**Translating GWAS Findings Into Therapies For Depression And Anxiety Disorders: Gene-Set Analyses Reveals Enrichment Of Psychiatric Drug Classes and Implications for Drug Repositioning**

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**Supplementary Tables**

Please refer to <https://drive.google.com/open?id=1Yzr4uxKCZ2aA4ePfZ6ChKmeHr9zmq6lu> for Tables S5-7, S10-11.

Table S1 Enrichment of repositioning hits derived from GWAS of depression-related phenotypes, with gene-sets **derived from *PubChem/ChEMBL only***

(***FDR-adjusted*** *p*-values presented)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Disorder | MDD-con Self | MDD-con Compet | MDD2018 sef | MDD2018 compet | DepSym Self | DepSym Compet |
| *ATC classification* |  |  |  |  |  |  |
| Antipsychotics | **3.69E-04** | **8.78E-04** | **0.001** | 0.149 | 0.622 | **0.017** |
| Antidepressants or anxiolytics | 0.138 | 0.322 | **0.014** | 0.476 | 1.000 | 0.251 |
| All ATC psychiatric drugs | **0.003** | **0.017** | **2.47E-05** | 0.170 | 1.000 | **0.005** |
|  |  |  |  |  |  |  |
| *MEDI-HPS* |  |  |  |  |  |  |
| Schizophrenia and Bipolar | **2.93E-04** | **8.83E-04** | **0.022** | 0.665 | 0.973 | *0.051* |
| Anxiety and Depression | **0.044** | 0.141 | **0.003** | 0.332 | 1.000 | *0.093* |
| All psychiatric drugs | **0.003** | **0.017** | **5.80E-04** | 0.433 | 0.994 | **0.002** |
|  |  |  |  |  |  |  |
| *ClinicalTrial.gov* |  |  |  |  |  |  |
| Anxiety disorders | **2.37E-04** | **0.020** | **5.89E-04** | 0.150 | 0.600 | **5.11E-04** |
| Depression | **0.003** | 0.230 | **1.37E-05** | **0.037** | 1.000 | **0.004** |
| Bipolar disorder | **0.007** | 0.211 | **0.010** | 0.414 | 0.889 | **0.014** |
| Schizophrenia | **7.70E-05** | **0.013** | **2.18E-04** | 0.155 | 0.973 | **0.002** |
| Anxiety + Depression | **6.17E-04** | 0.125 | **1.17E-06** | **0.021** | 0.994 | **7.62E-04** |
| Sczhiophrenia + Bipolar | **1.90E-05** | **0.006** | **5.96E-05** | 0.102 | 0.973 | **8.97E-04** |
| All psychiatric drugs | **3.79E-06** | **0.012** | **2.41E-07** | **0.044** | 1.000 | **0.003** |

Please also refer to legends of Table 1 (main text). Note that we present the ***FDR-adjusted*** *p*-values, which are already corrected for multiple testing. **Gene-sets were derived from the entire DSigDB.** We used three databases to define psychiatric drug categories. ATC and MEDI-HPS records known psychiatric drugs while clinicalTrial.gov records the drugs that were tested in clinical trials. Test results with *FDR* < 0.05 are in bold. Results with *FDR* between 0.05 and 0.1 are in italics.

Self: self-contained test; Compet, competitive test. In the context of gene-set analysis, the self-contained test examines the null hypothesis that none of the genes in the gene-set are associated with the phenotype, while the competitive test examines the null hypothesis that genes in the set are *no* more strongly associated with the phenotype than those outside the set. MDD-CONVERGE, MDD with GWAS data from the CONVERGE Consortium; MDD with GWAS data from the Psychiatric Genomics Consortium; DepSym, GWAS of depressive symptoms from the Social Science Genetics Association Consortium (SSGAC).

Table S2 Enrichment of repositioning hits derived from GWAS of anxiety and neuroticism, with gene-sets **derived from *PubChem/ChEMBL only***

(**FDR-adjusted** *p*-values presented)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Disorder | AnxietyCC Self | AnxietyCC Compet | Neurotic Self | Neurotic Compet |
| *ATC classification* |  |  |  |  |
| Antipsychotics | **8.65E-06** | **7.44E-07** | **2.40E-11** | **2.61E-08** |
| Antidepressants or anxiolytics | **0.035** | **0.011** | **2.18E-04** | **0.010** |
| All ATC psychiatric drugs | **0.003** | **2.37E-04** | **5.35E-13** | **3.20E-07** |
|  |  |  |  |  |
| *MEDI-HPS* |  |  |  |  |
| Schizophrenia and Bipolar | **0.010** | **0.002** | **6.17E-04** | **0.022** |
| Anxiety and Depression | **0.010** | **0.002** | **3.82E-04** | **0.037** |
| All psychiatric drugs | **0.006** | **3.69E-04** | **3.18E-04** | *0.072* |
|  |  |  |  |  |
| *ClinicalTrial.gov* |  |  |  |  |
| Anxiety disorders | **0.046** | **0.009** | **0.040** | 0.558 |
| Depression | *0.072* | **0.010** | 0.443 | 1.000 |
| Bipolar disorder | 0.370 | 0.125 | 0.138 | 0.781 |
| Schizophrenia | *0.072* | **0.008** | **0.007** | 0.410 |
| Anxiety + Depression | 0.105 | **0.014** | 0.322 | 1.000 |
| Sczhiophrenia + Bipolar | *0.063* | **0.006** | **0.003** | 0.297 |
| All psychiatric drugs | **0.047** | **0.002** | **0.009** | 0.777 |

Please also refer to legends of Table S1.

