Supplementary Materials

Cost-effectiveness of genetic and clinical predictors for choosing combined psychotherapy and pharmacotherapy in major depression

Table of contents

Supplementary Methods

Predictive models

The predictive models used in this study were developed in a previous paper (Fabbri et al., 2020) and the corresponding receiver operating characteristic (ROC) curves are shown in Supplementary Figure 1. Each predictive model was developed in a training set of patients treated with serotonergic antidepressants (n=269) and the ROC curves were obtained by testing the models in an independent testing sample treated with serotonergic antidepressants (n=118).

The genetic predictors were the burden of rare (from exome sequencing) and common variants (from genome-wide genotyping) in 83 genes selected as predictors of treatment-resistant depression (TRD) in the training sample. These genes are involved in the regulation of immune response, second messenger cascades, gene expression, cell growth, differentiation and survival; 39 (47%) of them were previously associated with psychiatric traits (Supplementary Table 2). These 83 genes were selected in the training sample based on their Correlation-Adjusted T (CAT) score and Local False Discovery Rate (LFDR) using a five-fold cross-validation repeated 20 times (100 rounds in total). The CAT score is a multivariate generalization of the standard univariate T-test statistic that takes the correlation among variables explicitly into account and the LFDR estimates the probability of a predictor to be non-informative with regard to phenotype prediction given its CAT score (Zuber and Strimmer, 2009) (Zuber and Strimmer, 2011). We selected predictors that had a LFDR smaller than 0.8 in > 50% of the rounds (Iniesta et al., 2018). This process reduces dimensionality and select variables with higher probability of being informative, reducing the risk of overfitting.

For each gene, a weighted score reflecting the burden of variants was calculated as follows:

$$\sum_{i=1}^{n} v_{all} \times w_s \times w_f$$

where n is the number of genetic variants within the gene, v_{all} is the number of alternative alleles, w_s is the corresponding Eigen score (reflecting the functionality of the variant (Ionita-Laza et al., 2016)) and w_f is the frequency weight for that variant (the rarest a variant is, the highest the risk of having functional consequences) (Ionita-Laza et al., 2013). Thus, the score is not dependent from the presence of specific variants which could not be observed in some of the tested samples, but from the general burden of variants in a certain gene and their risk of having functional effects on protein function/levels. This approach was used in order to estimate the effect of rare variants for which the effect size cannot be reliably estimated even in large samples. Further details can be found in a previous publication (Fabbri et al., 2020).

The clinical predictors consisted in a weighted sum of five clinical variables, independently associated with TRD in the training set and weighted for their z score:

$$\sum_{predictor=1}^{n} predictor \times z/n$$

Where n is the number of predictors available in each subject (to avoid exclusion of subjects with one or two missing variables). The predictors were: chronic depression, number of depressive episodes > 3, suicidal ideation, MADRS interest-activity score (items 6, 7 and 8) ≥ 13 and MADRS pessimism score (items 9 and 10) ≥ 7. For continuous variables, cut-offs were set at the 75th percentile of the distribution in the training sample.

Weights were 6.76 for chronic depression, 2.71 for number of depressive episodes > 3, 2.80 for suicidal ideation, 2.81 for MADRS interest-activity score, and 2.01 for MADRS pessimism score. MADRS interest-activity and pessimism scores were calculated as previously described (Uher et al., 2012). In GENDEP and TRD2, there were no subjects with chronic depression according to the DSM-IV definition (duration of the episode of at least two years), thus we used one year as threshold since there is some evidence that outcome is poorer after one year (Khan et al., 1991). The maximum number of depressive episodes in GENDEP was 3, thus we used >2 (75^{th} percentile) as threshold instead of >3.

We decided to no select the combination of sensitivity and specificity which maximizes the area under the curve (AUC) of the ROC, because it would imply values of specificity which are not compatible with clinical application (for example, for the curve in A it would mean a specificity of 0.67, thus 33% of non-TRD patients would be wrongly classified as TRD, significantly increasing the number of patients in the combined treatment arm, with increased costs and no additional clinical benefit). It is desiderable to reduce the risk of false positives also in order to avoid a possible nocebo effect in this group of patients. Under this view, we selected combinations of sensitivity-specificity which maximized specificity and had still reasonably good sensitivity (sensitivity=0.62 and specificity=0.77 for clinical and genetic predictors, sensitivity=0.62 and specificity=0.70 for clinical predictors, red arrows in Supplementary Figure 1). We performed a sensitivity analysis by selecting a further reduced sensitivity and an optimized specificity in both A (sensitivity=0.38 and specificity=0.92) and B (sensitivity=0.42 and specificity=0.82), as indicated by the purple arrows in Supplementary Figure 1.

Estimation of transition probabilities

The probabilities of transition from depression to remission and response in the standard care (ST) group were based on a previous meta-analysis at T1 (first cycle, 12 weeks) (Jakobsen et al., 2017), while they were based on the percentage reduction in response and remission probabilities reported in STAR*D levels 2-4 from T2 (second cycle) forward (Sinyor et al., 2010). Response probabilities are lower than remission probabilities because the overlap between the two groups was eliminated (i.e., at T1 we assumed that all remitters were also responders; from T2, the overlap between response and remission was based on STAR*D levels 2-4). For example, at T1 remission to pharmacotherapy was reported to occur in 38% of patients and response in 49% of patients (Jakobsen et al., 2017), thus response was set to 11%. At T2, there was a decrease of 0.16 in response probability according to STAR*D, and 78.8% of responders were also remitters, thus response was set to (0.49 – 0.16) - (0.49 – 0.16) *0.788 = 0.07 (Warden et al., 2007). This process is detailed in Supplementary Table 4 for all time points. Remission and response probabilities stabilized between levels 3 and 4 according to

the Quick Inventory of Depressive Symptomatology–Self report (QIDS-SR) scale, thus we assumed that they would remain stable from T4 forward.

Two meta-analyses were used to estimate the probabilities of response and remission to combined pharmacotherapy and psychotherapy (de Maat et al., 2007) (Cuijpers et al., 2014). Remission at T1 was reported to be 0.46 (de Maat et al., 2007), while response was calculated based the number needed to treat (NNT) in community samples (Cuijpers et al., 2014), which is 6.41 ($NNT = \frac{1}{Resp_{combined} - Resp_{pharmacotherapy}}$; $6.41 = \frac{1}{Resp_{combined} - 0.49}$; $resp_{combined} = 0.64$). A total response of 0.64 corresponds to 0.18 after exclusion of remitters (0.46). Response and remission from T2 forward are hypothesized to follow the same reduction pattern described above for pharmacotherapy. The procedure applied is exemplified in Supplementary Table 4 and the resulting response and remission probabilities are shown in Figure 1. According to the response and remission probabilities estimated in the pharmacotherapy group, the prevalence of TRD to pharmacotherapy is 31%, which is in line with the literature (Souery et al., 1999) (Conway et al., 2017) and confirms the validity of our approach.

For calculating response and remission probabilities in the PGx-CL-R and CL-R groups, we assumed that patients treated with combined treatment (true positives and false positives) would have the response and remission probabilities reported for this treatment in the literature, as the meta-analyses used for calculating the response and remission rates to combined treatment were not focused on TRD. However, it is interesting to note that effect size of combined treatment vs. pharmacotherapy does not seem to change between general MDD samples and TRD samples (Ijaz et al., 2018), supporting the hypothesis that combined treatment works in a similar way in patients who are predisposed to pharmacotherapy resistance and those who are not. For patients identified as non-TRD by the test (true negatives), we hypothesized that response and remission probabilities would be the ones observed in the pharmacotherapy group considering that TRD patients have virtually zero response-remission probability to pharmacotherapy. For example, remission at T1 in non-TRD would be

$$x \times 0.69 + \sim 0 \times 0.31 = 0.38;\ x = 0.38/0.69 = 0.55$$

In this way, non-TRD have response and remission probabilities to pharmacotherapy which are similar or better to the ones reported for combined therapy, which supports the hypothesis that the increased benefit of combined therapy is selectively observed in patients who are predisposed to pharmacotherapy resistance. In summary, remission probability at T1 in the PGx-CL-R group would be (assuming sensitivity of 0.62 and specificity of 0.77):

$$(\text{true positives} + \text{false positives}) \times 0.46 + \text{true negatives} \times 0.551 + \text{false negatives} \times 0 = (0.192 + 0.166) \times 0.46 + 0.524 \times 0.551 + 118 \times 0 = 0.454$$

Probabilities for the other time points and response were calculated according to the same approach and are reported in Supplementary Table 5.

The probability of transition from depression to suicide was considered the same for all treatment strategies and it was based on the rate of suicide in 2016 in the United Kingdom (UK) (World Health Organization (WHO), 2016) and the data that 50% of death by suicide are related to depressive disorders (Bachmann, 2018).

The probability of transition from response to remission was considered the same for all treatment strategies and it was based on STAR*D level 1 and 2 data (0.51).

The probabilities of relapse in the ST group (response -> depression or remission -> depression) were based on a previous meta-analysis (Hansen et al., 2008) and the observation that the risk is higher (OR=3.68 [2.64-5.21]) in patients who did not reach remission (Judd et al., 1998). There is evidence that the risk of relapse is reduced using pharmacotherapy combined with psychotherapy by 50% (0.35-0.72) in 12 months compared to pharmacotherapy (Zhang et al., 2018). This result was obtained by a meta-analysis of studies comparing pharmacotherapy combined with brief psychotherapy after the patient reached remission vs. prophylactic pharmacotherapy only. We assumed that the prophylactic effect of psychotherapy would be similar independently from the fact that it is delivered before or after remission. For example, the cumulative probability of transition from remission to depression in 12 months in ST was:

$$0.028 \text{ (probability at T1)} + 0.004 \text{ (probability from T2 forward)} \times 3 = 0.04 \text{ (Hansen et al., 2008)},$$

while in the PGx-CL-R group (assuming sensitivity=0.62 and specificity=0.77) it was:

$$(0.014 + 0.002 \times 3) \times 0.351 + (0.028 + 0.004 \times 3) \times 0.649 = 0.0329$$

Given the lack of literature data on the risk of transition for remission to response, we assumed that it was the same as the probability of transition from response to depression, because it can be considered as a milder form of relapse and it may the first step leading to a new depressive episode. Relapse transition probabilities are reported in Supplementary Table 5.

Supplementary Table 1: clinical-demographic characteristics of the samples. MADRS= Montgomery-Asberg Depression Rating Scale. TRD=treatment-resistant depression.

Variable	**Original training sample** (n=269)	**Original testing sample** (n=118)	**TRD2** (n=407)	**GENDEP** (n=336)
Age	49.56±14.16	50.18±14.50	47.14±12.58	41.16±11.56
Gender F (%)	178 (66.2%)	80 (67.8%)	268 (65.8%)	211 (62.8%)
Total MADRS at baseline	33.67±6.79	32.65±6.41	31.54±6.25	29.00±6.14
MADRS interest-activity score (base)	10.88±2.30	10.29±2.63	10.28±2.40	9.27±2.38
MADRS pessimism score (base)	5.21±2.38	4.98±2.17	4.73±1.97	4.43±1.92
TRD (%)	159 (59.1%)	71 (60.2%)	185 (45.5%)	109 (32.4%)
Responders (%)	110 (40.1%)	47 (39.8%)	222 (54.5%)	227 (67.6%)
Chronic depression (%)	34 (12.6%)	10 (8.5%)	48 (11.8%)	26 (7.7%)
N previous depressive episodes	3.43±2.69	3.25±2.83	3.65±2.98	1.73±0.71
Suicidal ideation (%)	114 (42.4%)	51 (43%)	225 (55.3%)	64 (19%)

Supplementary Table 2: genes included in the clinical-genetic predictive model of treatment-resistant depression. Information on gene function was taken from https://www.genecards.org and the cited papers.

