SUPPLEMENTARY MATERIAL
"Insulin/IGF-1 signaling modulation in prefrontal cortex is linked to antisuicidal effects in MDD"

Supplementary Methods

Cohort collection and phenotyping

The study was approved by the Independent Ethics Committee of the V.M. Bekhterev National Medical Research Center for Psychiatry and Neurology in 2019 (protocol #7 from 22.06.2018) and was performed under the supervision of the Russian National Consortium for Psychiatric Genetics (RNCPG, http://rncpg.org).

The subjects were recruited in eight research centers in the Russian Federation:

1. Scientific Center for Psychological Health (Moscow);
2. V.M. Bekhterev National Medical Research Center for Psychiatry and Neurology (Saint Petersburg);
3. Lipetsk Regional Addiction Hospital (Lipetsk);
4. Peoples' Friendship University of Russia (Moscow);
5. Serbsky National Medical Research Centre on Psychiatry and Addictions (Moscow);
6. Moscow Scientific and Practical Center for Narcology;
7. Rostov State Medical University (Rostov-on-Don);
8. Institute of Biochemistry and Genetics of Ufa Federal Research Center of the Russian Academy of Sciences (Ufa).

Participants were recruited between 2019 and 2022. Upon signing an informed consent and enrollment in the study, all subjects were assigned a unique anonymous identifier.

A structured clinical interview based on the ICD-10 criteria was conducted with all study participants to confirm clinical diagnoses and identify comorbid psychiatric disorders.

The study included patients aged 18 years or older who met the diagnostic criteria for major depressive disorder. The case report for each participant included suicide attempt count, C-SSRS scores for suicidal behavior and ideation.

Excluded from the study were patients with bipolar disorder (BD), schizophrenic spectrum disorders, organic mental disorders, a history of seizure syndrome, or severe decompensated diseases, including cardiovascular, neurological, endocrine, hematological diseases, liver, kidney, gastrointestinal tract, respiratory system, and thyroid diseases. Exclusion criteria also encompassed patient refusal to participate in the study and the care provider's decision to exclude patients openly exhibiting

aggressive behavior or posing a threat to themselves or others.

Following the ICD-10 criteria, all comorbid psychiatric disorders within the anxiety spectrum (including generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), panic disorder (PD), social anxiety disorder (SAD), eating disorders such as anorexia nervosa (AN) and bulimia nervosa (BN)), substance use disorders, and psychotic symptoms were assessed and documented based on diagnostic criteria. Presence and family history of somatic diseases, including diabetes mellitus types I and II, cancer, gastrointestinal diseases, thyroid diseases, history of myocardial infarction and stroke were also documented.

Genetic data generation

Genotyping of the cohort was performed in two centers: Lopukhin Federal Research and Clinical Center of Physical-Chemical Medicine and Genotek Ltd. laboratory. In the first center, DNA was extracted using the MagMAX™ Microbiome Ultra Nucleic Acid Isolation Kit and KingFisher™ Purification System (Thermo Fisher Scientific, USA) according to the manufacturer's protocol. The DNA was subsequently quantified on Qubit 4 fluorometer by Quant-iT dsDNA BR Assay Kit (Thermo Fisher Scientific, USA). In the second center DNA extraction was performed with QIAamp DNA Mini Kit (Qiagen).

Genotyping of samples was performed using the Illumina Infinium Global Screening Array-24 v3.0 beadchips on the iScan, Illumina in both centers. Alternative allele frequencies did not differ significantly between the genotyping centers ($r2=0.995$, $p=0.000$).

Samples with a call rate less than 95% were removed. From pairs of related individuals (with kinship statistic obtained using PC-Relate method >0.125) only one randomly chosen was retained in the dataset. Variants with call rate less than 95%, minor allele frequency <0.01 and showing Hardy-Weinberg equilibrium test $p<1x10^{-6}$ were also excluded. Additional genotypes were imputed using the 1000 genomes phase 3 reference panel using Beagle v5.4(1,2). The variants with dosage R-squared DR2<0.7 were eliminated.

The initial cohort comprised 231 patients. After exclusion of the patients with missing information on suicide attempt history and related individuals, 172 patients were left in the study, which constituted the final cohort.

Integration of genomic data with GTEx v8 MASHR models

To predict genetically determined expression in the studied cohort, we used individual-level implementation of PrediXCan(3) with a MASHR transcriptomic prediction model trained on GTEx v8 data for BA9 (4,5). The model uses effect sizes computed with MASHR(4,6). We measured association of genetically determined expression with suicide attempt count and C-SSRS suicidal behavior (lifetime) total score using linear regression. Logistic regression was used for suicide attempt history. Age and sex were used as covariates. Statsmodels (7) package was used to perform regression. The results of the transcriptome-wide association studies (TWAS) were visualized using GWASLab (8).

Construction of the TWAS-based signature for small molecule prioritization

We constructed two genetic signatures for small molecule prioritization from the genes, which were associated with at least one of the three studied phenotypes at study-wide

significance level ($p<0.05/n$ genes/n TWAS=$0.05/13019/3=3.84x10^{-6} / 3 = 1.28x10^{-6}$). The first signature (s1) included only the genes, which replicated at within-study replication significance level in all the phenotypes ($p<0.05 / n$ TWAS $= 0.05 / 3 = 1.67x10^{-2}$). The second signature (s2) included all genes, which were transcriptome-wide significant for any of the studied phenotypes.

To evaluate replicability of the genetic associations used to construct the signature, we used the summary statistics for the phenotype “Ever attempted suicide” available from IEU OpenGWAS (UKB-d-20483) (9,10) and the summary statistics for a large-scale meta-analysis of suicide attempt performed by PGC for the European population (11). For both studies, we performed harmonization of the summary statistics with the MASHR model using “summary-gwas-imputation” tool (12). The PGC summary statistics lacked the variants linked with the genes found to be associated with suicidality in our study. We performed summary-based imputation of these variants with “summary-gwas-imputation” tool as described in (13). We used S-PrediXcan to measure associations between genetically determined expression and suicide attempt history in these studies.

We also ranked patients by cosine similarities of their genetically determined expression in the BA9 with the signatures, and measured enrichment of the obtained patient ranking with patients who had suicide attempts (n=40) to verify the power of the signatures to discriminate patients with and without such attempts.

Small molecule prioritization

We used L1000 chemical perturbations' consensus signatures from SigCom LINCS (14) as the source of data on small molecule-induced transcriptomic changes. The small molecules were ranked by negative cosine similarity between the TWAS-derived signatures and their profiles to prioritize the molecules which alleviate genetically determined expression associated with suicide. We measured enrichment of the approved anti-suicide drug set (ketamine and clozapine), a set of drugs, associated with decreased (n=38) and with increased (n=8, as a control) suicide rates based on a recent study (which were also present in the L1000 dataset) (15)in the obtained drug rankings. An analogous procedure was performed for individual genes from the signatures to evaluate their contribution to the prioritization. For the prioritization based on the more conservative signature s1, we tested enrichment with 9 antidepressant drugs (citalopram, fluvoxamine, paroxetine, fluoxetine, sertraline, venlafaxine, mirtazapine, nefazodone, bupropion), which were assigned the black box warning by FDA based on the study by Hammad et al., 2006(16). We also examined how clozapine ranked among other antipsychotics present in L1000 in the prioritizations.

