding data from 23andMe, Inc.) are available on request to the corresponding authors.

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AUTHOR CONTRIBUTIONS

EK, OAA, and KSO conceived the study and were involved in study design. EK, TP, GE, BLM, AH, LMGM, KK, YL, YX, and KSO conducted analyses. EK drafted the initial manuscript. EK, TP, GE, BLM, AH, YL, LMGM, KK, AAS, YX, OF, YL, SH, MER, SEM, NRW, NGM, CH, GB, TT, HS, KS, KL, LM, OAA, KSO contributed to data interpretation and editing of the manuscript.

COMPETING INTERESTS

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Correspondence and requests for materials should be addressed to Elise Koch, Ole A. Andreassen or Kevin S. O'Connell.

ESTONIAN BIOBANK RESEARCH TEAM

Andres Metspalu[2], Tõnu Esko[2], Reedik Mägi[2], Mari Nelis[2], Kelli Lehto[2] and Georgi Hudjashov[2]

A full list of members and their affiliations appears in the Supplementary Information.