Gene symbol	Function	Implicated in psychiatric traits by independent studies in humans
LYRM1	Mitochondrial protein involved in cell proliferation and survival	Psychosis (Glatt et al., 2009)
CACNA1I	Calcium voltage-gated channel subunit	Schizophrenia and autism spectrum disorders (Andrade et al., 2016) (Heyes et al., 2015)
SCMH1	Regulation of gene transcription, including synaptic plasticity-related genes, and putatively involved in regulation of depressive-like behaviors in mice (Wang et al., 2019)	General risk tolerance (Karlsson Linnér et al., 2019)
ACSM5	Fatty acid beta-oxidation and amino acid conjugation	Response to d-amphetamine (Yarosh et al., 2015)
PTPRU	Protein tyrosine phosphatase regulating cell growth and differentiation, involved in the development of meso-diencephalic dopamine neurons (Jacobs et al., 2009) and in stress response in the hippocampus (S. Li et al., 2016)	Schizophrenia (Huang et al., 2014)
REM1	GTPase regulating reorganization of the actin cytoskeleton	No
ZNF418	Regulation of gene transcription	Major depressive disorder (PGC meta-analysis) (Subaran et al., 2016)
MTF2	Regulation of gene transcription, associated with emotionality in mice in interaction with brain derived neurotrophic factor (Marrocco et al., 2018)	Bipolar disorder (Goes et al., 2019)
RORC	Regulation of gene transcription, modulates inflammation through regulation of Th17-cells and depression-like behavior in mice (Beurel et al., 2013)	Schizophrenia (Subbanna et al., 2018) (Debnath and Berk, 2014), depressive symptoms (Noordam et al., 2015)
SP7	Regulation of gene transcription	No
PRG4	Proteoglycan involved in extracellular matrix structure, plays a role in the regulation of inflammation (Das et al., 2019) and depressive-like behavior in mice (Yang et al., 2018)	Antidepressant response (Turck et al., 2017), response to paliperidone in schizophrenia (Li et al., 2017)
BIK	Regulation of cell survival, including survival of human cells exposed to sertraline in vitro (Chen et al., 2014)	No
ZNF19	Regulation of gene transcription	No
SNRNP25	Regulation of mRNA processing (splicing), dysfunction causes neuron degeneration in mice (Jia et al., 2012)	No
CPSF6	Regulation of mRNA processing, key role in regulating the expression of GluA1, a subunit of AMPA receptor, in mice (Udagawa et al., 2015); target of miR-132, a regulator of neuroplasticity and sleep/wake cycles with a hypothesized role in depression (Hansen and Obrietan, 2013)	Schizophrenia (Koga et al., 2009), smoking behavior (Karlsson Linnér et al., 2019)

LPCAT1	Phospholipid metabolism, it regulates transcription through histone H4 palmitoylation (Zou et al., 2011)	Depressive symptoms (Story Jovanova et al., 2018)
CEACAM20	Cell adhesion molecule	No
HPSE	Proteoglycan involved in membrane and extracellular matrix structure	No
LRRN4	Leucine rich neural protein involved in neurite growth (Chen et al., 2006)	Schizophrenia (Vitale et al., 2017)
PDE6G	Phosphodiesterase involved in regulation of second messenger cascades	No
CTNND1	Cell adhesion and signal transduction	Schizophrenia (PGC meta-analysis) (Ripke et al., 2014), major depression (Carboni et al., 2018), major depressive disorder (PGC meta-analysis) (Wray et al., 2018), autism spectrum disorders(Autism Spectrum Disorders Working Group of The Psychiatric Genomics Consortium, 2017), possible cross-disorder role (Hawi et al., 2018)
HAMP	Iron homeostasis (including the brain), involved in inflammation in microglial cells (W.-Y. Li et al., 2016), may play a role in stress-induced depressive disorders in mice (Farajdokht et al., 2015)	No
GATS	Regulation of signal transduction and TORC1 signaling, which is involved in long-term synaptic potentiation (Zhou et al., 2006)	No
LCE1B	Peptide cross-linking	Schizophrenia (Bergen et al., 2014)
FGFBP3	Fibroblast growth factor binding protein involved in brain development and neuroplasticity (Turner et al., 2012) (Taetzsch et al., 2018); inactivation of FGFBP3 increased anxiety behavior in rodents (Yamanaka et al., 2011)	Autism spectrum disorders (Salyakina et al., 2011)
PI15	Peptidase inhibitor	No
RNASEK-C17orf49	Regulation of mRNA translation (nonsense-mediated mRNA decay)	Cognitive deficits in schizophrenia (Nakahara et al., 2018)
ADH1A	Oxidative metabolism of ethanol, retinol and neurotransmitters	Alcohol use disorders (Walters et al., 2018) and personality traits (Zuo et al., 2010)
HIST1H2BK	Chromatin structure and regulation of gene expression	Schizophrenia (Shi et al., 2009), Major depressive disorder (PGC meta-analysis) (Wray et al., 2018)
NFKB1	Gene transcription regulation involved in regulation of immune response and neuroinflammation	Schizophrenia, suicide, alcohol dependence (Altinoz et al., 2018)
AMPD2	Purine metabolism, linked to adenosine-mediated neurotoxicity (Kortüm et al., 2018), expression affected	No

	following chronic restrained stress and reversed by antidepressants in mice (Jungke et al., 2011)	
ARHGAP35	Regulation of glucocorticoid receptor gene expression, involved in neurodevelopment (Héraud et al., 2019)	No
MTG2	Signal transduction, associated with the inner mitochondrial membrane and involved in mitoribosome assembly (Mai et al., 2017)	No
TOM1L1	Signal transduction	Depressive symptoms (Yi et al., 2012)
C14orf93	Promotes cell survival under stress and enhances cell migration (Liu et al., 2017, p. 93) PMID 27864143	No
PRMT5	Methyltransferase (regulation of gene expression), associated with early life stress (Nieratschker et al., 2014), involved in glial cells differentiation (Huang et al., 2011) and D2-like dopamine receptor signaling (Likhite et al., 2015)	No
RHBDF1	Regulates ADAM17 protease and TNF, thereby plays a role in cell survival, proliferation, migration and inflammation	No
PLEKHA2	Involved in phosphatidylinositol metabolism and IL-2 pathway, modulated by lithium and fluoxetine (Kittel-Schneider et al., 2019) (Huang et al., 2012)	Neuroticism (Genetics of Personality Consortium et al., 2015)
ZNF154	Transcription factor	No
SIGLEC15	Involved in innate immune system	Response to paliperidone in schizophrenia (Li et al., 2017)
FAAP20	DNA damage repair	No
CCL16	Cytokine with chemotactic activity for lymphocytes and monocytes and myelosuppressive activity	Schizophrenia (Chan et al., 2017)
TMEM68	Integral endoplasmic reticulum membrane protein and putatively involved in brain glycerolipid metabolism (Chang et al., 2017)	Methadone dose in opioid dependence (Smith et al., 2017, p. 1)
SPAM1	Proteoglycan involved in membrane and extracellular matrix structure	Schizophrenia (Bitanihirwe et al., 2016)
CNOT8	Transcription and translation regulator	No
PMS2	DNA mismatches repair during DNA duplication	No
UMPS	Nucleic acid (pyrimidine) biosynthesis, putatively involved in lithium effects (Breen et al., 2016) and antidepressant effects (Park et al., 2016)	No
KIAA1024	Regulates mTOR signaling pathway and cell growth	No
ZNF366	Transcription factor, acts as negative regulator of glucocorticoid receptor function and may act through histone deacetylases to modulate immune response (Arnau-Soler et al., 2018)	Childhood chronic physical aggression (Guillemin et al., 2014), alcohol dependence, stress-sensitivity (Arnau-Soler et al., 2018), schizophrenia (Need et al., 2009)
HMGN4	Chromatin structure and regulation of gene expression	Major depressive disorder (PGC meta-analysis) (Wray et al., 2018), schizophrenia (Shi et al., 2009), autism spectrum disorder (Autism Spectrum Disorders

		Working Group of The Psychiatric Genomics Consortium, 2017)
LCA5L	Cytoskeleton structure (den Hollander et al., 2007)	No
KRTAP24-1	Regulation of extracellular matrix structure, brain expression affected by ischemia (Surles-Zeigler et al., 2018)	No
EFCAB2	Key regulator of cell motility which maintains the alignment and integrity of the distal axoneme and regulates microtubule sliding in motile axonemes	Anhedonia (Ren et al., 2018), schizophrenia (Need et al., 2009)
MRPS36	Mitochondrial protein synthesis, altered by exposure to methamphetamine in rat prefrontal cortex (Wearne et al., 2015)	No
DGCR6	Involved in neurodevelopment by regulation of neural crest cell migration	Psychosis (Liu et al., 2002) (Kumarasinghe et al., 2013), anxiety, impaired attention (Das Chakraborty et al., 2012)
DUSP23	Protein phosphatase for MAPK3, JNK and p38	Generalized anxiety disorder (Davies et al., 2015)
MBIP	Chromatin structure and regulation of gene expression, regulation of the JNK/SAPK pathway, involved in neurodevelopment (Thorwarth et al., 2014)	No
ZBTB32	Transcription factor	Major depressive disorder (Song et al., 2013)
C1R	Mediator of innate immune response, it may contribute to inflammatory and degenerative diseases of the CNS including Alzheimer's disease (Hawrylycz et al., 2015)	Schizophrenia (Kim et al., 2016), psychotic experiences (Föcking et al., 2019), major recurrent depression (Hamilton et al., 2012)
R3HDM4	Nucleic acid binding protein	Antidepressant response (Cook et al., 2019)
IQCF5	Putatively involved in calmodulin binding	No
RSBN1L	Demethylates methylated lysine residues of proteins	No
BTBD6	Involved in immune system, neuronal development and neurogenesis (Bury et al., 2008) (He et al., 2014)	No
GZMM	Serine protease expressed in natural killer cells and activated lymphocytes	No
MMP27	Regulation of extracellular matrix structure	Psychosis (Glatt et al., 2009)
VDR	Vitamin D, modulates neurodevelopment, neuroprotection, and immunomodulation	Schizophrenia (Chiang et al., 2016) (Amato et al., 2010), depressive symptoms (Jo et al., 2015)
NODAL	Ligand of the TGF-beta, involved in embryonic development and neurogenesis, altered in iPSC derived neurons from bipolar disorder patients (O'Shea and McInnis, 2016)	No
SLC17A4	Membrane potential-dependent organic anion transporter	No
EMC4	Endoplasmic reticulum membrane protein, altered expression after brain ischemia (Surles-Zeigler et al.,	Attention deficit hyperactivity disorder (Martin et al., 2014)

	2018) , it has a possible role in neurodegeneration (Zhu et al., 2017)	
TCAF1	Regulates the plasma membrane cation channel TRPM8 and in turn the influx of calcium and sodium, resulting in membrane depolarization as well as the activation of second messenger signaling cascades; regulation of pain (Dussor and Cao, 2016)	No
OGFR	Receptor for opioid growth factor, involved in the regulation of cell growth and hippocampal neurogenesis (Sargeant et al., 2008)	No
ZNF599	Transcription factor	No
SMC5	DNA repair and telomere maintenance	Response to paliperidone in schizophrenia (Li et al., 2017)
COL8A1	Short chain collagen and component of the basement membrane, it may affect prefrontal cortex neural plasticity (Smagin et al., 2019), upregulated by ketamine (Qiao et al., 2019)	Depression in maltreated children (Kaufman et al., 2018)
OR5AS1	Signal transduction	No
RORB-AS1	Long non-coding (lncRNA) with possible regulatory function on gene expression/mRNA processing	Alcohol consumption (Karlsson Linnér et al., 2019)
LOC102723824	ncRNA with possible regulatory function on gene expression/mRNA processing	No
IQCF5-AS1	Long non-coding (lncRNA) with possible regulatory function on gene expression/mRNA processing	No
PTOV1-AS2	Long non-coding (lncRNA) with possible regulatory function on gene expression/mRNA processing	No
PART1	Long non-coding (lncRNA) with possible regulatory function on gene expression/mRNA processing	No
GUSBP5	Non-coding gene, associated with autism-spectrum disorders (Vardarajan et al., 2013)	No
IDH1-AS1	Long non-coding (lncRNA) with possible regulatory function on gene expression/mRNA processing	No
WWC2-AS2	Long non-coding (lncRNA) with possible regulatory function on gene expression/mRNA processing	No

Supplementary Table 3: Estimation of costs.

Cost	Description	Value	Variability	Source
Antidepressant medication	Mean costs of 23 antidepressant drugs (NHS prices)	£31.4 per 12 weeks	SD=34.65	RDCT, April 2019 (REGIONAL DRUG AND THERAPEUTICS CENTRE, 2019)
Antidepressant combination or augmentation	Mean cost of first line pharmacological treatments for TRD (Maudsley guidelines (Taylor et al., 2018))	£40.78 per 12 weeks	SD=47.4	RDCT, April 2019 (REGIONAL DRUG AND THERAPEUTICS CENTRE, 2019)
Psychotherapy	Mean cost	£118 per hour	SD=16.26	PSSRU (Personal Social Services Research Unit (PSSRU), 2018a)
Cost PGx	Mean cost exome sequencing Mean cost genome-wide genotyping	£388.5 £67.4	SD=156.51 SD=40.8	(Suwinski et al., 2019) (Science exchange, 2019) (Genetic Resources Core Facility of John Hopkins University, School of Medicine, 2019) (Iowa Institute of Human Genetics, 2019) (Center for Genome Technology, University of Miami, 2019)
GP visits	1st visit 30 min, following 10 min; dep: 8 visits per cycle; resp: 4 visits per cycle; rem: 1 visit per cycle	£204 per hour of patient contact	dep: 6-12 visits per cycle; resp: 3-6 visits per cycle	PSSRU (Personal Social Services Research Unit (PSSRU), 2018a) NICE guidelines (NICE, 2018)
Hospitalization	Mean cost multiplied by risk of hospitalization during a depressive episode in 12 weeks (0.012) and mean n of days (26)	£414 per day	SD=46.49	PSSRU (Personal Social Services Research Unit (PSSRU), 2018b), NHS digital (NHS digital, 2018), and literature (Citrome et al., 2019) (Ten Have et al., 2017)
Hospital liaison consultation	Mean cost per consultation multiplied	£196	SD=47.49	PSSRU (Personal Social Services

	by risk of emergency room access in 12 weeks (0.016)			Research Unit (PSSRU), 2018b) and NHS digital (NHS digital, 2018)

Dep=depressive state; resp=response state; rem=remission state. NHS=UK national health system. GP=general practitioner. The duration of one cycle was 12 weeks.

Supplementary Table 4: procedure used to calculate response and remission probabilities in the pharmacotherapy and combined groups from T1 to T4. In STAR*D the QIDS-SR scale was used as reference. T1-T4: cycles 1-4, each cycle was of 12 weeks.