Lithium chloride is also present among the L1000 signatures and was proposed to have a similar mechanism of activity as the lithium salts widely used for bipolar disorder treatment, such as lithium carbonate. Lithium chloride is stated currently as an experimental drug, being used primarily in animal studies due to safety concerns, but is has been shown previously to reduce mania in bipolar disorder patients at medium and high dosages(17). We thus tested enrichment of the prioritization with addition of lithium chloride to the ketamine and clozapine set.

An empirical p-value based on 500 random signatures from genes with expression level in GTEx BA9 matching with the signature (the genes were grouped into 10 groups by expression level) was calculated to test whether there is a significant association between ketamine and clozapine - induced transcriptomic changes and the genetic signature based on suicide data.

The L1000 dataset in the study includes over 30,000 small molecule compounds, primarily investigational. For more than 26,000 compounds with provided canonical SMILES, we calculated BBB scores using BBB_calc (18,19). Above 90% of compounds scoring > 5 tend to be CNS drugs (18). SigCom LINCS annotates well-characterized compounds with common names. We evaluated ketamine and clozapine ranks across the dataset and among known compounds and those with BBB scores > 5 to assess drug repurposing opportunities. We also tested enrichment of the ketamine and clozapine set with and without lithium chloride among the commonly known compounds with BBB score > 5.

We formed sets of small molecules belonging to different mechanisms of action in the L1000 dataset and tested enrichment of these sets in the ranking based on the more conservative signature s1. We also tested enrichment of this ranking with small molecules having different targets.

Hail (20) was used for preprocessing of genomic data, pandas (21), polars (22), and numpy (23) were used for data manipulation, sklearn (24)was used to calculate cosine similarities, seaborn (25), matplotlib (26), and matplotlib-venn (27)- for data visualization, gseapy (28) - for enrichment analysis.

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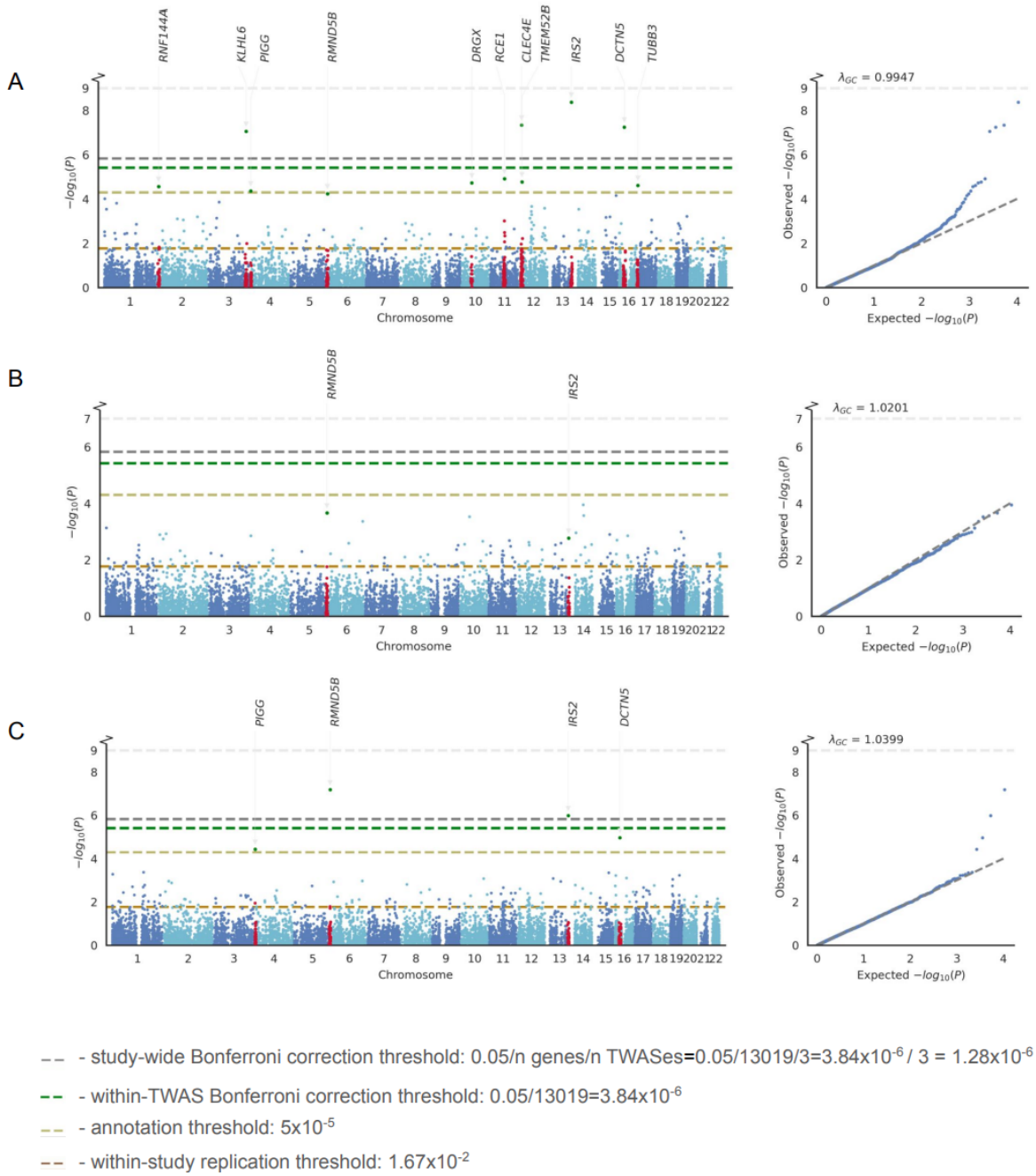
Supplementary Figures and Tables



Supplementary Fig. 1. Manhattan and q-q plots of the TWAS studies.

(A). Suicide attempt count. (B). Ever attempted suicide. (C). CSSRS suicidal behavior. RMND5B and IRS2 - the genes, which showed transcriptome-wide association after Bonferroni correction with at least one suicidality phenotype definition and replicated in TWASes for other definitions, - are marked in each Manhattan plot. Annotation threshold for the other genes - $5x10^{-5}$.

Supplementary Table 1. Significant results of TWAS analyses and their within-study cross-phenotype replication.