Table S3 Enrichment of repositioning hits derived from meta-analyzed GWAS results, with gene-sets **derived from *PubChem/ChEMBL only***

(**FDR-adjusted** *p*-values presented)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Disorder | Brown Self | Brown Compet | Simes Self | Simes Compet |
| *ATC classification* |  |  |  |  |
| Antipsychotics | **2.97E-07** | **2.97E-07** | **2.70E-04** | **5.96E-05** |
| Antidepressants or anxiolytics | **0.025** | **0.030** | 0.132 | *0.064* |
| All ATC psychiatric drugs | **1.51E-05** | **1.51E-05** | **0.008** | **0.001** |
|  |  |  |  |  |
| *MEDI-HPS* |  |  |  |  |
| Schizophrenia and Bipolar | **5.80E-04** | **5.89E-04** | **0.017** | **0.006** |
| Anxiety and Depression | **0.003** | **0.004** | **0.035** | **0.011** |
| All psychiatric drugs | **7.48E-04** | **7.65E-04** | **0.017** | **0.003** |
|  |  |  |  |  |
| *ClinicalTrial.gov* |  |  |  |  |
| Anxiety disorders | **0.003** | **0.003** | **0.046** | **0.013** |
| Depression | *0.054* | *0.072* | *0.090* | **0.022** |
| Bipolar disorder | **0.037** | **0.046** | 0.102 | **0.035** |
| Schizophrenia | **0.002** | **0.002** | **0.018** | **0.003** |
| Anxiety + Depression | **0.021** | **0.029** | *0.072* | **0.015** |
| Sczhiophrenia + Bipolar | **9.57E-04** | **0.001** | **0.011** | **0.002** |
| All psychiatric drugs | **0.003** | **0.004** | **0.044** | **0.004** |

Please also refer to legends of Table S1.

Table S4 Enrichment *p*-values of repositioning hits derived from GWAS of **MDD-PGC-2012**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Gene-set from whole DSigDB | |  | Gene-set from PubChem and ChEMBL only | |
| Disorder | MDD-PGC-2012 Self | MDD-PGC-2012 Compet |  | MDD-PGC-2012 Self | MDD-PGC-2012 Compet |
| *ATC classification* |  |  |  |  |  |
| Antipsychotics | 1.000 | 0.998 |  | 1.000 | 1.000 |
| Antidepressants or anxiolytics | 1.000 | 0.982 |  | 1.000 | 0.748 |
| All ATC psychiatric drugs | 1.000 | 0.998 |  | 1.000 | 0.971 |
|  |  |  |  |  |  |
| *MEDI-HPS* |  |  |  |  |  |
| Schizophrenia and Bipolar | 1.000 | 1.000 |  | 1.000 | 0.999 |
| Anxiety and Depression | 1.000 | 0.999 |  | 1.000 | 0.967 |
| All psychiatric drugs | 1.000 | 1.000 |  | 1.000 | 0.998 |
|  |  |  |  |  |  |
| *ClinicalTrial.gov* |  |  |  |  |  |
| Anxiety disorders | 1.000 | 0.992 |  | 1.000 | 0.948 |
| Depression | 1.000 | 0.999 |  | 1.000 | 0.995 |
| Bipolar disorder | 1.000 | 0.997 |  | 1.000 | 0.997 |
| Schizophrenia | 1.000 | 0.996 |  | 1.000 | 0.982 |
| Anxiety + Depression | 1.000 | 1.000 |  | 1.000 | 0.997 |
| Sczhiophrenia + Bipolar | 1.000 | 0.996 |  | 1.000 | 0.986 |
| All psychiatric drugs | 1.000 | 1.000 |  | 1.000 | 1.000 |

***Please refer to*** [***https://drive.google.com/open?id=1Yzr4uxKCZ2aA4ePfZ6ChKmeHr9zmq6lu***](https://drive.google.com/open?id=1Yzr4uxKCZ2aA4ePfZ6ChKmeHr9zmq6lu) ***for Tables S5-7, S10-11.***

Table S5 Enrichment test results of all ATC (level 3) drug classes *(gene-sets derived from the whole DSigDB)*

[see attached excel file]

Legends: Self: self-contained test; Compet, competitive test. FDR-adjusted p-values are presented. We only present the drug categories with FDR-adjusted *p* <0.2 in either the self-contained or competitive tests. By default, the drug categories are ranked in ascending order of the FDR-adjusted *p* in the competitive test.