Outcome	Treatment	Value	Estimation	Reference
Remission at T1	Pharmacotherapy	0.38	Reported in meta-analysis	(Jakobsen et al., 2017)
	Combined	0.46	Reported in meta-analysis	(de Maat et al., 2007)
Remission at T2	Pharmacotherapy	0.32	Remission probability reduces of 0.06 between level 1 and 2 of STAR*D	(Sinyor et al., 2010) (Warden et al., 2007)
	Combined	0.40		
Remission at T3	Pharmacotherapy	0.15	Remission probability reduces of 0.17 between level 2 and 3 of STAR*D	(Warden et al., 2007)
	Combined	0.23		
Remission at T4	Pharmacotherapy	0.14	Remission probability reduces of 0.01 between level 3 and 4 of STAR*D	(Warden et al., 2007)
	Combined	0.22		
Response at T1	Pharmacotherapy	0.11	0.49 (reported in meta-analysis) – 0.38 (proportion of remitters, assuming that all remitters are also responders) = 0.11	(Jakobsen et al., 2017)
	Combined	0.18	0.64 (proportion of responders + remitters based on meta-analysis) – 0.46 (proportion of remitters, assuming that all remitters are also responders) = 0.18	(Cuijpers et al., 2014) (Sinyor et al., 2010)
Response at T2	Pharmacotherapy	0.07	Response probability reduces of 0.16 between level 1 and 2 of STAR*D, responders who are also remitters are excluded (78.8% in STAR*D level 2) -> (0.49 – 0.16) - (0.49 – 0.16) *0.788 = 0.07	(Sinyor et al., 2010)
	Combined	0.10	Response probability reduces of 0.16 between level 1 and 2 of STAR*D, responders who are also remitters are excluded (78.8% in STAR*D level 2) -> (0.64 – 0.16) – (0.64 – 0.16)*0.788 = 0.10	

Response at T3	Pharmacotherapy	0.054	Response probability reduces of 0.13 between level 2 and 3 of STAR*D, responders who are also remitters are excluded (73% in STAR*D level 3) -> (0.33 – 0.13) – (0.33 – 0.13) *0.73 = 0.054	(Sinyor et al., 2010) (Gaynes et al., 2009)
	Combined	0.095	Response probability reduces of 0.13 between level 2 and 3 of STAR*D, responders who are also remitters are excluded (73% in STAR*D level 3) -> (0.48 – 0.13) – (0.48 – 0.13)*0.73 = 0.15	
Response at T4	Pharmacotherapy	0.054	Response probability remains stable between level 3 and 4 of STAR*D	(Sinyor et al., 2010) (Gaynes et al., 2009)
	Combined	0.095		

Supplementary Table 5: transition probabilities calculated according to the procedure explained in the paragraph "Estimation of transition probabilities". **A.** Main analysis: sensitivity=0.62 and specificity=0.77 and sensitivity=0.62 and specificity=0.70 in the in the PGx-CL-R group and CL-R group, respectively. **B.** Sensitivity analysis: sensitivity=0.38 and specificity=0.92 and sensitivity=0.42 and specificity=0.82 in the PGx-CL-R group and CL-R group, respectively. Dep.=major depressive episode. The probabilities of transition dep. -> suicide and response -> remission were the same between A. and B., thus they were not repeated in B.

A.

Initial state	Following state	cycle	Probability PGx-CL-R	Probability CL-R	Probability ST
Dep.	Remission	1st	0.454	0.450	0.380
		2nd	0.387	0.383	0.320
		3rd	0.196	0.197	0.150
		4th and following	0.185	0.186	0.140
Dep.	Response	1st	0.148	0.149	0.110
		2nd	0.089	0.089	0.070
		3rd	0.081	0.082	0.060
		4th and following	0.081	0.082	0.060
Remission	Response	1st	0.084	0.082	0.102
		following	0.013	0.013	0.016
Remission	Dep.	1st	0.023	0.022	0.028
		following	0.003	0.003	0.004
Response	Dep.	1st	0.084	0.082	0.102
		following	0.013	0.013	0.016
Response	Remission	all	0.51	0.51	0.51
Dep.	Suicide	all	0.00001 (0.001%)	0.00001	0.00001

B.

Initial state	Following state	cycle	Probability PGx-CL-R	Probability CL-R	Probability ST
Dep.	Remission	1st	0.429	0.429	0.380
		2nd	0.364	0.364	0.320
		3rd	0.178	0.181	0.150
		4th and following	0.167	0.171	0.140
Dep.	Response	1st	0.132	0.136	0.11
		2nd	0.082	0.083	0.07
		3rd	0.073	0.075	0.06
		4th and following	0.073	0.075	0.06
Remission	Response	1st	0.093	0.089	0.102
		following	0.015	0.014	0.016
Remission	Dep.	1st	0.026	0.024	0.028
		following	0.0037	0.0035	0.004
Response	Dep.	1st	0.093	0.090	0.102
		following	0.015	0.014	0.016

Supplementary Table 6: input data used for the sensitivity analyses using a probabilistic analysis for the scenario described in Supplementary Table 4A.

Parameter	Distribution type	Description	Calculation and source
Depression -> remission (PGx-CL-R)	binomial, size = 500	Mean=0.3055	Mean T1-T4, see Table S2A
Depression -> response (PGx-CL-R)		Mean=0.09975	Mean T1-T4, see Table S2A
Depression -> suicide (all strategies)		Mean=0.000010235	Table S2A
Response -> remission (all strategies)		Mean=0.51	Table S2A
Remission -> depression (PGx-CL-R)		Mean=0.013	Mean T1-T2, see Table S2A
Response -> depression (PGx-CL-R)		Mean=0.0485	Mean T1-T2, see Table S2A
Remission -> response (PGx-CL-R)		Mean=0.0485	Mean T1-T2, see Table S2A
Depression -> remission (ST)		Mean=0.248	Mean T1-T4, see Table S2A
Depression -> response (ST)		Mean=0.075	Mean T1-T4, see Table S2A
Remission -> depression (ST)		Mean=0.016	Mean T1-T2, see Table S2A
Response -> depression (ST)		Mean=0.059	Mean T1-T2, see Table S2A
Remission -> response (ST)		Mean=0.059	Mean T1-T2, see Table S2A
Depression -> remission (CL-R)		Mean=0.304	Mean T1-T4, see Table S2A
Depression -> response (CL-R)		Mean=0.1005	Mean T1-T4, see Table S2A
Remission -> depression (CL-R)		Mean=0.0125	Mean T1-T2, see Table S2A
Response -> depression (CL-R)		Mean=0.0475	Mean T1-T2, see Table S2A
Remission -> response (CL-R)		Mean=0.0475	Mean T1-T2, see Table S2A
Cost psychotherapy (per cycle, 16 sessions)	gamma	Mean=1928, SD= 265.72	Cost based on Table 1 taking into account inflation
Cost visits during depression (per cycle)		Mean=347, SD= 147.30	Cost based on Table 1 taking into account inflation

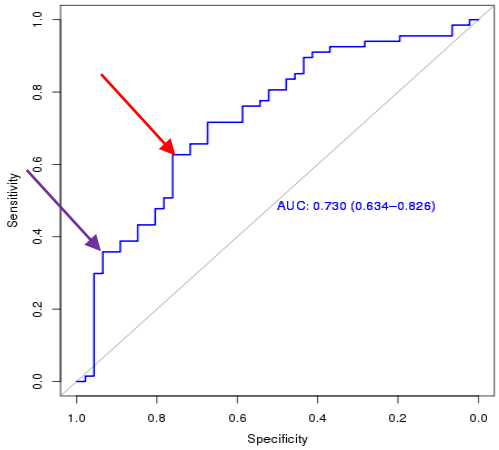
Cost visits during response (per cycle)		Mean=139, SD= 73.65	Cost based on Table 1 taking into account inflation
Cost hospitalization (per cycle)		Mean=10,992, SD= 12,34.30	Cost based on Table 1 taking into account inflation
Cost hospital liaison consultation (per cycle)		Mean=200, SD= 47.49	Cost based on Table 1 taking into account inflation
Cost PGx-CL-R test		Mean=455.9, SD= 176.18	See Table 1
Cost antidepressant drug (per cycle)		Mean=31.4, SD=34.65	See Table 1
Cost antidepressant combination or augmentation (per cycle)		Mean=40.78, SD=47.4	See Table 1
QALYs during remission state	normal	Mean=0.88, SD=0.1	See paragraph Cost and utility estimation in the main manuscript
QALYs during response state		Mean=0.67, SD=0.1	
QALYs during depressive state		Mean=0.40, SD=0.1	

Supplementary Table 7: transition probabilities in GENDEP and TRD2.

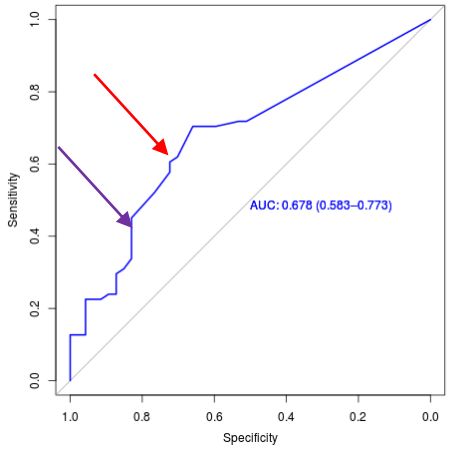
Initial state	Following state	cycle	Probability CL-R GENDEP	Probability CL-R TRD2	Probability ST
Dep.	Remission	1st	0.413	0.408	0.380
		2nd	0.351	0.347	0.320
		3rd	0.176	0.173	0.150
		4th and following	0.166	0.163	0.140
Dep.	Response	1st	0.132	0.130	0.110
		2nd	0.080	0.079	0.070
		3rd	0.073	0.071	0.060
		4th and following	0.073	0.071	0.060
Remission	Response	1st	0.088	0.089	0.102
		following	0.014	0.014	0.016
Remission	Dep.	1st	0.024	0.024	0.028
		following	0.0035	0.0035	0.004
Response	Dep.	1st	0.088	0.089	0.102
		following	0.014	0.014	0.016
Response	Remission	all	0.51	0.51	0.51
Dep.	Suicide	all	0.00001 (0.001%)	0.00001	0.00001

Supplementary Figure 1: ROC curves showing the sensitivity and specificity of the used predictive models in the testing sample. The red arrows indicate the combinations of sensitivity and specificity tested in the study and the purple arrows indicate the combinations of sensitivity and specificity which were tested as part of the sensitivity analyses. **A**: ROC curve using both genetic and clinical risk factors. **B**: ROC using only clinical risk factors.