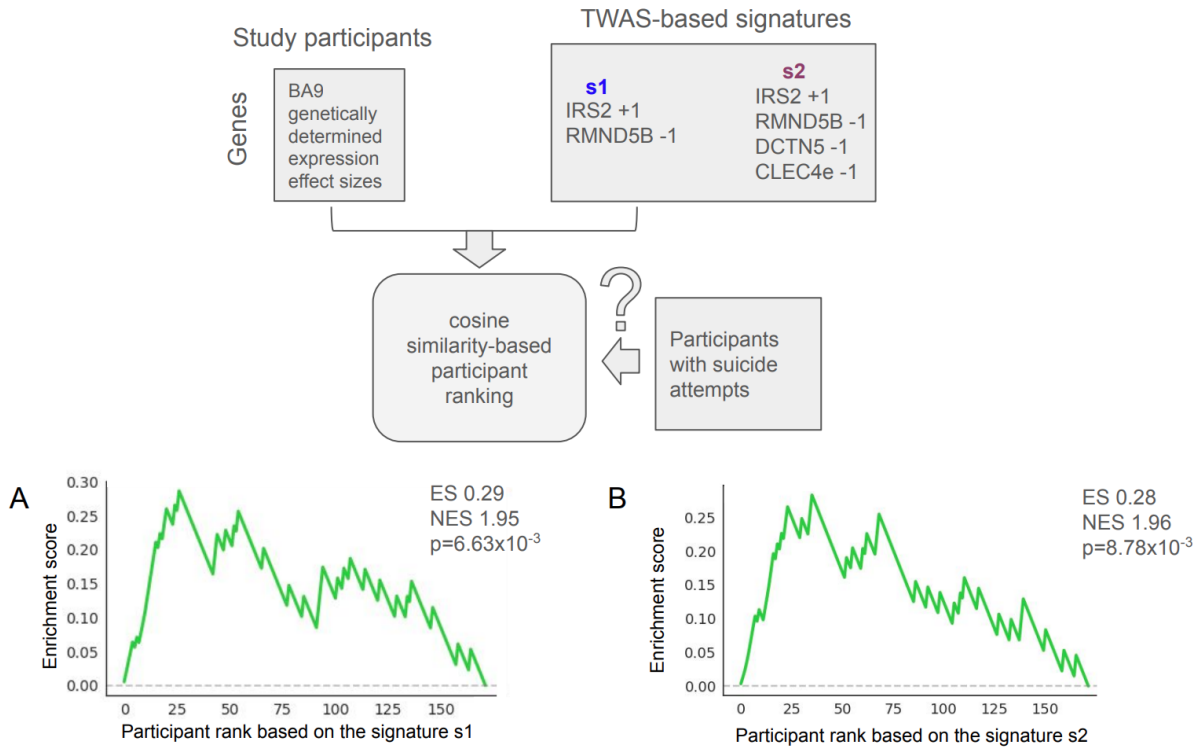
Gene	**Suicide attempt count**	**Ever attempted suicide**	**CSSRS suicidal behavior**
IRS2	**40.61 ($p=4.31\times10^{-9}$)**	42.74 ($p=1.93\times10^{-3}$)	**45.65 ($p=1.03\times10^{-6}$)**
CLEC4E	**-195.15 ($p=4.68\times10^{-8}$)**	-43.27 ($p=4.79\times10^{-1}$)	-65.29 ($p=1.67\times10^{-1}$)
DCTN5	**-40.41 ($p=5.73\times10^{-8}$)**	-27.90 ($p=4.37\times10^{-2}$)	-50.26 ($p=1.07\times10^{-5}$)
KLHL6	**188.47 ($p=8.92\times10^{-8}$)**	120.50 ($p=6.61\times10^{-2}$)	94.48 ($p=4.18\times10^{-2}$)
RMND5B	-16.98 ($p=5.82\times10^{-5}$)	-33.78 ($p=2.61\times10^{-4}$)	**-29.66 ($p=6.58\times10^{-8}$)**

a - associations which crossed study-wide Bonferroni correction threshold (0.05/n genes/n TWASes = 0.05/13019/3 = 1.28×10^{-6})

a - associations, which passed study-wide replication threshold (0.05 / n studies = 1.67×10^{-2}) for the genes, which are associated with any of the other phenotypes after study-wide Bonferroni correction

Supplementary Table 2. Replication of the TWAS results in summary statistics-based TWASes of suicide attempt based on other cohorts.

Gene	**PGC (EUR): Attempted suicide (z-scores)**	**UKB-d-20483: Attempted suicide (effect sizes)**
IRS2	1.47 ($p_{os}=7.05\times10^{-2}$)	0.61 ($p_{os}=8.97\times10^{-2}$)
RMND5B	-0.89 ($p_{os}=1.88\times10^{-1}$)	-0.47 ($p_{os}=4.76\times10^{-2}$)
DCTN5	0.24 ($p_{os}=6.00\times10^{-1}$)	-1.42 ($p_{os}=7.82\times10^{-2}$)
CLEC4E	-	-
KLHL6	-	-0.46 ($p_{os}=6.78\times10^{-1}$)



Supplementary Fig. 2. Enrichment of the vector of study participants, arranged by cosine similarities of their predicted genetically determined expression in the BA9 (A) to the signature s1, (B) to the signature s2 with participants having suicide attempts.

Supplementary Table 3. Commonly known small molecules (annotated with common names in the L1000 SigCom LINCS portal metadata), which ranked higher or at the level of clozapine and ketamine in the drug prioritization based on the signature s1 (IRS2, RMND5B genes).

	drug	target	moa	BBB score	score
0	acetylcholine	-	-	4.06	0.052
1	deguelin	AKT1	NADH-ubiquinone oxidoreductase (Complex I) inhibitor	4.15	0.043
2	efatutazone	PPARG	PPAR receptor agonist	2.02	0.043
3	aniracetam	GRIA1, DRD2, HTR2A, GRIA2, GRIA3	Glutamate receptor agonist	4.62	0.041
4	batimastat	-	-	3.18	0.041
5	tetroquinone	-	-	1.93	0.04
6	tetramisole	-	-	8.69	0.04
7	deoxycorticosterone-acetate	-	-	3.85	0.039
8	liothyronine	THRA, THRB	Thyroid hormone stimulant	3.87	0.039

9	fluprostenol	-	-	2.53	0.038
10	rotundine	DRD1, HTR1A, DRD2, DRD3	Serotonin receptor agonist	6.01	0.038
11	enoximone	-	-	3.88	0.038
12	enzastaurin	PRKCB	PKC inhibitor	3.00	0.038
13	dicyclohexylurea	-	-	4.22	0.037
14	veliparib	PARP2, PARP1	PARP inhibitor	5.55	0.037
15	myriocin	-	-	1.16	0.037
16	metoprolol	ADRB1, ADRB2	Adrenergic receptor antagonist	7.39	0.037
17	disopyramide	SCN5A	Sodium channel blocker	5.67	0.037
18	glipizide	KCNJ11, ABCC8	Sulfonylurea	2.26	0.036
19	damnacanthal	-	-	4.45	0.036
20	methyltyramine	-	-	8.71	0.036
21	propofol	GABRG2, GABRG3, GABRD, GABRQ, GABRE, GABRA6, GABRP, GABRB2, GABRA2, GABRA3, GABRB1, GABRG1, GABRA1, GABRB3, GABRA4, GABRA5	GABA receptor agonist	4.77	0.036
22	benidipine	CACNA1C, CACNA1G	Calcium channel blocker	4.79	0.036
23	totaralolal	-	-	9.91	0.036
24	cefazolin	-	-	1.79	0.036
25	delavirdine	CYP3A4	Non-nucleoside reverse transcriptase inhibitor	2.70	0.036
26	bms	-	-		0.035
27	dosulepin	SLC6A2, SLC6A4	Tricyclic antidepressant, Norepinephrine reuptake inhibitor, Serotonin reuptake inhibitor	8.82	0.035
28	quetiapine	DRD2, DRD1, HTR1A, HTR2A, HRH1, HTR1D, HTR1E	Dopamine receptor antagonist, Serotonin receptor antagonist	6.08	0.035
29	alda-1	ALDH2	Aldehyde dehydrogenase activator	4.82	0.035
30	nitrocaramiphen	CHRM1	Cholinergic receptor antagonist	7.01	0.035
31	nepafenac	PTGS1, PTGS2	Cyclooxygenase inhibitor	4.14	0.035
32	dienestrol	ESR1	Estrogen receptor agonist	9.08	0.035
33	bexarotene	RXRB, RXRG, RXRA	Retinoid receptor agonist	5.19	0.034
34	614_7033_4267	-	-	4.28	0.034
35	fenigam	GABBR1, GABBR2	GABA receptor agonist	4.00	0.034
36	alogliptin	DPP4	Dipeptidyl peptidase inhibitor	4.22	0.034
37	hemado	ADORA3	Adenosine receptor agonist	1.89	0.033
38	solanine	-	-	5.37	0.033
39	denbufylline	-	-	4.36	0.033
40	isradipine	CACNA2D1, CACNA1C, CACNA1S, CACNA1D, CACNA1F	Calcium channel blocker	3.68	0.033
41	icosapent	PTGS1, PTGS2	Platelet aggregation	4.83	0.033