The definitions of self-contained and competitive tests are very similar to those in Tables 1-3. In the context the above “drug-group” analysis, the self-contained test examines the null hypothesis that none of the drugs in the group are associated with repositioning potential, while the competitive test examines the null hypothesis that drugs inside the group are *no* more significantly associated with repositioning potential than those outside the group.

Test results with *FDR* < 0.05 are in bold. Results with *FDR* between 0.05 and 0.1 are in italics.

**The excel file contains *7 tabs*,** each showing the results for a different depression/anxiety phenotype.

Table S6 Enrichment test results of all ATC (level 3) drug classes *(gene-sets derived from PubChem/ChEMBL)*

[see attached excel file]

Please refer to the descriptions of Table S5 above.

**The excel file contains *7 tabs*,** each showing the results for a different depression/anxiety phenotype.

Table S7 Overlap of the top-ranked ATC categories.

[see attached excel file]

This file describes the extent of overlap in the top-ranked ATC categories. In table S7a, all the top-ranked drug classes in Table 4-5 (main text) are listed with the number and names of the constituent drugs. Table S7b shows the presence and extent of overlap. The number of overlap is shown, and we also compute “normalized” overlap counts. This is obtained by dividing the absolute count of overlap by the number of drugs in each category. Overlap >30% are highlighted in blue.

Table S8 Correlations between p-values of drug candidates and the number of research articles supporting association with depression/anxiety (based on gene-sets derived ***from the whole DSigDB database***)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Correlation Estimate | |  | FDR-adjusted *p* |  |
|  | Spearman’s rho | Kendall’s tau | Spearman | Kendall | Wilcoxon |
|  |  |  | correlation | correlation | Rank-sum |
| MDD-CON | -0.0435 | -0.0344 | **9.17E-04** | **9.17E-04** | **0.00121** |
| MDD-2018 | -0.0456 | -0.0361 | **6.50E-04** | **6.50E-04** | **7.44E-04** |
| Depressive symptoms | -0.0743 | -0.0588 | **9.08E-08** | **9.08E-08** | **9.08E-08** |
| Anxiety Disorder | -0.0572 | -0.0452 | **3.49E-05** | **3.49E-05** | **1.10E-04** |
| Neuroticism | -0.0473 | -0.0374 | **4.73E-04** | **4.73E-04** | **9.52E-04** |
| Simes p | -0.0837 | -0.0662 | **3.15E-09** | **3.15E-09** | **7.35E-09** |
| Brown p | -0.0914 | -0.0724 | **2.01E-10** | **2.01E-10** | **7.63E-10** |

The ***FDR-adjusted*** *p*-values are presented, which are already corrected for multiple testing. Test results with *FDR* < 0.05 are in bold. Results with *FDR* between 0.05 and 0.1 are in italics.

The search was conducted in PubMed. Wilcoxon rank-sum test assessed the difference in *p*-values for drugs having no article support versus those with at least one article support.

A *negative* correlation suggests that the drugs with stronger significance from our analysis (i.e. lower p-values) tend to have greater number of research articles supporting their association with depressive or anxiety disorders.

Table S9 Correlations between p-values of drug candidates and the number of research articles supporting association with depression/anxiety (based on gene-sets derived ***from PubChem/ChEMBL only***)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Correlation Estimate | |  | FDR-adjusted *p* |  |
|  | Spearman’s rho | Kendall’s tau | Spearman | Kendall | Wilcoxon |
|  |  |  | correlation | correlation | Rank-sum |
| MDD-CON | -0.013 | -0.011 | 0.366 | 0.366 | 0.435 |
| MDD-2018 | -0.076 | -0.059 | **5.92E-03** | **5.92E-03** | **7.77E-03** |
| Depressive symptoms | -0.079 | -0.061 | **5.92E-03** | **5.92E-03** | **5.92E-03** |
| Anxiety Disorder | -0.026 | -0.020 | 0.228 | 0.228 | 0.342 |
| Neuroticism | 0.031 | 0.024 | 0.940 | 0.940 | 0.949 |
| Simes p | -0.051 | -0.040 | **0.041** | **0.041** | *0.087* |
| Brown p | -0.051 | -0.040 | **0.041** | **0.041** | *0.099* |

The ***FDR-adjusted*** *p*-values are presented, which are already corrected for multiple testing. Test results with *FDR* < 0.05 are in bold. Results with *FDR* between 0.05 and 0.1 are in italics.

TableS10 Top 20 repositioning candidates with manual curations ***(gene-sets derived from the entire DSigDB)***

[see attached excel file]

Note that there are ***7 tabs*,** each containing the results for one phenotype. We also list out the number and the names of the constituent genes in each gene-set.

TableS11 Top 20 repositioning candidates with manual curations ***(gene-sets derived*** ***from PubChem/ChEMBL only)***

[see attached excel file]

Note that there are ***7 tabs*,** each containing the results for one phenotype. We also list out the number and the names of the constituent genes in each gene-set.