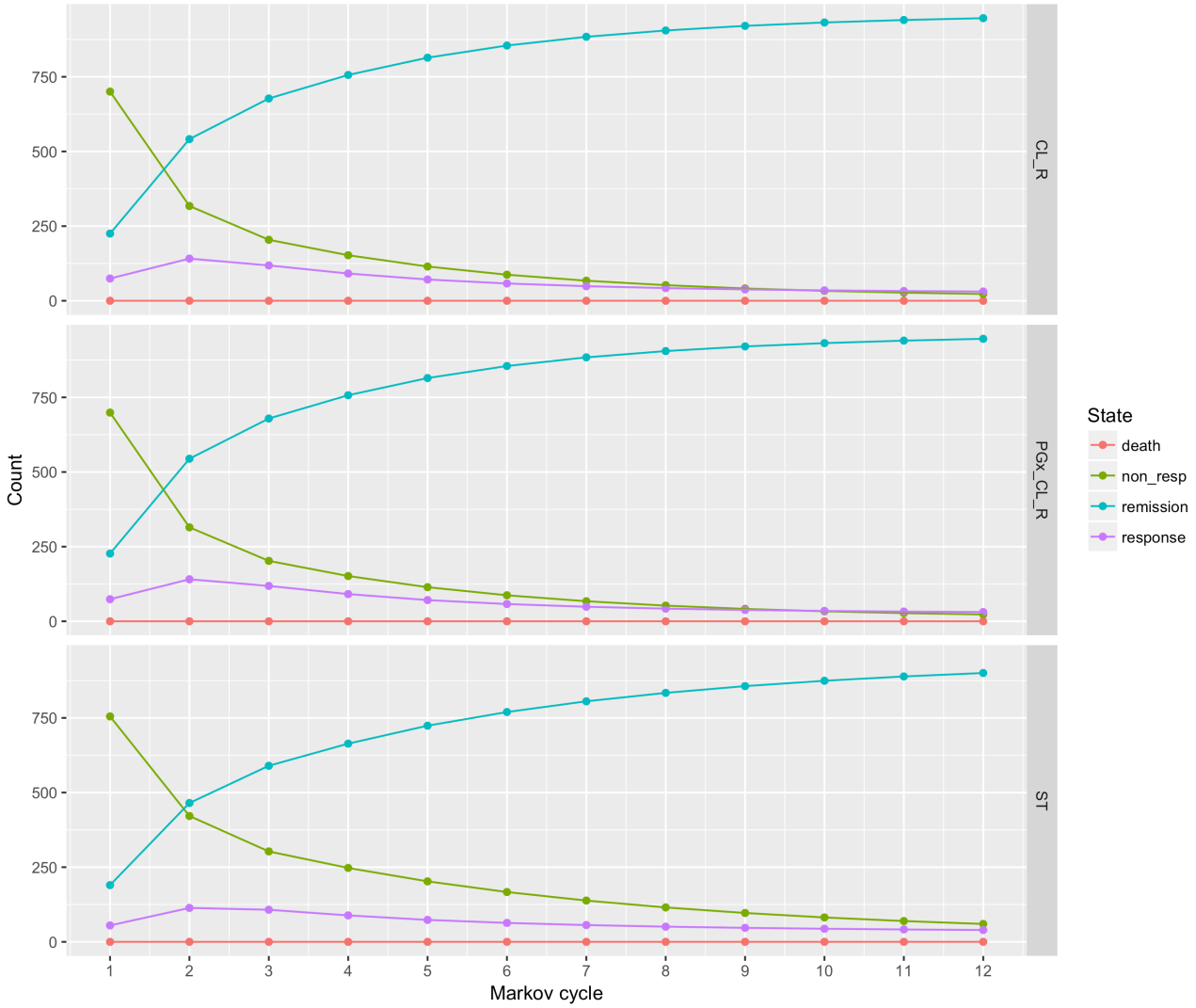
A. Clinical and genetic predictors



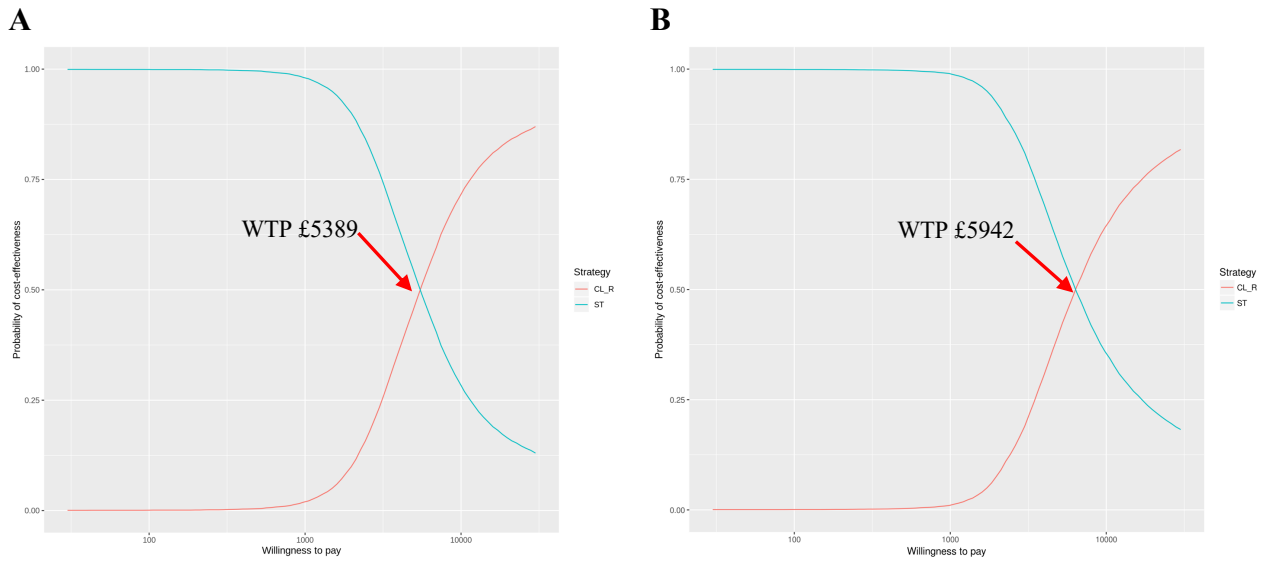
B. Clinical predictors only



Supplementary Figure 2: number of patients in each health state in the three treatment groups within the 3 years horizon (from cycle 1 to 12, each cycle lasts 12 weeks). CL-R=clinical-risk predictive model; PGx-CL-R=clinical-genetic risk predictive model; ST=standard care.



Supplementary Figure 3: cost-effectiveness acceptability curve (CEAC) in GENDEP (**A**) TRD2 (**B**) ST=standard care. CL-R=clinical risk guided group. WTP=willingness to pay measured in British pound sterling (£).



References

Altinoz, M.A., Ince, B., Tek, C., Srihari, V.H., Guloksuz, S., 2018. The NF-κB signaling pathway: an important therapeutic target in psychiatric disorders. Mol. Psychiatry 23, 490–491. https://doi.org/10.1038/mp.2016.207

Amato, R., Pinelli, M., Monticelli, A., Miele, G., Cocozza, S., 2010. Schizophrenia and vitamin D related genes could have been subject to latitude-driven adaptation. BMC Evol. Biol. 10, 351. https://doi.org/10.1186/1471-2148-10-351

Andrade, A., Hope, J., Allen, A., Yorgan, V., Lipscombe, D., Pan, J.Q., 2016. A rare schizophrenia risk variant of CACNA1I disrupts CaV3.3 channel activity. Sci. Rep. 6, 34233. https://doi.org/10.1038/srep34233

Arnau-Soler, A., Adams, M.J., Generation Scotland, Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, Hayward, C., Thomson, P.A., 2018. Genome-wide interaction study of a proxy for stress-sensitivity and its prediction of major depressive disorder. PloS One 13, e0209160. https://doi.org/10.1371/journal.pone.0209160

Autism Spectrum Disorders Working Group of The Psychiatric Genomics Consortium, 2017. Meta-analysis of GWAS of over 16,000 individuals with autism spectrum disorder highlights a novel locus at 10q24.32 and a significant overlap with schizophrenia. Mol. Autism 8, 21. https://doi.org/10.1186/s13229-017-0137-9

Bachmann, S., 2018. Epidemiology of Suicide and the Psychiatric Perspective. Int. J. Environ. Res. Public. Health 15. https://doi.org/10.3390/ijerph15071425

Bergen, S.E., O'Dushlaine, C.T., Lee, P.H., Fanous, A.H., Ruderfer, D.M., Ripke, S., International Schizophrenia Consortium, Swedish Schizophrenia Consortium, Sullivan, P.F., Smoller, J.W., Purcell, S.M., Corvin, A., 2014. Genetic modifiers and subtypes in schizophrenia: investigations of age at onset, severity, sex and family history. Schizophr. Res. 154, 48–53. https://doi.org/10.1016/j.schres.2014.01.030

Beurel, E., Harrington, L.E., Jope, R.S., 2013. Inflammatory T helper 17 cells promote depression-like behavior in mice. Biol. Psychiatry 73, 622–630. https://doi.org/10.1016/j.biopsych.2012.09.021

Bitanihirwe, B.K.Y., Mauney, S.A., Woo, T.-U.W., 2016. Weaving a Net of Neurobiological Mechanisms in Schizophrenia and Unraveling the Underlying Pathophysiology. Biol. Psychiatry 80, 589–598. https://doi.org/10.1016/j.biopsych.2016.03.1047

Breen, M.S., White, C.H., Shekhtman, T., Lin, K., Looney, D., Woelk, C.H., Kelsoe, J.R., 2016. Lithium-responsive genes and gene networks in bipolar disorder patient-derived lymphoblastoid cell lines. Pharmacogenomics J. 16, 446–453. https://doi.org/10.1038/tpj.2016.50

Bury, F.J., Moers, V., Yan, J., Souopgui, J., Quan, X.-J., De Geest, N., Kricha, S., Hassan, B.A., Bellefroid, E.J., 2008. Xenopus BTBD6 and its Drosophila homologue lute are required for neuronal development. Dev. Dyn. Off. Publ. Am. Assoc. Anat. 237, 3352–3360. https://doi.org/10.1002/dvdy.21748

Carboni, L., Marchetti, L., Lauria, M., Gass, P., Vollmayr, B., Redfern, A., Jones, L., Razzoli, M., Malki, K., Begni, V., Riva, M.A., Domenici, E., Caberlotto, L., Mathé, A.A., 2018. Cross-species evidence from human and rat brain transcriptome for growth factor signaling pathway dysregulation in major depression. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 43, 2134–2145. https://doi.org/10.1038/s41386-018-0117-6

Center for Genome Technology, University of Miami, 2019. GWAS pricing details [WWW Document]. URL http://hihg.med.miami.edu/cgt/genotyping/whole-genome-genotyping-copy-number

Chan, M.K., Cooper, J.D., Heilmann-Heimbach, S., Frank, J., Witt, S.H., Nöthen, M.M., Steiner, J., Rietschel, M., Bahn, S., 2017. Associations between SNPs and immune-related circulating proteins in schizophrenia. Sci. Rep. 7, 12586. https://doi.org/10.1038/s41598-017-12986-0

Chang, P., Heier, C., Qin, W., Han, L., Huang, F., Sun, Q., 2017. Molecular identification of transmembrane protein 68 as an endoplasmic reticulum-anchored and brain-specific protein. PloS One 12, e0176980. https://doi.org/10.1371/journal.pone.0176980

Chen, S., Xuan, J., Wan, L., Lin, H., Couch, L., Mei, N., Dobrovolsky, V.N., Guo, L., 2014. Sertraline, an antidepressant, induces apoptosis in hepatic cells through the mitogen-activated protein kinase pathway. Toxicol. Sci. Off. J. Soc. Toxicol. 137, 404–415. https://doi.org/10.1093/toxsci/kft254

Chen, Y., Aulia, S., Li, L., Tang, B.L., 2006. AMIGO and friends: an emerging family of brain-enriched, neuronal growth modulating, type I transmembrane proteins with leucine-rich repeats (LRR) and cell adhesion molecule motifs. Brain Res. Rev. 51, 265–274. https://doi.org/10.1016/j.brainresrev.2005.11.005

Chiang, M., Natarajan, R., Fan, X., 2016. Vitamin D in schizophrenia: a clinical review. Evid. Based Ment. Health 19, 6–9. https://doi.org/10.1136/eb-2015-102117

Citrome, L., Jain, R., Tung, A., Landsman-Blumberg, P.B., Kramer, K., Ali, S., 2019. Prevalence, treatment patterns, and stay characteristics associated with hospitalizations for major depressive disorder. J. Affect. Disord. 249, 378–384. https://doi.org/10.1016/j.jad.2019.01.044

Conway, C.R., George, M.S., Sackeim, H.A., 2017. Toward an Evidence-Based, Operational Definition of Treatment-Resistant Depression: When Enough Is Enough. JAMA Psychiatry 74, 9–10. https://doi.org/10.1001/jamapsychiatry.2016.2586

Cook, I.A., Congdon, E., Krantz, D.E., Hunter, A.M., Coppola, G., Hamilton, S.P., Leuchter, A.F., 2019. Time Course of Changes in Peripheral Blood Gene Expression During Medication Treatment for Major Depressive Disorder. Front. Genet. 10, 870. https://doi.org/10.3389/fgene.2019.00870

Cuijpers, P., Sijbrandij, M., Koole, S.L., Andersson, G., Beekman, A.T., Reynolds, C.F., 2014. Adding psychotherapy to antidepressant medication in depression and anxiety disorders: a meta-analysis. World Psychiatry Off. J. World Psychiatr. Assoc. WPA 13, 56–67. https://doi.org/10.1002/wps.20089

Das Chakraborty, R., Chakraborty, D., Bernal, A.J., Schoch, K., Howard, T.D., Ip, E.H., Hooper, S.R., Keshavan, M.S., Jirtle, R.L., Shashi, V., 2012. Dysregulation of DGCR6 and DGCR6L: psychopathological outcomes in chromosome 22q11.2 deletion syndrome. Transl. Psychiatry 2, e105. https://doi.org/10.1038/tp.2012.31

Das, N., Schmidt, T.A., Krawetz, R.J., Dufour, A., 2019. Proteoglycan 4: From Mere Lubricant to Regulator of Tissue Homeostasis and Inflammation: Does proteoglycan 4 have the ability to buffer the inflammatory response? BioEssays News Rev. Mol. Cell. Dev. Biol. 41, e1800166. https://doi.org/10.1002/bies.201800166

Davies, M.N., Verdi, S., Burri, A., Trzaskowski, M., Lee, M., Hettema, J.M., Jansen, R., Boomsma, D.I., Spector, T.D., 2015. Generalised Anxiety Disorder--A Twin Study of Genetic Architecture, Genome-Wide Association and Differential Gene Expression. PloS One 10, e0134865. https://doi.org/10.1371/journal.pone.0134865

de Maat, S.M., Dekker, J., Schoevers, R.A., de Jonghe, F., 2007. Relative efficacy of psychotherapy and combined therapy in the treatment of depression: a meta-analysis. Eur. Psychiatry J. Assoc. Eur. Psychiatr. 22, 1–8. https://doi.org/10.1016/j.eurpsy.2006.10.008

Debnath, M., Berk, M., 2014. Th17 pathway-mediated immunopathogenesis of schizophrenia: mechanisms and implications. Schizophr. Bull. 40, 1412–1421. https://doi.org/10.1093/schbul/sbu049

den Hollander, A.I., Koenekoop, R.K., Mohamed, M.D., Arts, H.H., Boldt, K., Towns, K.V., Sedmak, T., Beer, M., Nagel-Wolfrum, K., McKibbin, M., Dharmaraj, S., Lopez, I., Ivings, L., Williams, G.A., Springell, K., Woods, C.G., Jafri, H., Rashid, Y., Strom, T.M., van der Zwaag, B., Gosens, I., Kersten, F.F.J., van Wijk, E., Veltman, J.A., Zonneveld, M.N., van Beersum, S.E.C., Maumenee, I.H., Wolfrum, U., Cheetham, M.E., Ueffing, M., Cremers, F.P.M., Inglehearn, C.F., Roepman, R., 2007. Mutations in LCA5, encoding the ciliary protein lebercilin, cause Leber congenital amaurosis. Nat. Genet. 39, 889–895. https://doi.org/10.1038/ng2066

Dussor, G., Cao, Y.-Q., 2016. TRPM8 and Migraine. Headache 56, 1406–1417. https://doi.org/10.1111/head.12948

Fabbri, C., Kasper, S., Kautzky, A., Zohar, J., Montgomery, S., Albani, D., Forloni, G., Ferentinos, P., Rujescu, D., Mendlewicz, J., Uher, R., Lewis, C., Serretti, A., 2020. A polygenic predictor of treatment-resistant depression using whole exome sequencing and genome-wide genotyping. Transl. Psychiatry 10.