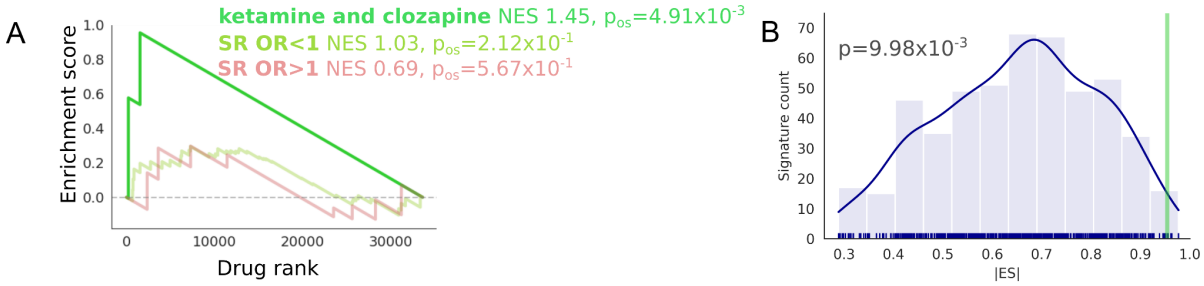
			inhibitor		
42	harmane	MAOA, MAOB	Monoamine oxidase inhibitor	4.57	0.033
43	hymecromone	MAOA, MAOB	Monoamine oxidase inhibitor	6.83	0.033
44	epibatidine	-	-	5.17	0.033
45	hydroquinine	-	-	5.58	0.033
46	tacrine	BCHE, ACHE	Acetylcholinesterase inhibitor	5.64	0.033
47	diclofenamide	CA2, CA4, CA1, CA12	Carbonic anhydrase inhibitor	3.07	0.033
48	iproniazid	-	-	4.07	0.033
49	halofantrine	-	-	8.23	0.033
50	betulinic-acid	GPBAR1	NFkB pathway activator, HIV integrase inhibitor, Topoisomerase inhibitor, Apoptosis stimulant, Diacylglycerol O acyltransferase inhibitor, SARS coronavirus 3C-like protease inhibitor, Caspase activator	4.17	0.033
51	pinitol	-	-	1.64	0.032
52	enflurane	GABRG2, GABRG3, GABRD, GABRQ, GABRE, GABRA6, GABRP, GABRB2, GLRB, GABRA2, GABRA3, GABRB1, GLRA1, GABRG1, GABRA1, GABRB3, GABRA4, GABRA5	Membrane permeability inhibitor	3.69	0.032
53	nilvadipine	CACNA1D, CACNA1C	Calcium channel blocker	1.64	0.032
54	eprosartan	AGTR1	Angiotensin receptor antagonist	3.21	0.032
55	acronycine				0.032
56	leucodin	-	-	4.22	0.032
57	ostarine	AR	Androgen receptor modulator	3.45	0.032
58	clozapine	CHRM3, ADRA1A, DRD3, HTR2C, CHRM2, CHRM4, HTR7, HTR1B, HTR2A, HTR1E, DRD2, DRD1, HTR1A, HRH1, HTR1D, DRD4, HRH4, ADRA1B, CHRM1, HTR6	Dopamine receptor antagonist, Serotonin receptor antagonist	6.69	0.032
59	ramelteon	MTNR1B, MTNR1A	Melatonin receptor agonist	4.77	0.032
60	nystatin	-	-	0.6	0.032
61	ampicillin	-	-	2.19	0.031
62	hydroxyurea	RRM1, RRM2	Ribonucleoside reductase inhibitor	1.82	0.031
63	acitretin	RXRG, RARA	Retinoid receptor agonist	5.27	0.031
64	eliprodil	GRIN2B, GRIN1	Glutamate receptor antagonist	8.14	0.031
65	dinaciclib	CDK9, CDK2, CDK1, CDK5	CDK inhibitor	3.37	0.031
66	talniflumate	CLCA1	Cyclooxygenase inhibitor	3.39	0.031
67	abiraterone	CYP17A1	Androgen biosynthesis inhibitor	5.56	0.031

68	robustic-acid	-	-	3.88	0.031
69	clonazepam	GABRG2, GABRG3, GABRD, GABRQ, GABRE, GABRA6, GABRP, GABRB2, GABRA2, GABRA3, GABRB1, GABRG1, GABRA1, GABRB3, GABRA4, GABRA5	GABA benzodiazepine site receptor agonist	4.29	0.03
70	cobicistat	CYP3A4	Cytochrome P450 inhibitor	1.28	0.03
71	dofequidar	ABCB1, ABCC1	P-glycoprotein inhibitor, MRP inhibitor	4.15	0.03
72	felbinac	-	-	5.32	0.03
73	ketamine	-	-		0.03

Supplementary Table 4. Commonly known small molecules (annotated with common names in the L1000 SigCom LINCS portal metadata), which ranked or at the level of ketamine in the drug prioritization based on the signature s2 (IRS2, RMND5B, DCTN5, CLEC4E genes).

	drug	target	moa	BBB score	score
0	acetylcholine	-	-	4.06	0.036
1	efatutazone	PPARG	PPAR receptor agonist	2.02	0.033
2	damnacanthal	-	-	4.45	0.033
3	enoximone	-	-	3.88	0.033
4	myriocin	-	-	1.16	0.032
5	enflurane	GABRG2, GABRG3, GABRD, GABRQ, GABRE, GABRA6, GABRP, GABRB2, GLRB, GABRA2, GABRA3, GABRB1, GLRA1, GABRG1, GABRA1, GABRB3, GABRA4, GABRA5	Membrane permeability inhibitor	3.69	0.031
6	aniracetam	GRIA1, DRD2, HTR2A, GRIA2, GRIA3	Glutamate receptor agonist	4.62	0.031
7	liothyronine	THRA, THRB	Thyroid hormone stimulant	3.87	0.031
8	disopyramide	SCN5A	Sodium channel blocker	5.67	0.031
9	deguelin	AKT1	NADH-ubiquinone oxidoreductase (Complex I) inhibitor	4.15	0.031
10	cefazolin	-	-	1.79	0.03
11	dalcetrapib	CETP	Cholesterylester transfer protein inhibitor	4.76	0.03
12	fenigam	GABBR1, GABBR2	GABA receptor agonist	4.0	0.03
13	deoxycorticosterone-acetate	-	-	3.85	0.029
14	tetramisole	-	-	8.69	0.029
15	batimastat	-	-	3.18	0.029