Farajdokht, F., Soleimani, M., Mehrpouya, S., Barati, M., Nahavandi, A., 2015. The role of hepcidin in chronic mild stress-induced depression. Neurosci. Lett. 588, 120–124. https://doi.org/10.1016/j.neulet.2015.01.008

Föcking, M., Sabherwal, S., Cates, H.M., Scaife, C., Dicker, P., Hryniewiecka, M., Wynne, K., Rutten, B.P.F., Lewis, G., Cannon, M., Nestler, E.J., Heurich, M., Cagney, G., Zammit, S., Cotter, D.R., 2019. Complement pathway changes at age 12 are associated with psychotic experiences at age 18 in a longitudinal population-based study: evidence for a role of stress. Mol. Psychiatry. https://doi.org/10.1038/s41380-018-0306-z

Gaynes, B.N., Warden, D., Trivedi, M.H., Wisniewski, S.R., Fava, M., Rush, A.J., 2009. What did STAR*D teach us? Results from a large-scale, practical, clinical trial for patients with depression. Psychiatr. Serv. Wash. DC 60, 1439–1445. https://doi.org/10.1176/ps.2009.60.11.1439

Genetic Resources Core Facility of John Hopkins University, School of Medicine, 2019. GWAS pricing details. [WWW Document]. URL https://grcf.jhmi.edu/dna-services/genotyping/genome-wide-association/

Genetics of Personality Consortium, de Moor, M.H.M., van den Berg, S.M., Verweij, K.J.H., Krueger, R.F., Luciano, M., Arias Vasquez, A., Matteson, L.K., Derringer, J., Esko, T., Amin, N., Gordon, S.D., Hansell, N.K., Hart, A.B., Seppälä, I., Huffman, J.E., Konte, B., Lahti, J., Lee, M., Miller, M., Nutile, T., Tanaka, T., Teumer, A., Viktorin, A., Wedenoja, J., Abecasis, G.R., Adkins, D.E., Agrawal, A., Allik, J., Appel, K., Bigdeli, T.B., Busonero, F., Campbell, H., Costa, P.T., Davey Smith, G., Davies, G., de Wit, H., Ding, J., Engelhardt, B.E., Eriksson, J.G., Fedko, I.O., Ferrucci, L., Franke, B., Giegling, I., Grucza, R., Hartmann, A.M., Heath, A.C., Heinonen, K., Henders, A.K., Homuth, G., Hottenga, J.-J., Iacono, W.G., Janzing, J., Jokela, M., Karlsson, R., Kemp, J.P., Kirkpatrick, M.G., Latvala, A., Lehtimäki, T., Liewald, D.C., Madden, P.A.F., Magri, C., Magnusson, P.K.E., Marten, J., Maschio, A., Medland, S.E., Mihailov, E., Milaneschi, Y., Montgomery, G.W., Nauck, M., Ouwens, K.G., Palotie, A., Pettersson, E., Polasek, O., Qian, Y., Pulkki-Råback, L., Raitakari, O.T., Realo, A., Rose, R.J., Ruggiero, D., Schmidt, C.O., Slutske, W.S., Sorice, R., Starr, J.M., St Pourcain, B., Sutin, A.R., Timpson, N.J., Trochet, H., Vermeulen, S., Vuoksimaa, E., Widen, E., Wouda, J., Wright, M.J., Zgaga, L., Porteous, D., Minelli, A., Palmer, A.A., Rujescu, D., Ciullo, M., Hayward, C., Rudan, I., Metspalu, A., Kaprio, J., Deary, I.J., Räikkönen, K., Wilson, J.F., Keltikangas-Järvinen, L., Bierut, L.J., Hettema, J.M., Grabe, H.J., van Duijn, C.M., Evans, D.M., Schlessinger, D., Pedersen, N.L., Terracciano, A., McGue, M., Penninx, B.W.J.H., Martin, N.G., Boomsma, D.I., 2015. Meta-analysis of Genome-wide Association Studies for Neuroticism, and the Polygenic Association With Major Depressive Disorder. JAMA Psychiatry 72, 642–650. https://doi.org/10.1001/jamapsychiatry.2015.0554

Glatt, S.J., Chandler, S.D., Bousman, C.A., Chana, G., Lucero, G.R., Tatro, E., May, T., Lohr, J.B., Kremen, W.S., Everall, I.P., Tsuang, M.T., 2009. Alternatively Spliced Genes as Biomarkers for Schizophrenia, Bipolar Disorder and Psychosis: A Blood-Based Spliceome-Profiling Exploratory Study. Curr. Pharmacogenomics Pers. Med. 7, 164–188. https://doi.org/10.2174/1875692110907030164

Goes, F.S., Pirooznia, M., Tehan, M., Zandi, P.P., McGrath, J., Wolyniec, P., Nestadt, G., Pulver, A.E., 2019. De novo variation in bipolar disorder. Mol. Psychiatry. https://doi.org/10.1038/s41380-019-0611-1

Guillemin, C., Provençal, N., Suderman, M., Côté, S.M., Vitaro, F., Hallett, M., Tremblay, R.E., Szyf, M., 2014. DNA methylation signature of childhood chronic physical aggression in T cells of both men and women. PloS One 9, e86822. https://doi.org/10.1371/journal.pone.0086822

Hamilton, G., Evans, K.L., Macintyre, D.J., Deary, I.J., Dominiczak, A., Smith, B.H., Morris, A.D., Porteous, D.J., Thomson, P.A., 2012. Alzheimer's disease risk factor complement receptor 1 is associated with depression. Neurosci. Lett. 510, 6–9. https://doi.org/10.1016/j.neulet.2011.12.059

Hansen, K.F., Obrietan, K., 2013. MicroRNA as therapeutic targets for treatment of depression. Neuropsychiatr. Dis. Treat. 9, 1011–1021. https://doi.org/10.2147/NDT.S34811

Hansen, R., Gaynes, B., Thieda, P., Gartlehner, G., Deveaugh-Geiss, A., Krebs, E., Lohr, K., 2008. Meta-analysis of major depressive disorder relapse and recurrence with second-generation antidepressants. Psychiatr. Serv. Wash. DC 59, 1121–1130. https://doi.org/10.1176/ps.2008.59.10.1121

Hawi, Z., Tong, J., Dark, C., Yates, H., Johnson, B., Bellgrove, M.A., 2018. The role of cadherin genes in five major psychiatric disorders: A literature update. Am. J. Med. Genet. Part B Neuropsychiatr. Genet. Off. Publ. Int. Soc. Psychiatr. Genet. 177, 168–180. https://doi.org/10.1002/ajmg.b.32592

Hawrylycz, M., Miller, J.A., Menon, V., Feng, D., Dolbeare, T., Guillozet-Bongaarts, A.L., Jegga, A.G., Aronow, B.J., Lee, C.-K., Bernard, A., Glasser, M.F., Dierker, D.L., Menche, J., Szafer, A., Collman, F., Grange, P., Berman, K.A., Mihalas, S., Yao, Z., Stewart, L., Barabási, A.-L., Schulkin, J., Phillips, J., Ng, L., Dang, C., Haynor, D.R., Jones, A., Van Essen, D.C., Koch, C., Lein, E., 2015. Canonical genetic signatures of the adult human brain. Nat. Neurosci. 18, 1832–1844. https://doi.org/10.1038/nn.4171

He, Y., Zhang, H., Yung, A., Villeda, S.A., Jaeger, P.A., Olayiwola, O., Fainberg, N., Wyss-Coray, T., 2014. ALK5-dependent TGF-β signaling is a major determinant of late-stage adult neurogenesis. Nat. Neurosci. 17, 943–952. https://doi.org/10.1038/nn.3732

Héraud, C., Pinault, M., Lagrée, V., Moreau, V., 2019. p190RhoGAPs, the ARHGAP35- and ARHGAP5-Encoded Proteins, in Health and Disease. Cells 8. https://doi.org/10.3390/cells8040351

Heyes, S., Pratt, W.S., Rees, E., Dahimene, S., Ferron, L., Owen, M.J., Dolphin, A.C., 2015. Genetic disruption of voltage-gated calcium channels in psychiatric and neurological disorders. Prog. Neurobiol. 134, 36–54. https://doi.org/10.1016/j.pneurobio.2015.09.002

Huang, G.-J., Ben-David, E., Tort Piella, A., Edwards, A., Flint, J., Shifman, S., 2012. Neurogenomic evidence for a shared mechanism of the antidepressant effects of exercise and chronic fluoxetine in mice. PloS One 7, e35901. https://doi.org/10.1371/journal.pone.0035901

Huang, J., Vogel, G., Yu, Z., Almazan, G., Richard, S., 2011. Type II arginine methyltransferase PRMT5 regulates gene expression of inhibitors of differentiation/DNA binding Id2 and Id4 during glial cell differentiation. J. Biol. Chem. 286, 44424–44432. https://doi.org/10.1074/jbc.M111.277046

Huang, K.-C., Yang, K.-C., Lin, H., Tsao, T.T.-H., Lee, S.-A., 2014. Transcriptome alterations of mitochondrial and coagulation function in schizophrenia by cortical sequencing analysis. BMC Genomics 15 Suppl 9, S6. https://doi.org/10.1186/1471-2164-15-S9-S6

Ijaz, S., Davies, P., Williams, C.J., Kessler, D., Lewis, G., Wiles, N., 2018. Psychological therapies for treatment-resistant depression in adults. Cochrane Database Syst. Rev. 5, CD010558. https://doi.org/10.1002/14651858.CD010558.pub2

Iniesta, R., Hodgson, K., Stahl, D., Malki, K., Maier, W., Rietschel, M., Mors, O., Hauser, J., Henigsberg, N., Dernovsek, M.Z., Souery, D., Dobson, R., Aitchison, K.J., Farmer, A., McGuffin, P., Lewis, C.M., Uher, R., 2018. Antidepressant drug-specific prediction of depression treatment outcomes from genetic and clinical variables. Sci. Rep. 8, 5530. https://doi.org/10.1038/s41598-018-23584-z

Ionita-Laza, I., Lee, S., Makarov, V., Buxbaum, J.D., Lin, X., 2013. Sequence kernel association tests for the combined effect of rare and common variants. Am. J. Hum. Genet. 92, 841–853. https://doi.org/10.1016/j.ajhg.2013.04.015

Ionita-Laza, I., McCallum, K., Xu, B., Buxbaum, J.D., 2016. A spectral approach integrating functional genomic annotations for coding and noncoding variants. Nat. Genet. 48, 214–220. https://doi.org/10.1038/ng.3477

Iowa Institute of Human Genetics, 2019. GWAS pricing details [WWW Document]. URL https://medicine.uiowa.edu/humangenetics/research/genomics-division/microarray/microarrays-and-fees

Jacobs, F.M.J., van der Linden, A.J.A., Wang, Y., von Oerthel, L., Sul, H.S., Burbach, J.P.H., Smidt, M.P., 2009. Identification of Dlk1, Ptpru and Klhl1 as novel Nurr1 target genes in meso-diencephalic dopamine neurons. Dev. Camb. Engl. 136, 2363–2373. https://doi.org/10.1242/dev.037556

Jakobsen, J.C., Katakam, K.K., Schou, A., Hellmuth, S.G., Stallknecht, S.E., Leth-Møller, K.,

Iversen, M., Banke, M.B., Petersen, I.J., Klingenberg, S.L., Krogh, J., Ebert, S.E., Timm, A., Lindschou, J., Gluud, C., 2017. Selective serotonin reuptake inhibitors versus placebo in patients with major depressive disorder. A systematic review with meta-analysis and Trial Sequential Analysis. BMC Psychiatry 17, 58. https://doi.org/10.1186/s12888-016-1173-2

Jia, Y., Mu, J.C., Ackerman, S.L., 2012. Mutation of a U2 snRNA gene causes global disruption of alternative splicing and neurodegeneration. Cell 148, 296–308. https://doi.org/10.1016/j.cell.2011.11.057

Jo, W.K., Zhang, Y., Emrich, H.M., Dietrich, D.E., 2015. Glia in the cytokine-mediated onset of depression: fine tuning the immune response. Front. Cell. Neurosci. 9, 268. https://doi.org/10.3389/fncel.2015.00268

Judd, L.L., Akiskal, H.S., Maser, J.D., Zeller, P.J., Endicott, J., Coryell, W., Paulus, M.P., Kunovac, J.L., Leon, A.C., Mueller, T.I., Rice, J.A., Keller, M.B., 1998. Major depressive disorder: a prospective study of residual subthreshold depressive symptoms as predictor of rapid relapse. J. Affect. Disord. 50, 97–108.

Jungke, P., Ostrow, G., Li, J.-L., Norton, S., Nieber, K., Kelber, O., Butterweck, V., 2011. Profiling of hypothalamic and hippocampal gene expression in chronically stressed rats treated with St. John's wort extract (STW 3-VI) and fluoxetine. Psychopharmacology (Berl.) 213, 757–772. https://doi.org/10.1007/s00213-010-2032-3

Karlsson Linnér, R., Biroli, P., Kong, E., Meddens, S.F.W., Wedow, R., Fontana, M.A., Lebreton, M., Tino, S.P., Abdellaoui, A., Hammerschlag, A.R., Nivard, M.G., Okbay, A., Rietveld, C.A., Timshel, P.N., Trzaskowski, M., Vlaming, R. de, Zünd, C.L., Bao, Y., Buzdugan, L., Caplin, A.H., Chen, C.-Y., Eibich, P., Fontanillas, P., Gonzalez, J.R., Joshi, P.K., Karhunen, V., Kleinman, A., Levin, R.Z., Lill, C.M., Meddens, G.A., Muntané, G., Sanchez-Roige, S., Rooij, F.J. van, Taskesen, E., Wu, Y., Zhang, F., 23and Me Research Team, eQTLgen Consortium, International Cannabis Consortium, Social Science Genetic Association Consortium, Auton, A., Boardman, J.D., Clark, D.W., Conlin, A., Dolan, C.C., Fischbacher, U., Groenen, P.J.F., Harris, K.M., Hasler, G., Hofman, A., Ikram, M.A., Jain, S., Karlsson, R., Kessler, R.C., Kooyman, M., MacKillop, J., Männikkö, M., Morcillo-Suarez, C., McQueen, M.B., Schmidt, K.M., Smart, M.C., Sutter, M., Thurik, A.R., Uitterlinden, A.G., White, J., Wit, H. de, Yang, J., Bertram, L., Boomsma, D.I., Esko, T., Fehr, E., Hinds, D.A., Johannesson, M., Kumari, M., Laibson, D., Magnusson, P.K.E., Meyer, M.N., Navarro, A., Palmer, A.A., Pers, T.H., Posthuma, D., Schunk, D., Stein, M.B., Svento, R., Tiemeier, H., Timmers, P.R.H.J., Turley, P., Ursano, R.J., Wagner, G.G., Wilson, J.F., Gratten, J., Lee, J.J., Cesarini, D., Benjamin, D.J., Koellinger, P.D., Beauchamp, J.P., 2019. Genome-wide association analyses of risk tolerance and risky behaviors in over 1 million individuals identify hundreds of loci and shared genetic influences. Nat. Genet. 51, 245–257. https://doi.org/10.1038/s41588-018-0309-3

Kaufman, J., Wymbs, N.F., Montalvo-Ortiz, J.L., Orr, C., Albaugh, M.D., Althoff, R., O'Loughlin, K., Holbrook, H., Garavan, H., Kearney, C., Yang, B.-Z., Zhao, H., Peña, C., Nestler, E.J., Lee, R.S., Mostofsky, S., Gelernter, J., Hudziak, J., 2018. Methylation in OTX2 and related genes, maltreatment, and depression in children. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 43, 2204–2211. https://doi.org/10.1038/s41386-018-0157-y

Khan, A., Dager, S.R., Cohen, S., Avery, D.H., Scherzo, B., Dunner, D.L., 1991. Chronicity of depressive episode in relation to antidepressant-placebo response. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 4, 125–130.

Kim, S., Hwang, Y., Lee, D., Webster, M.J., 2016. Transcriptome sequencing of the choroid plexus in schizophrenia. Transl. Psychiatry 6, e964. https://doi.org/10.1038/tp.2016.229

Kittel-Schneider, S., Hilscher, M., Scholz, C.-J., Weber, H., Grünewald, L., Schwarz, R.,

Chiocchetti, A.G., Reif, A., 2019. Lithium-induced gene expression alterations in two peripheral cell models of bipolar disorder. World J. Biol. Psychiatry Off. J. World Fed. Soc. Biol. Psychiatry 20, 462–475. https://doi.org/10.1080/15622975.2017.1396357

Koga, M., Ishiguro, H., Yazaki, S., Horiuchi, Y., Arai, M., Niizato, K., Iritani, S., Itokawa, M., Inada, T., Iwata, N., Ozaki, N., Ujike, H., Kunugi, H., Sasaki, T., Takahashi, M., Watanabe, Y., Someya, T., Kakita, A., Takahashi, H., Nawa, H., Muchardt, C., Yaniv, M., Arinami, T., 2009. Involvement of SMARCA2/BRM in the SWI/SNF chromatin-remodeling complex in schizophrenia. Hum. Mol. Genet. 18, 2483–2494. https://doi.org/10.1093/hmg/ddp166

Kortüm, F., Jamra, R.A., Alawi, M., Berry, S.A., Borck, G., Helbig, K.L., Tang, S., Huhle, D., Korenke, G.C., Hebbar, M., Shukla, A., Girisha, K.M., Steinlin, M., Waldmeier-Wilhelm, S., Montomoli, M., Guerrini, R., Lemke, J.R., Kutsche, K., 2018. Clinical and genetic spectrum of AMPD2-related pontocerebellar hypoplasia type 9. Eur. J. Hum. Genet. EJHG 26, 695–708. https://doi.org/10.1038/s41431-018-0098-2

Kumarasinghe, N., Beveridge, N.J., Gardiner, E., Scott, R.J., Yasawardene, S., Perera, A., Mendis, J., Suriyakumara, K., Schall, U., Tooney, P.A., 2013. Gene expression profiling in treatment-naive schizophrenia patients identifies abnormalities in biological pathways involving AKT1 that are corrected by antipsychotic medication. Int. J. Neuropsychopharmacol. 16, 1483–1503. https://doi.org/10.1017/S1461145713000035

Li, Q., Wineinger, N.E., Fu, D.-J., Libiger, O., Alphs, L., Savitz, A., Gopal, S., Cohen, N., Schork, N.J., 2017. Genome-wide association study of paliperidone efficacy. Pharmacogenet. Genomics 27, 7–18. https://doi.org/10.1097/FPC.0000000000000250

Li, S., Papale, L.A., Zhang, Q., Madrid, A., Chen, L., Chopra, P., Keleş, S., Jin, P., Alisch, R.S., 2016. Genome-wide alterations in hippocampal 5-hydroxymethylcytosine links plasticity genes to acute stress. Neurobiol. Dis. 86, 99–108. https://doi.org/10.1016/j.nbd.2015.11.010

Li, W.-Y., Li, F.-M., Zhou, Y.-F., Wen, Z.-M., Ma, J., Ya, K., Qian, Z.-M., 2016. Aspirin down Regulates Hepcidin by Inhibiting NF-κB and IL6/JAK2/STAT3 Pathways in BV-2 Microglial Cells Treated with Lipopolysaccharide. Int. J. Mol. Sci. 17. https://doi.org/10.3390/ijms17121921

Likhite, N., Jackson, C.A., Liang, M.-S., Krzyzanowski, M.C., Lei, P., Wood, J.F., Birkaya, B., Michaels, K.L., Andreadis, S.T., Clark, S.D., Yu, M.C., Ferkey, D.M., 2015. The protein arginine methyltransferase PRMT5 promotes D2-like dopamine receptor signaling. Sci. Signal. 8, ra115. https://doi.org/10.1126/scisignal.aad0872

Liu, C., Yu, Y., Yin, G., Zhang, J., Wen, W., Ruan, X., Li, D., Zhang, S., Cai, W., Gao, M., Chen, L., 2017. C14orf93 (RTFC) is identified as a novel susceptibility gene for familial nonmedullary thyroid cancer. Biochem. Biophys. Res. Commun. 482, 590–596. https://doi.org/10.1016/j.bbrc.2016.11.078

Liu, H., Heath, S.C., Sobin, C., Roos, J.L., Galke, B.L., Blundell, M.L., Lenane, M., Robertson, B., Wijsman, E.M., Rapoport, J.L., Gogos, J.A., Karayiorgou, M., 2002. Genetic variation at the 22q11 PRODH2/DGCR6 locus presents an unusual pattern and increases susceptibility to schizophrenia. Proc. Natl. Acad. Sci. U. S. A. 99, 3717–3722. https://doi.org/10.1073/pnas.042700699

Mai, N., Chrzanowska-Lightowlers, Z.M.A., Lightowlers, R.N., 2017. The process of mammalian mitochondrial protein synthesis. Cell Tissue Res. 367, 5–20. https://doi.org/10.1007/s00441-016-2456-0

Marrocco, J., Einhorn, N.R., Petty, G.H., Li, H., Dubey, N., Hoffman, J., Berman, K.F., Goldman, D., Lee, F.S., Schmidt, P.J., McEwen, B.S., 2018. Epigenetic intersection of BDNF Val66Met genotype with premenstrual dysphoric disorder transcriptome in a cross-species model of estradiol add-back. Mol. Psychiatry. https://doi.org/10.1038/s41380-018-0274-3

Martin, J., Cooper, M., Hamshere, M.L., Pocklington, A., Scherer, S.W., Kent, L., Gill, M., Owen, M.J., Williams, N., O'Donovan, M.C., Thapar, A., Holmans, P., 2014. Biological overlap of attention-deficit/hyperactivity disorder and autism spectrum disorder: evidence from copy number variants. J. Am. Acad. Child Adolesc. Psychiatry 53, 761-770.e26. https://doi.org/10.1016/j.jaac.2014.03.004

Nakahara, S., Medland, S., Turner, J.A., Calhoun, V.D., Lim, K.O., Mueller, B.A., Bustillo, J.R., O'Leary, D.S., Vaidya, J.G., McEwen, S., Voyvodic, J., Belger, A., Mathalon, D.H., Ford, J.M., Guffanti, G., Macciardi, F., Potkin, S.G., van Erp, T.G.M., 2018. Polygenic risk score, genome-wide association, and gene set analyses of cognitive domain deficits in schizophrenia. Schizophr. Res. 201, 393–399. https://doi.org/10.1016/j.schres.2018.05.041

Need, A.C., Ge, D., Weale, M.E., Maia, J., Feng, S., Heinzen, E.L., Shianna, K.V., Yoon, W., Kasperaviciūte, D., Gennarelli, M., Strittmatter, W.J., Bonvicini, C., Rossi, G., Jayathilake, K., Cola, P.A., McEvoy, J.P., Keefe, R.S.E., Fisher, E.M.C., St Jean, P.L., Giegling, I., Hartmann, A.M., Möller, H.-J., Ruppert, A., Fraser, G., Crombie, C., Middleton, L.T., St Clair, D., Roses, A.D., Muglia, P., Francks, C., Rujescu, D., Meltzer, H.Y., Goldstein, D.B., 2009. A genome-wide investigation of SNPs and CNVs in schizophrenia. PLoS Genet. 5, e1000373. https://doi.org/10.1371/journal.pgen.1000373

NHS digital, 2018. Hospital episode statistics 2017-18 [WWW Document]. URL https://digital.nhs.uk

NICE, 2018. Depression in adults: recognition and management [WWW Document]. URL https://www.nice.org.uk/guidance/cg90

Nieratschker, V., Massart, R., Gilles, M., Luoni, A., Suderman, M.J., Krumm, B., Meier, S., Witt, S.H., Nöthen, M.M., Suomi, S.J., Peus, V., Scharnholz, B., Dukal, H., Hohmeyer, C., Wolf, I. a.-C., Cirulli, F., Gass, P., Sütterlin, M.W., Filsinger, B., Laucht, M., Riva, M.A., Rietschel, M., Deuschle, M., Szyf, M., 2014. MORC1 exhibits cross-species differential methylation in association with early life stress as well as genome-wide association with MDD. Transl. Psychiatry 4, e429. https://doi.org/10.1038/tp.2014.75

Noordam, R., Direk, N., Sitlani, C.M., Aarts, N., Tiemeier, H., Hofman, A., Uitterlinden, A.G., Psaty, B.M., Stricker, B.H., Visser, L.E., 2015. Identifying genetic loci associated with antidepressant drug response with drug-gene interaction models in a population-based study. J. Psychiatr. Res. 62, 31–37. https://doi.org/10.1016/j.jpsychires.2015.01.005

O'Shea, K.S., McInnis, M.G., 2016. Neurodevelopmental origins of bipolar disorder: iPSC models. Mol. Cell. Neurosci. 73, 63–83. https://doi.org/10.1016/j.mcn.2015.11.006

Park, D.I., Dournes, C., Sillaber, I., Uhr, M., Asara, J.M., Gassen, N.C., Rein, T., Ising, M., Webhofer, C., Filiou, M.D., Müller, M.B., Turck, C.W., 2016. Purine and pyrimidine metabolism: Convergent evidence on chronic antidepressant treatment response in mice and humans. Sci. Rep. 6, 35317. https://doi.org/10.1038/srep35317

Personal Social Services Research Unit (PSSRU), 2018a. Community-based health care staff costs [WWW Document]. URL https://www.pssru.ac.uk

Personal Social Services Research Unit (PSSRU), 2018b. NHS services cost [WWW Document]. URL https://www.pssru.ac.uk

Qiao, J., Sun, Y., Wu, J., Wang, L., 2019. Investigation of the underling mechanism of ketamine for antidepressant effects in treatment-refractory affective disorders via molecular profile analysis. Exp. Ther. Med. 18, 580–588. https://doi.org/10.3892/etm.2019.7633

REGIONAL DRUG AND THERAPEUTICS CENTRE, 2019. Cost comparison charts [WWW Document]. URL http://gmmmg.nhs.uk/docs/cost_comparison_charts.pdf

Ren, H., Fabbri, C., Uher, R., Rietschel, M., Mors, O., Henigsberg, N., Hauser, J., Zobel, A., Maier, W., Dernovsek, M.Z., Souery, D., Cattaneo, A., Breen, G., Craig, I.W., Farmer, A.E., McGuffin, P., Lewis, C.M., Aitchison, K.J., 2018. Genes associated with anhedonia: a new analysis in a large clinical trial (GENDEP). Transl. Psychiatry 8. https://doi.org/10.1038/s41398-018-0198-3