16	hydroxyurea	RRM1, RRM2	Ribonucleoside reductase inhibitor	1.82	0.029
17	veliparib	PARP2, PARP1	PARP inhibitor	5.55	0.028
18	ketamine	-	-		0.028



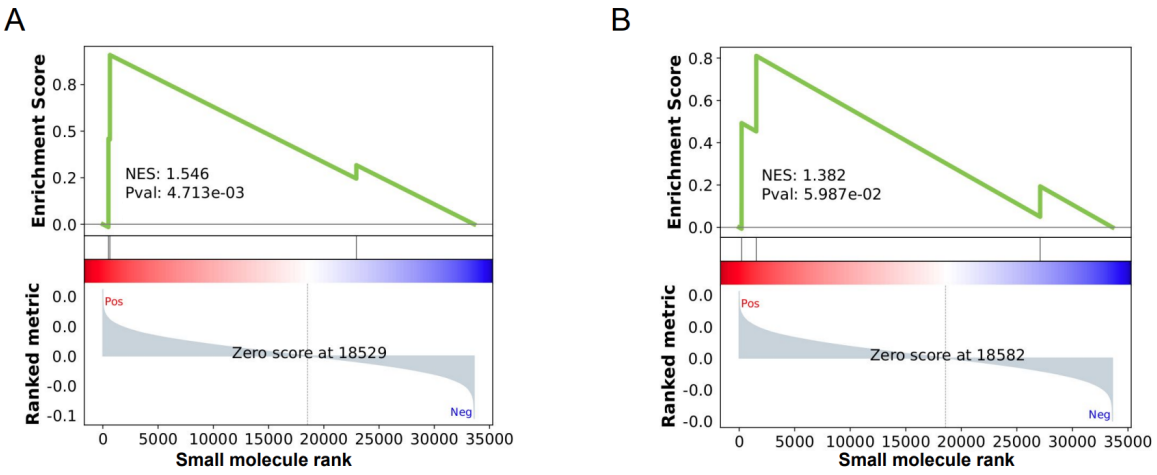
Supplementary Fig. 3. (A). Enrichment of the small molecule prioritization obtained using signature s2 with 3 sets of drugs: ketamine and clozapine; drugs, increasing or decreasing suicide rate according to [Gibbons et al., 2018]. (B). Results of testing whether enrichment of known antisuicidal drugs (ketamine, clozapine) in the prioritization based on the TWAS-derived signature is higher than in the prioritizations based on random signatures matched by expression in the BA9 and the results of the test for the s2 signature: distributions of absolute enrichment scores obtained using random signatures with the same expression as s2 in BA9 according to GTEx and the observed enrichment score using s2.

Supplementary Table 7. Enrichment of antisuicidal drugs (ketamine and clozapine), drugs, increasing or decreasing suicide risk according to Gibbons et al., 2019 in the drug prioritization by negative cosine similarity to the genetic signature associated with the studied suicide behavior phenotypes.

Signature for prioritization	antisuicide drugs (ket+clz)	ket	clz	drugs, associated with decreased suicide rate	drugs, associated with increased suicide rate
IRS2 +1 RMND5B -1	ES=0.98 NES=1.49 $p_{os}=4.85x10^{-4}$	ES=0.98 NES=1.31 $p_{os}=2.45x10^{-2}$	ES=0.98 NES=1.32 $p_{os}=1.30x10^{-2}$	ES=0.36 NES=1.28 $p_{os}=6.77x10^{-2}$	ES=-0.34 NES=-0.84 $p_{os}=3.26x10^{-1}$
IRS2 +1 RMND5B -1 DCTN5 -1 CLEC4E -1	ES=0.95 NES=1.45 $p_{os}=4.91x10^{-3}$	ES=0.99 NES=1.33 $p_{os}=6.79x10^{-3}$	ES=-0.95 NES=1.27 $p_{os}=5.09x10^{-2}$	ES=0.29 NES=1.03 $p_{os}=2.12x10^{-1}$	ES=0.30 NES=0.69 $p_{os}=5.67x10^{-1}$
IRS2 +1	ES=0.90 NES=1.34 $p_{os}=3.12x10^{-2}$	ES=0.99 NES=1.34 $p_{os}=7.19x10^{-3}$	ES=0.90 NES=1.21 $p_{os}=9.80x10^{-2}$	ES=0.29 NES=1.04 $p_{os}=1.96x10^{-1}$	ES=-0.36 NES=-0.88 $p_{os}=2.93x10^{-1}$

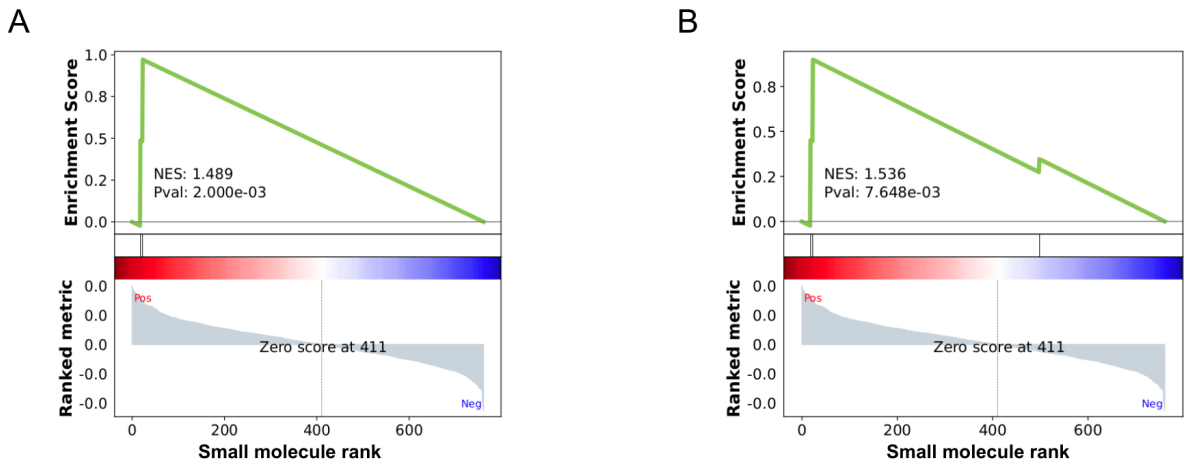
RMND5B -1	ES=0.81 NES=1.23 p_{os}=8.56x10^{-2}	ES=-0.80 NES=-1.07 p_{os}=7.99x10^{-1}	ES=1.00 NES=1.33 p_{os}=3.07x10^{-3}	ES=0.44 NES=1.54 p_{os}=1.51x10^{-2}	ES=-0.27 NES=-0.68 p_{os}=4.35x10^{-1}
DCTN5 -1	ES=0.78 NES=1.20 p_{os}=1.16x10^{-1}	ES=0.98 NES=1.33 p_{os}=1.52x10^{-2}	ES=-0.72 NES=-0.97 p_{os}=7.2x10^{-1}	ES=0.36 NES=1.25 p_{os}=7.78x10^{-2}	ES=0.24 NES=0.58 p_{os}=5.3x10^{-1}
CLEC4E -1	ES=-0.39 NES=-0.61 p_{os}=9.34x10^{-1}	ES=0.60 NES=0.81 p_{os}=7.82x10^{-1}	ES=-0.61 NES=-0.81 p_{os}=6.20x10^{-1}	ES=0.35 NES=1.25 p_{os}=7.78x10^{-2}	ES=0.30 NES=0.75 p_{os}=6.06x10^{-1}

ES - enrichment score
NES - normalized enrichment score
p_{os} - one-sided enrichment p-values (for anti-suicide and drugs, associated with decreased suicide rate, the hypotheses of positive enrichment were tested; for the drugs, associated with an increase in suicide rates, the hypothesis of negative enrichment was tested)



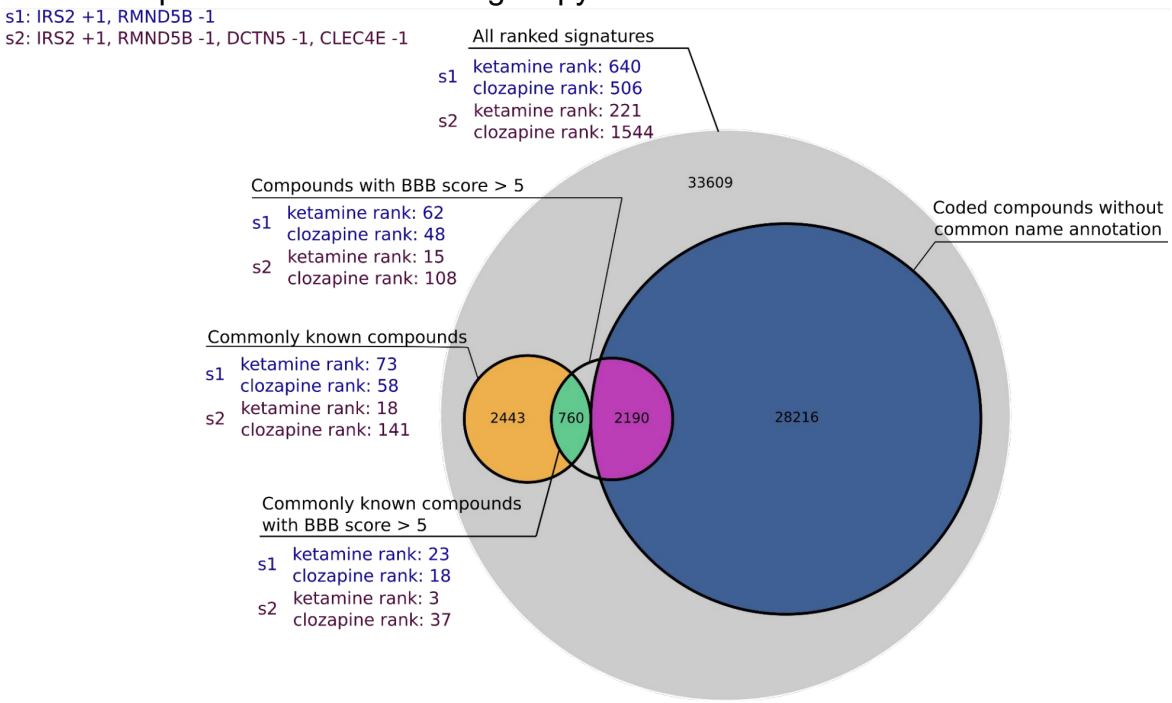
Supplementary Fig. 4. Plots of enrichment of the sets of known antisuicidal drugs (ketamine and clozapine) with addition of lithium chloride

based on the signature s1 (A) and s2 (B). The plots are obtained with gseapy.



Supplementary Fig. 5. Plots of enrichment of the sets of known antisuicidal drugs (ketamine and clozapine) without (A) and with (B) addition of lithium chloride among the commonly known small molecules (annotated with common names in the L1000 metadata) with BBB score > 5 based on the signature s1.

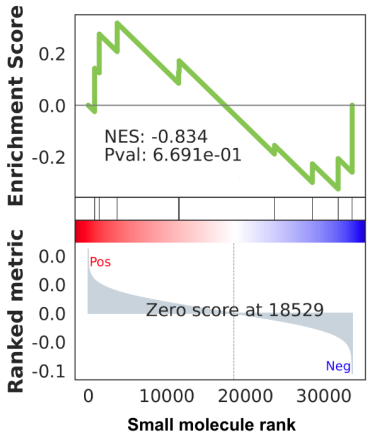
The plots are obtained with gseapy.



Supplementary Fig. 6. Ranks of ketamine and clozapine in the subsets of the SigCom L1000 Consensus Signatures dataset in s1- and s2- based prioritizations.

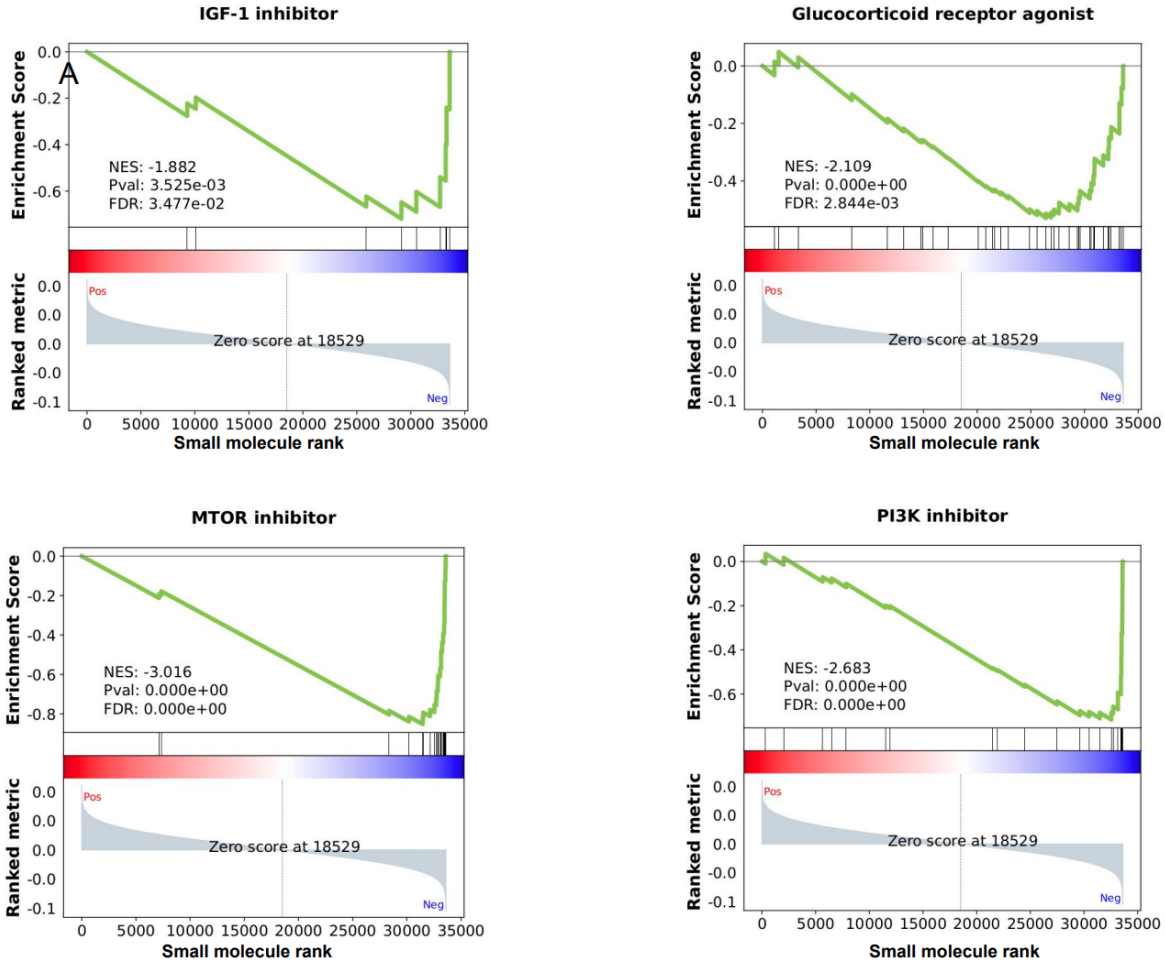
Supplementary Table 8. Comparison of 23 antipsychotic drugs and clomipramine in LINCS L1000 by their negative cosine similarities to the whole TWAS, IRS2, and RMND5B signatures.