Ripke, S., Neale, B.M., Corvin, A., Walters, J.T.R., Farh, K.-H., Holmans, P.A., Lee, P., Bulik-Sullivan, B., Collier, D.A., Huang, H., Pers, T.H., Agartz, I., Agerbo, E., Albus, M., Alexander, M., Amin, F., Bacanu, S.A., Begemann, M., Belliveau Jr, R.A., Bene, J., Bergen, S.E., Bevilacqua, E., Bigdeli, T.B., Black, D.W., Bruggeman, R., Buccola, N.G., Buckner, R.L., Byerley, W., Cahn, W., Cai, G., Campion, D., Cantor, R.M., Carr, V.J., Carrera, N., Catts, S.V., Chambert, K.D., Chan, R.C.K., Chen, R.Y.L., Chen, E.Y.H., Cheng, W., Cheung, E.F.C., Ann Chong, S., Robert Cloninger, C., Cohen, D., Cohen, N., Cormican, P., Craddock, N., Crowley, J.J., Curtis, D., Davidson, M., Davis, K.L., Degenhardt, F., Del Favero, J., Demontis, D., Dikeos, D., Dinan, T., Djurovic, S., Donohoe, G., Drapeau, E., Duan, J., Dudbridge, F., Durmishi, N., Eichhammer, P., Eriksson, J., Escott-Price, V., Essioux, L., Fanous, A.H., Farrell, M.S., Frank, J., Franke, L., Freedman, R., Freimer, N.B., Friedl, M., Friedman, J.I., Fromer, M., Genovese, G., Georgieva, L., Giegling, I., Giusti-Rodríguez, P., Godard, S., Goldstein, J.I., Golimbet, V., Gopal, S., Gratten, J., de Haan, L., Hammer, C., Hamshere, M.L., Hansen, M., Hansen, T., Haroutunian, V., Hartmann, A.M., Henskens, F.A., Herms, S., Hirschhorn, J.N., Hoffmann, P., Hofman, A., Hollegaard, M.V., Hougaard, D.M., Ikeda, M., Joa, I., Julià, A., Kahn, R.S., Kalaydjieva, L., Karachanak-Yankova, S., Karjalainen, J., Kavanagh, D., Keller, M.C., Kennedy, J.L., Khrunin, A., Kim, Y., Klovins, J., Knowles, J.A., Konte, B., Kucinskas, V., Ausrele Kucinskiene, Z., Kuzelova-Ptackova, H., Kähler, A.K., Laurent, C., Lee Chee Keong, J., Hong Lee, S., Legge, S.E., Lerer, B., Li, M., Li, T., Liang, K.-Y., Lieberman, J., Limborska, S., Loughland, C.M., Lubinski, J., Lönnqvist, J., Macek Jr, M., Magnusson, P.K.E., Maher, B.S., Maier, W., Mallet, J., Marsal, S., Mattheisen, M., Mattingsdal, M., McCarley, R.W., McDonald, C., McIntosh, A.M., Meier, S., Meijer, C.J., Melegh, B., Melle, I., Mesholam-Gately, R.I., Metspalu, A., Michie, P.T., Milani, L., Milanova, V., Mokrab, Y., Morris, D.W., Mors, O., Murphy, K.C., Murray, R.M., Myin-Germeys, I., Müller-Myhsok, B., Nelis, M., Nenadic, I., Nertney, D.A., Nestadt, G., Nicodemus, K.K., Nikitina-Zake, L., Nisenbaum, L., Nordin, A., O'Callaghan, E., O'Dushlaine, C., O'Neill, F.A., Oh, S.-Y., Olincy, A., Olsen, L., Van Os, J., Endophenotypes International Consortium, P., Pantelis, C., Papadimitriou, G.N., Papiol, S., Parkhomenko, E., Pato, M.T., Paunio, T., Pejovic-Milovancevic, M., Perkins, D.O., Pietiläinen, O., Pimm, J., Pocklington, A.J., Powell, J., Price, A., Pulver, A.E., Purcell, S.M., Quested, D., Rasmussen, H.B., Reichenberg, A., Reimers, M.A., Richards, A.L., Roffman, J.L., Roussos, P., Ruderfer, D.M., Salomaa, V., Sanders, A.R., Schall, U., Schubert, C.R., Schulze, T.G., Schwab, S.G., Scolnick, E.M., Scott, R.J., Seidman, L.J., Shi, J., Sigurdsson, E., Silagadze, T., Silverman, J.M., Sim, K., Slominsky, P., Smoller, J.W., So, H.-C., Spencer, ChrisC.A., Stahl, E.A., Stefansson, H., Steinberg, S., Stogmann, E., Straub, R.E., Strengman, E., Strohmaier, J., Scott Stroup, T., Subramaniam, M., Suvisaari, J., Svrakic, D.M., Szatkiewicz, J.P., Söderman, E., Thirumalai, S., Toncheva, D., Tosato, S., Veijola, J., Waddington, J., Walsh, D., Wang, D., Wang, Q., Webb, B.T., Weiser, M., Wildenauer, D.B., Williams, N.M., Williams, S., Witt, S.H., Wolen, A.R., Wong, E.H.M., Wormley, B.K., Simon Xi, H., Zai, C.C., Zheng, X., Zimprich, F., Wray, N.R., Stefansson, K., Visscher, P.M., Trust Case-Control Consortium, W., Adolfsson, R., Andreassen, O.A., Blackwood, D.H.R., Bramon, E., Buxbaum, J.D., Børglum, A.D., Cichon, S., Darvasi, A., Domenici, E., Ehrenreich, H., Esko, T., Gejman, P.V., Gill, M., Gurling, H., Hultman, C.M., Iwata, N., Jablensky, A.V., Jönsson, E.G., Kendler, K.S., Kirov, G., Knight, J., Lencz, T., Levinson, D.F., Li, Q.S., Liu, J., Malhotra, A.K., McCarroll, S.A., McQuillin, A., Moran, J.L., Mortensen, P.B., Mowry, B.J., Nöthen, M.M., Ophoff, R.A., Owen, M.J., Palotie, A., Pato, C.N., Petryshen, T.L., Posthuma, D., Rietschel, M., Riley, B.P., Rujescu, D., Sham, P.C., Sklar, P., St Clair, D., Weinberger, D.R., Wendland, J.R., Werge, T., Daly, M.J., Sullivan, P.F., O'Donovan, M.C., 2014. Biological insights from 108 schizophrenia-associated genetic loci. Nature 511, 421–427. https://doi.org/10.1038/nature13595

Salyakina, D., Cukier, H.N., Lee, J.M., Sacharow, S., Nations, L.D., Ma, D., Jaworski, J.M., Konidari, I., Whitehead, P.L., Wright, H.H., Abramson, R.K., Williams, S.M., Menon, R., Haines, J.L., Gilbert, J.R., Cuccaro, M.L., Pericak-Vance, M.A., 2011. Copy number variants in extended autism spectrum disorder families reveal candidates potentially involved in autism risk. PloS One 6, e26049. https://doi.org/10.1371/journal.pone.0026049

Sargeant, T.J., Miller, J.H., Day, D.J., 2008. Opioidergic regulation of astroglial/neuronal proliferation: where are we now? J. Neurochem. 107, 883–897. https://doi.org/10.1111/j.1471-4159.2008.05671.x

Science exchange, 2019. Whole exome sequencing cost comparison [WWW Document]. URL https://www.scienceexchange.com/marketplace/whole-exome-seq?page=1

Shi, J., Levinson, D.F., Duan, J., Sanders, A.R., Zheng, Y., Pe'er, I., Dudbridge, F., Holmans, P.A., Whittemore, A.S., Mowry, B.J., Olincy, A., Amin, F., Cloninger, C.R., Silverman, J.M., Buccola, N.G., Byerley, W.F., Black, D.W., Crowe, R.R., Oksenberg, J.R., Mirel, D.B., Kendler, K.S., Freedman, R., Gejman, P.V., 2009. Common variants on chromosome 6p22.1 are associated with schizophrenia. Nature 460, 753–757. https://doi.org/10.1038/nature08192

Sinyor, M., Schaffer, A., Levitt, A., 2010. The sequenced treatment alternatives to relieve depression (STAR*D) trial: a review. Can. J. Psychiatry Rev. Can. Psychiatr. 55, 126–135. https://doi.org/10.1177/070674371005500303

Smagin, D.A., Galyamina, A.G., Kovalenko, I.L., Babenko, V.N., Kudryavtseva, N.N., 2019. Aberrant Expression of Collagen Gene Family in the Brain Regions of Male Mice with Behavioral Psychopathologies Induced by Chronic Agonistic Interactions. BioMed Res. Int. 2019, 7276389. https://doi.org/10.1155/2019/7276389

Smith, A.H., Jensen, K.P., Li, J., Nunez, Y., Farrer, L.A., Hakonarson, H., Cook-Sather, S.D., Kranzler, H.R., Gelernter, J., 2017. Genome-wide association study of therapeutic opioid dosing identifies a novel locus upstream of OPRM1. Mol. Psychiatry 22, 346–352. https://doi.org/10.1038/mp.2016.257

Song, G.G., Kim, J.-H., Lee, Y.H., 2013. Genome-wide pathway analysis in major depressive disorder. J. Mol. Neurosci. MN 51, 428–436. https://doi.org/10.1007/s12031-013-0047-z

Souery, D., Amsterdam, J., de Montigny, C., Lecrubier, Y., Montgomery, S., Lipp, O., Racagni, G., Zohar, J., Mendlewicz, J., 1999. Treatment resistant depression: methodological overview and operational criteria. Eur. Neuropsychopharmacol. J. Eur. Coll. Neuropsychopharmacol. 9, 83–91.

Story Jovanova, O., Nedeljkovic, I., Spieler, D., Walker, R.M., Liu, C., Luciano, M., Bressler, J., Brody, J., Drake, A.J., Evans, K.L., Gondalia, R., Kunze, S., Kuhnel, B., Lahti, J., Lemaitre, R.N., Marioni, R.E., Swenson, B., Himali, J.J., Wu, H., Li, Y., McRae, A.F., Russ, T.C., Stewart, J., Wang, Z., Zhang, G., Ladwig, K.-H., Uitterlinden, A.G., Guo, X., Peters, A., Räikkönen, K., Starr, J.M., Waldenberger, M., Wray, N.R., Whitsel, E.A., Sotoodehnia, N., Seshadri, S., Porteous, D.J., van Meurs, J., Mosley, T.H., McIntosh, A.M., Mendelson, M.M., Levy, D., Hou, L., Eriksson, J.G., Fornage, M., Deary, I.J., Baccarelli, A., Tiemeier, H., Amin, N., 2018. DNA Methylation Signatures of Depressive Symptoms in Middle-aged and Elderly Persons: Meta-analysis of Multiethnic Epigenome-wide Studies. JAMA Psychiatry 75, 949–959. https://doi.org/10.1001/jamapsychiatry.2018.1725

Subaran, R.L., Odgerel, Z., Swaminathan, R., Glatt, C.E., Weissman, M.M., 2016. Novel variants in ZNF34 and other brain-expressed transcription factors are shared among early-onset MDD relatives. Am. J. Med. Genet. Part B Neuropsychiatr. Genet. Off. Publ. Int. Soc. Psychiatr. Genet. 171B, 333–341. https://doi.org/10.1002/ajmg.b.32408

Subbanna, M., Shivakumar, V., Talukdar, P.M., Narayanaswamy, J.C., Venugopal, D., Berk, M.,

Varambally, S., Venkatasubramanian, G., Debnath, M., 2018. Role of IL-6/RORC/IL-22 axis in driving Th17 pathway mediated immunopathogenesis of schizophrenia. Cytokine 111, 112–118. https://doi.org/10.1016/j.cyto.2018.08.016

Surles-Zeigler, M.C., Li, Y., Distel, T.J., Omotayo, H., Ge, S., Ford, B.D., 2018. Transcriptomic analysis of neuregulin-1 regulated genes following ischemic stroke by computational identification of promoter binding sites: A role for the ETS-1 transcription factor. PloS One 13, e0197092. https://doi.org/10.1371/journal.pone.0197092

Suwinski, P., Ong, C., Ling, M.H.T., Poh, Y.M., Khan, A.M., Ong, H.S., 2019. Advancing Personalized Medicine Through the Application of Whole Exome Sequencing and Big Data Analytics. Front. Genet. 10, 49. https://doi.org/10.3389/fgene.2019.00049

Taetzsch, T., Brayman, V.L., Valdez, G., 2018. FGF binding proteins (FGFBPs): Modulators of FGF signaling in the developing, adult, and stressed nervous system. Biochim. Biophys. Acta Mol. Basis Dis. 1864, 2983–2991. https://doi.org/10.1016/j.bbadis.2018.06.009

Taylor, D., Barnes, T.R.E., Young, A.H., 2018. The Maudsley Prescribing Guidelines in Psychiatry, 13th Edition. ed. Wiley-Blackwell.

Ten Have, M., Penninx, B.W.J.H., Tuithof, M., van Dorsselaer, S., Kleinjan, M., Spijker, J., de Graaf, R., 2017. Duration of major and minor depressive episodes and associated risk indicators in a psychiatric epidemiological cohort study of the general population. Acta Psychiatr. Scand. 136, 300–312. https://doi.org/10.1111/acps.12753

Thorwarth, A., Schnittert-Hübener, S., Schrumpf, P., Müller, I., Jyrch, S., Dame, C., Biebermann, H., Kleinau, G., Katchanov, J., Schuelke, M., Ebert, G., Steininger, A., Bönnemann, C., Brockmann, K., Christen, H.-J., Crock, P., deZegher, F., Griese, M., Hewitt, J., Ivarsson, S., Hübner, C., Kapelari, K., Plecko, B., Rating, D., Stoeva, I., Ropers, H.-H., Grüters, A., Ullmann, R., Krude, H., 2014. Comprehensive genotyping and clinical characterisation reveal 27 novel NKX2-1 mutations and expand the phenotypic spectrum. J. Med. Genet. 51, 375–387. https://doi.org/10.1136/jmedgenet-2013-102248

Turck, C.W., Guest, P.C., Maccarrone, G., Ising, M., Kloiber, S., Lucae, S., Holsboer, F., Martins-de-Souza, D., 2017. Proteomic Differences in Blood Plasma Associated with Antidepressant Treatment Response. Front. Mol. Neurosci. 10, 272. https://doi.org/10.3389/fnmol.2017.00272

Turner, C.A., Watson, S.J., Akil, H., 2012. The fibroblast growth factor family: neuromodulation of affective behavior. Neuron 76, 160–174. https://doi.org/10.1016/j.neuron.2012.08.037

Udagawa, T., Fujioka, Y., Tanaka, M., Honda, D., Yokoi, S., Riku, Y., Ibi, D., Nagai, T., Yamada, K., Watanabe, H., Katsuno, M., Inada, T., Ohno, K., Sokabe, M., Okado, H., Ishigaki, S., Sobue, G., 2015. FUS regulates AMPA receptor function and FTLD/ALS-associated behaviour via GluA1 mRNA stabilization. Nat. Commun. 6, 7098. https://doi.org/10.1038/ncomms8098

Uher, R., Perlis, R.H., Henigsberg, N., Zobel, A., Rietschel, M., Mors, O., Hauser, J., Dernovsek, M.Z., Souery, D., Bajs, M., Maier, W., Aitchison, K.J., Farmer, A., McGuffin, P., 2012. Depression symptom dimensions as predictors of antidepressant treatment outcome: replicable evidence for interest-activity symptoms. Psychol. Med. 42, 967–980. https://doi.org/10.1017/S0033291711001905

Vardarajan, B.N., Eran, A., Jung, J.-Y., Kunkel, L.M., Wall, D.P., 2013. Haplotype structure enables prioritization of common markers and candidate genes in autism spectrum disorder. Transl. Psychiatry 3, e262. https://doi.org/10.1038/tp.2013.38