drug	whole TWAS signature s1 (IRS2 +1; RMND5B -1)	whole TWAS signature s2 (IRS2 +1; RMND5B -1; DCTN5 -1; CLEC4E -1)	**IRS2**	**RMND5B**
quetiapine	0.035 (rank 1)	0.024 (rank 1)	0.037 (rank 1)	0.012 (rank 5)
clozapine	0.032 (rank 2)	0.020 (rank 2)	0.025 (rank 3)	0.020 (rank 1)
clomipramine	0.024	0.016	0.017	0.018
thioproperazine	0.023	0.018	0.031 (rank 2)	0.001
aripiprazole	0.016	0.012	0.018	0.005
haloperidol	0.016	0.013	0.019	0.004
cariprazine	0.014	0.005	0.012	0.008
risperidone	0.014	0.010	0.007	0.013
olanzapine	0.010	0.007	-0.001	0.016
mesoridazine	0.010	0.009	0.021	-0.007
lurasidone	0.009	0.008	0.021	-0.008
brexpiprazole	0.008	0.005	0.008	0.003
remoxipride	0.007	0.008	0.001	0.008
asenapine	0.006	0.007	0.015	-0.006
fluspirilene	-0.001	0.004	-0.002	0.001
melperone	-0.001	0.003	-0.003	0.002
sertindole	-0.006	-0.003	-0.016	0.008
loxapine	-0.013	-0.003	-0.024	0.006
prochlorperazine	-0.017	-0.015	-0.031	0.007
blonanserin	-0.017	-0.015	-0.012	-0.011
iloperidone	-0.017	-0.014	-0.020	-0.005
thioridazine	-0.018	-0.016	-0.023	-0.003
thiothixene	-0.027	-0.017	-0.030	-0.008
perphenazine	-0.031	-0.025	-0.045	0.001



Supplementary Fig. 7. Plot of enrichment of the set of 9 antidepressants (citalopram, fluvoxamine, paroxetine, fluoxetine, sertraline, venlafaxine, mirtazapine, nefazodone, bupropion) which were assigned the black box label by FDA based on Hammad et al., 2006 in the small molecule prioritization based on the signature s1.

The plot is obtained with gseapy

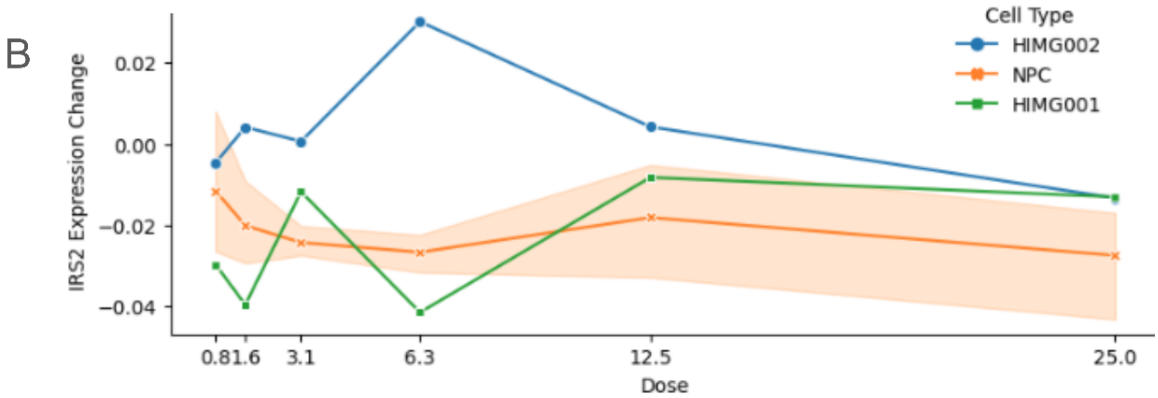


Supplementary Fig. 8. Plots of significant enrichments of the small molecule mechanisms of action in the prioritization based on s1.