Vitale, A.M., Matigian, N.A., Cristino, A.S., Nones, K., Ravishankar, S., Bellette, B., Fan, Y., Wood, S.A., Wolvetang, E., Mackay-Sim, A., 2017. DNA methylation in schizophrenia in different patient-derived cell types. NPJ Schizophr. 3, 6. https://doi.org/10.1038/s41537-016-0006-0

Walters, R.K., Polimanti, R., Johnson, E.C., McClintick, J.N., Adams, M.J., Adkins, A.E., Aliev, F., Bacanu, S.-A., Batzler, A., Bertelsen, S., Biernacka, J.M., Bigdeli, T.B., Chen, L.-S., Clarke, T.-K., Chou, Y.-L., Degenhardt, F., Docherty, A.R., Edwards, A.C., Fontanillas, P., Foo, J.C., Fox, L., Frank, J., Giegling, I., Gordon, S., Hack, L.M., Hartmann, A.M., Hartz, S.M., Heilmann-Heimbach, S., Herms, S., Hodgkinson, C., Hoffmann, P., Jan Hottenga, J., Kennedy, M.A., Alanne-Kinnunen, M., Konte, B., Lahti, J., Lahti-Pulkkinen, M., Lai, D., Ligthart, L., Loukola, A., Maher, B.S., Mbarek, H., McIntosh, A.M., McQueen, M.B., Meyers, J.L., Milaneschi, Y., Palviainen, T., Pearson, J.F., Peterson, R.E., Ripatti, S., Ryu, E., Saccone, N.L., Salvatore, J.E., Sanchez-Roige, S., Schwandt, M., Sherva, R., Streit, F., Strohmaier, J., Thomas, N., Wang, J.-C., Webb, B.T., Wedow, R., Wetherill, L., Wills, A.G., 23andMe Research Team, Boardman, J.D., Chen, D., Choi, D.-S., Copeland, W.E., Culverhouse, R.C., Dahmen, N., Degenhardt, L., Domingue, B.W., Elson, S.L., Frye, M.A., Gäbel, W., Hayward, C., Ising, M., Keyes, M., Kiefer, F., Kramer, J., Kuperman, S., Lucae, S., Lynskey, M.T., Maier, W., Mann, K., Männistö, S., Müller-Myhsok, B., Murray, A.D., Nurnberger, J.I., Palotie, A., Preuss, U., Räikkönen, K., Reynolds, M.D., Ridinger, M., Scherbaum, N., Schuckit, M.A., Soyka, M., Treutlein, J., Witt, S., Wodarz, N., Zill, P., Adkins, D.E., Boden, J.M., Boomsma, D.I., Bierut, L.J., Brown, S.A., Bucholz, K.K., Cichon, S., Costello, E.J., de Wit, H., Diazgranados, N., Dick, D.M., Eriksson, J.G., Farrer, L.A., Foroud, T.M., Gillespie, N.A., Goate, A.M., Goldman, D., Grucza, R.A., Hancock, D.B., Harris, K.M., Heath, A.C., Hesselbrock, V., Hewitt, J.K., Hopfer, C.J., Horwood, J., Iacono, W., Johnson, E.O., Kaprio, J.A., Karpyak, V.M., Kendler, K.S., Kranzler, H.R., Krauter, K., Lichtenstein, P., Lind, P.A., McGue, M., MacKillop, J., Madden, P.A.F., Maes, H.H., Magnusson, P., Martin, N.G., Medland, S.E., Montgomery, G.W., Nelson, E.C., Nöthen, M.M., Palmer, A.A., Pedersen, N.L., Penninx, B.W.J.H., Porjesz, B., Rice, J.P., Rietschel, M., Riley, B.P., Rose, R., Rujescu, D., Shen, P.-H., Silberg, J., Stallings, M.C., Tarter, R.E., Vanyukov, M.M., Vrieze, S., Wall, T.L., Whitfield, J.B., Zhao, H., Neale, B.M., Gelernter, J., Edenberg, H.J., Agrawal, A., 2018. Transancestral GWAS of alcohol dependence reveals common genetic underpinnings with psychiatric disorders. Nat. Neurosci. 21, 1656–1669. https://doi.org/10.1038/s41593-018-0275-1

Wang, S.E., Ko, S.Y., Jo, S., Jo, H.-R., Han, J., Kim, Y.-S., Son, H., 2019. Downregulation of SIRT2 by Chronic Stress Reduces Expression of Synaptic Plasticity-related Genes through the Upregulation of Ehmt2. Exp. Neurobiol. 28, 537–546. https://doi.org/10.5607/en.2019.28.4.537

Warden, D., Rush, A.J., Trivedi, M.H., Fava, M., Wisniewski, S.R., 2007. The STAR*D Project results: a comprehensive review of findings. Curr. Psychiatry Rep. 9, 449–459.

Wearne, T.A., Mirzaei, M., Franklin, J.L., Goodchild, A.K., Haynes, P.A., Cornish, J.L., 2015. Methamphetamine-induced sensitization is associated with alterations to the proteome of the prefrontal cortex: implications for the maintenance of psychotic disorders. J. Proteome Res. 14, 397–410. https://doi.org/10.1021/pr500719f

World Health Organization (WHO), 2016. Global Health Observatory (GHO) data - Suicide rates per 100000 population in UK, 2016 [WWW Document]. URL https://www.who.int/gho/mental_health/suicide_rates_crude/en/

Wray, N.R., Ripke, S., Mattheisen, M., Trzaskowski, M., Byrne, E.M., Abdellaoui, A., Adams, M.J., Agerbo, E., Air, T.M., Andlauer, T.M.F., Bacanu, S.-A., Bækvad-Hansen, M., Beekman, A.F.T., Bigdeli, T.B., Binder, E.B., Blackwood, D.R.H., Bryois, J., Buttenschøn, H.N., Bybjerg-Grauholm, J., Cai, N., Castelao, E., Christensen, J.H., Clarke, T.-K., Coleman, J.I.R., Colodro-Conde, L., Couvy-Duchesne, B., Craddock, N., Crawford, G.E., Crowley, C.A., Dashti, H.S., Davies, G., Deary, I.J., Degenhardt, F., Derks, E.M., Direk, N., Dolan, C.V., Dunn, E.C., Eley, T.C., Eriksson, N., Escott-Price, V., Kiadeh, F.H.F., Finucane, H.K., Forstner, A.J., Frank, J., Gaspar, H.A., Gill, M., Giusti-Rodríguez, P., Goes, F.S., Gordon, S.D., Grove, J., Hall, L.S., Hannon, E., Hansen, C.S., Hansen, T.F., Herms, S., Hickie, I.B., Hoffmann, P., Homuth, G., Horn, C., Hottenga, J.-J., Hougaard, D.M., Hu, M., Hyde, C.L., Ising, M., Jansen, R., Jin, F., Jorgenson,

E., Knowles, J.A., Kohane, I.S., Kraft, J., Kretzschmar, W.W., Krogh, J., Kutalik, Z., Lane, J.M., Li, Yihan, Li, Yun, Lind, P.A., Liu, X., Lu, L., MacIntyre, D.J., MacKinnon, D.F., Maier, R.M., Maier, W., Marchini, J., Mbarek, H., McGrath, P., McGuffin, P., Medland, S.E., Mehta, D., Middeldorp, C.M., Mihailov, E., Milaneschi, Y., Milani, L., Mill, J., Mondimore, F.M., Montgomery, G.W., Mostafavi, S., Mullins, N., Nauck, M., Ng, B., Nivard, M.G., Nyholt, D.R., O'Reilly, P.F., Oskarsson, H., Owen, M.J., Painter, J.N., Pedersen, C.B., Pedersen, M.G., Peterson, R.E., Pettersson, E., Peyrot, W.J., Pistis, G., Posthuma, D., Purcell, S.M., Quiroz, J.A., Qvist, P., Rice, J.P., Riley, B.P., Rivera, M., Saeed Mirza, S., Saxena, R., Schoevers, R., Schulte, E.C., Shen, L., Shi, J., Shyn, S.I., Sigurdsson, E., Sinnamon, G.B.C., Smit, J.H., Smith, D.J., Stefansson, H., Steinberg, S., Stockmeier, C.A., Streit, F., Strohmaier, J., Tansey, K.E., Teismann, H., Teumer, A., Thompson, W., Thomson, P.A., Thorgeirsson, T.E., Tian, C., Traylor, M., Treutlein, J., Trubetskoy, V., Uitterlinden, A.G., Umbricht, D., Van der Auwera, S., van Hemert, A.M., Viktorin, A., Visscher, P.M., Wang, Y., Webb, B.T., Weinsheimer, S.M., Wellmann, J., Willemsen, G., Witt, S.H., Wu, Y., Xi, H.S., Yang, J., Zhang, F., eQTLGen, 23andMe, Arolt, V., Baune, B.T., Berger, K., Boomsma, D.I., Cichon, S., Dannlowski, U., de Geus, E.C.J., DePaulo, J.R., Domenici, E., Domschke, K., Esko, T., Grabe, H.J., Hamilton, S.P., Hayward, C., Heath, A.C., Hinds, D.A., Kendler, K.S., Kloiber, S., Lewis, G., Li, Q.S., Lucae, S., Madden, P.F.A., Magnusson, P.K., Martin, N.G., McIntosh, A.M., Metspalu, A., Mors, O., Mortensen, P.B., Müller-Myhsok, B., Nordentoft, M., Nöthen, M.M., O'Donovan, M.C., Paciga, S.A., Pedersen, N.L., Penninx, B.W.J.H., Perlis, R.H., Porteous, D.J., Potash, J.B., Preisig, M., Rietschel, M., Schaefer, C., Schulze, T.G., Smoller, J.W., Stefansson, K., Tiemeier, H., Uher, R., Völzke, H., Weissman, M.M., Werge, T., Winslow, A.R., Lewis, C.M., Levinson, D.F., Breen, G., Børglum, A.D., Sullivan, P.F., Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, 2018. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. Nat. Genet. 50, 668–681. https://doi.org/10.1038/s41588-018-0090-3

Yamanaka, Y., Kitano, A., Takao, K., Prasansuklab, A., Mushiroda, T., Yamazaki, K., Kumada, T., Shibata, M., Takaoka, Y., Awaya, T., Kato, T., Abe, T., Iwata, N., Miyakawa, T., Nakamura, Y., Nakahata, T., Heike, T., 2011. Inactivation of fibroblast growth factor binding protein 3 causes anxiety-related behaviors. Mol. Cell. Neurosci. 46, 200–212. https://doi.org/10.1016/j.mcn.2010.09.003

Yang, C., Zhou, C., Li, J., Chen, Z., Shi, H., Yang, W., Qin, Y., Lü, L., Zhao, L., Fang, L., Wang, H., Hu, Z., Xie, P., 2018. Quantitative proteomic study of the plasma reveals acute phase response and LXR/RXR and FXR/RXR activation in the chronic unpredictable mild stress mouse model of depression. Mol. Med. Rep. 17, 93–102. https://doi.org/10.3892/mmr.2017.7855

Yarosh, H.L., Meda, S.A., de Wit, H., Hart, A.B., Pearlson, G.D., 2015. Multivariate analysis of subjective responses to d-amphetamine in healthy volunteers finds novel genetic pathway associations. Psychopharmacology (Berl.) 232, 2781–2794. https://doi.org/10.1007/s00213-015-3914-1

Yi, Z., Li, Z., Yu, S., Yuan, C., Hong, W., Wang, Z., Cui, J., Shi, T., Fang, Y., 2012. Blood-based gene expression profiles models for classification of subsyndromal symptomatic depression and major depressive disorder. PloS One 7, e31283. https://doi.org/10.1371/journal.pone.0031283

Zhang, Z., Zhang, L., Zhang, G., Jin, J., Zheng, Z., 2018. The effect of CBT and its modifications for relapse prevention in major depressive disorder: a systematic review and meta-analysis. BMC Psychiatry 18, 50. https://doi.org/10.1186/s12888-018-1610-5

Zhou, Y., Wu, H., Li, S., Chen, Q., Cheng, X.-W., Zheng, J., Takemori, H., Xiong, Z.-Q., 2006. Requirement of TORC1 for late-phase long-term potentiation in the hippocampus. PloS One 1, e16. https://doi.org/10.1371/journal.pone.0000016

Zhu, B., Jiang, L., Huang, T., Zhao, Y., Liu, T., Zhong, Y., Li, X., Campos, A., Pomeroy, K.,

Masliah, E., Zhang, D., Xu, H., 2017. ER-associated degradation regulates Alzheimer's amyloid pathology and memory function by modulating γ-secretase activity. Nat. Commun. 8, 1472. https://doi.org/10.1038/s41467-017-01799-4

Zou, C., Ellis, B.M., Smith, R.M., Chen, B.B., Zhao, Y., Mallampalli, R.K., 2011. Acyl-CoA:lysophosphatidylcholine acyltransferase I (Lpcat1) catalyzes histone protein O-palmitoylation to regulate mRNA synthesis. J. Biol. Chem. 286, 28019–28025. https://doi.org/10.1074/jbc.M111.253385

Zuber, V., Strimmer, K., 2011. High-dimensional regression and variable selection using CAR scores.

Zuber, V., Strimmer, K., 2009. Gene ranking and biomarker discovery under correlation. Bioinforma. Oxf. Engl. 25, 2700–2707. https://doi.org/10.1093/bioinformatics/btp460

Zuo, L., Gelernter, J., Kranzler, H.R., Stein, M.B., Zhang, H., Wei, F., Sen, S., Poling, J., Luo, X., 2010. ADH1A variation predisposes to personality traits and substance dependence. Am. J. Med. Genet. Part B Neuropsychiatr. Genet. Off. Publ. Int. Soc. Psychiatr. Genet. 153B, 376–386. https://doi.org/10.1002/ajmg.b.30990