A

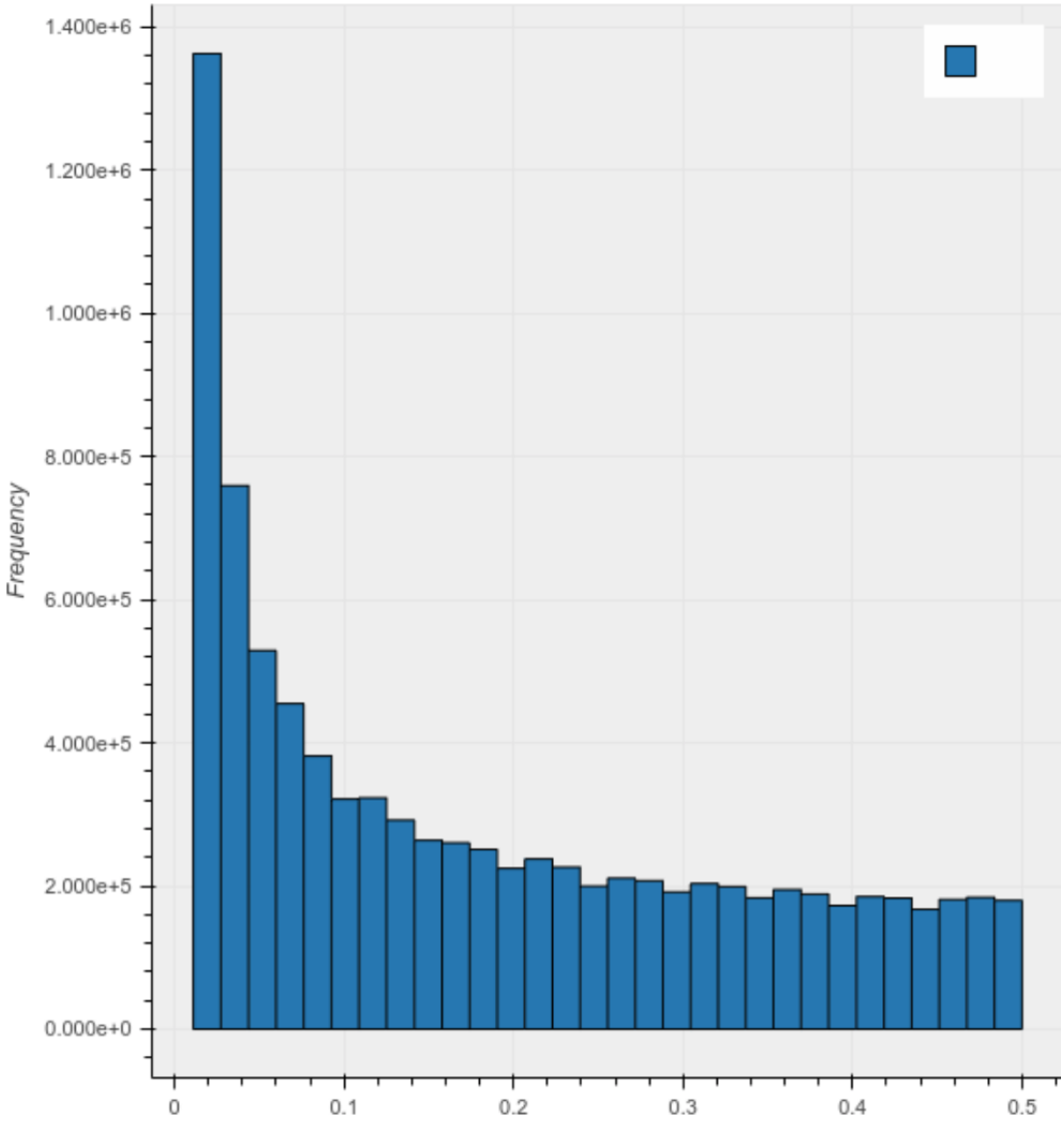
sig_id	pert_dose	pert_idose	pert_itime	cell_iname	IRS2
CEGS002_HIMG001_24H:J12	0.8	0.74 uM	24 h	HIMG001	-0.029719
CEGS002_HIMG001_24H:J11	1.6	1.67 uM	24 h	HIMG001	-0.039669
CEGS002_HIMG001_24H:J10	3.1	3.33 uM	24 h	HIMG001	-0.011780
CEGS002_HIMG001_24H:J09	6.3	6.66 uM	24 h	HIMG001	-0.041532
CEGS002_HIMG001_24H:J08	12.5	12.5 uM	24 h	HIMG001	-0.008229
CEGS002_HIMG001_24H:J07	25.0	25 uM	24 h	HIMG001	-0.013050
CEGS002_HIMG002_24H:J12	0.8	0.74 uM	24 h	HIMG002	-0.004634
CEGS002_HIMG002_24H:J11	1.6	1.67 uM	24 h	HIMG002	0.004167
CEGS002_HIMG002_24H:J10	3.1	3.33 uM	24 h	HIMG002	0.000653
CEGS002_HIMG002_24H:J09	6.3	6.66 uM	24 h	HIMG002	0.030195
CEGS002_HIMG002_24H:J08	12.5	12.5 uM	24 h	HIMG002	0.004243
CEGS002_HIMG002_24H:J07	25.0	25 uM	24 h	HIMG002	-0.013320
CEGS001_NPC.8330_24H:J12	0.8	0.74 uM	24 h	NPC	-0.028894
CEGS001_NPC.215_24H:J12	0.8	0.74 uM	24 h	NPC	-0.025023
CEGS001_NPC.170_24H:J12	0.8	0.74 uM	24 h	NPC	-0.024770
CEGS001_NPC.179_24H:J12	0.8	0.74 uM	24 h	NPC	-0.001226
CEGS001_NPC.177_24H:J12	0.8	0.74 uM	24 h	NPC	0.022132
CEGS001_NPC.177_24H:J11	1.6	1.67 uM	24 h	NPC	-0.034560
CEGS001_NPC.8330_24H:J11	1.6	1.67 uM	24 h	NPC	-0.027597
CEGS001_NPC.170_24H:J11	1.6	1.67 uM	24 h	NPC	-0.022637
CEGS001_NPC.179_24H:J11	1.6	1.67 uM	24 h	NPC	-0.012159
CEGS001_NPC.215_24H:J11	1.6	1.67 uM	24 h	NPC	-0.003672
CEGS001_NPC.170_24H:J10	3.1	3.33 uM	24 h	NPC	-0.028096
CEGS001_NPC.177_24H:J10	3.1	3.33 uM	24 h	NPC	-0.027736
CEGS001_NPC.8330_24H:J10	3.1	3.33 uM	24 h	NPC	-0.025708
CEGS001_NPC.215_24H:J10	3.1	3.33 uM	24 h	NPC	-0.023382
CEGS001_NPC.179_24H:J10	3.1	3.33 uM	24 h	NPC	-0.016547
CEGS001_NPC.177_24H:J09	6.3	6.66 uM	24 h	NPC	-0.036243
CEGS001_NPC.170_24H:J09	6.3	6.66 uM	24 h	NPC	-0.027367
CEGS001_NPC.215_24H:J09	6.3	6.66 uM	24 h	NPC	-0.025389
CEGS001_NPC.8330_24H:J09	6.3	6.66 uM	24 h	NPC	-0.024242
CEGS001_NPC.179_24H:J09	6.3	6.66 uM	24 h	NPC	-0.020156
CEGS001_NPC.170_24H:J08	12.5	12.5 uM	24 h	NPC	-0.043004
CEGS001_NPC.8330_24H:J08	12.5	12.5 uM	24 h	NPC	-0.027837
CEGS001_NPC.179_24H:J08	12.5	12.5 uM	24 h	NPC	-0.013989
CEGS001_NPC.177_24H:J08	12.5	12.5 uM	24 h	NPC	-0.007691
CEGS001_NPC.215_24H:J08	12.5	12.5 uM	24 h	NPC	0.001842
CEGS001_NPC.177_24H:J07	25.0	25 uM	24 h	NPC	-0.057415
CEGS001_NPC.8330_24H:J07	25.0	25 uM	24 h	NPC	-0.027440
CEGS001_NPC.179_24H:J07	25.0	25 uM	24 h	NPC	-0.020097
CEGS001_NPC.170_24H:J07	25.0	25 uM	24 h	NPC	-0.016425
CEGS001_NPC.215_24H:J07	25.0	25 uM	24 h	NPC	-0.015989

B



Supplementary Fig. 9. Variation of ketamine effect on IRS2 expression among individual L1000 signatures.

(A) Information on individual ketamine signatures in L1000. (B) Dosage-dependent variation in IRS2 expression change in reponse to ketamine treatment across cell lines. sig_id - ketamine L1000 signature ID, pert_dose - treatment dose, pert_itime - time after small molecule administration, cell_iname - name of cell line, IRS2 - expression change of IRS2 gene.



Supplementary Fig. 10. Distribution of minor allele frequencies (MAF) across 8919012 variants with MAF>0.01 in the studied cohort.

List of the supplementary tables attached in a separate .xlsx file

Supplementary Table 5. Small molecule prioritization scores based on the s1 signature (IRS2, RMND5B) with annotation from L1000 SigCom LINCS Metadata and BBB scores*.

Supplementary Table 6. Small molecule prioritization scores base on the s2 signature (IRS2, RMND5B, DCTN5, CLEC4E) and single-gene signatures with annotation from L1000 SigCom LINCS Metadata and BBB scores*.

Supplementary Table 9. Results of enrichment of small molecule mechanisms of action in the drug prioritization based on s1 (IRS2, RMND5B).

Supplementary Table 10. Results of enrichment of small molecule drug targets in the drug prioritization based on s1 (IRS2, RMND5B).

Supplementary Table 11. Individual-level TWAS results of suicide attempt count.

Supplementary Table 12. Individual-level TWAS results of C-SSRS suicidal behavior.

Supplementary Table 13. Individual-level TWAS results of suicide attempt presence.