*Supplementary Materials*

Genetic Overlap Between Alzheimer’s Disease and Bipolar Disorder Implicates the MARK2 and VAC14 Genes

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# Supplementary methods

## Conditional QQ-plots

A conditional Q-Q plot compares the quantiles of two probability distributions. We calculated the empirical cumulative distribution function (ecdf) of nominal p-values of all SNPs for the first trait. For the second trait, we stratified SNPs according to defined p-value thresholds; p<1 (all SNPs), <10-1, <10-2 and <10-3. We then plotted the nominal p-values, denoted *p*, on the y-axis, and 1-ecdf, denoted *q*, on the x-axis. To emphasize the tail probabilities of both distributions, we transformed the y and x axes to –log10(p) and –log10(q). This procedure was conducted with AD as the first and BIP as the second trait and *vice versa*.

Pleiotropic enrichment is present if the degree of leftward shift from the expected null line for the first trait is dependent on the degree of association with the second trait. A leftward shift from the expected null line in Q-Q plots translates to a reduction in the false discovery rate (FDR), as explained in the next section.

## Conditional false discovery rate

We translated the enrichment observed in QQ-plots to conditional false discovery rate (FDR) as outlined by Andreassen et al. (2013). A given p-value cut-off relates to FDR according to the equation

where π0 denotes the proportion of null SNPs, F0 denotes the null cumulative distribution function (cdf), and F(p) denotes the cdf of all SNPs. π0 is in GWAS of most complex traits close to one. F0 is a standard uniform distribution given that all intervals of the cdf are equally probable under the null hypothesis. F(p) is estimated by the empirical cdf, denoted q, by the equation

where Np denotes the number of SNPs with p-values < p, and N denotes the total number of SNPs. Incorporating these assumptions into the equation (1) gives

By conducting a logarithmic transformation and dividing by minus one on each side of equation (3) we get



which demonstrates that the horizontal shift in QQ-plots (i.e. an increase in q relative to p) relates negatively to FDR. The conditional FDR is defined as “the posterior probability that a given SNP is null for the first trait given that the p-values for both traits are as small or smaller than the observed p-values” (Andreassen et al., 2015), as given by

1. ,

where p1 denotes the p-value of one trait, p2 denotes the p-value the other trait, F(p1|p2) denotes the conditional cdf, and π0(p2) denotes the conditional proportion of null SNPs for one trait given that the p-values for the other trait are < p2. The conditional FDR is conservatively estimated if π0(p2) is set to 0. F(p1|p2) can be replaced by the empirical conditional cdf. Thus, we can calculate the conditional FDR value for one trait, trait1, conditioned on p-values for another trait, trait2, for each SNP. The values are denoted condFDR(trait1|trait2).

## Conjunctional false discovery rate

The conjunctional FDR is defined as the “the posterior probability that a given SNP is null for the first trait given that the p-values for both traits are as small or smaller than the observed p-values” (Andreassen et al., 2015), as given by

1. ,

where π0(p1,p2) denotes the proportion of SNPs null for both traits at the same time, F0(p1,p2) denotes the joint null cfd, and F(p1,p2) denotes the joint cfd. Equation (6) can be conservatively estimated by conditional empirical cdfs formulated by

as explained by Andreassen et al. (2013). Thus, we can calculate the conjuntional FDR value for both traits for each SNP. These values are denoted conjFDR(trait1&trait2).

## Cross-trait linkage disequilibrium score regression

In the case of an inflated signal in test statistics from a GWAS, single-trait linkage disequilibrium score regression (LDSR) distinguishes the effect of polygenicity from the effect of confounding (e.g. from population stratification) (Bulik-Sullivan et al., 2015b). Cross-trait LDSR is a simple extension from single-trait LDSR that estimates the overall degree of genetic overlap between two traits (Bulik-Sullivan et al., 2015a).

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# Supplementary tables

Supplementary table 1: SNPs with related genes associated with Alzheimer’s disease (AD) conditioned on their association with bipolar disorder (BIP) at a conditional false discovery rate <0.01.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Locus no. | SNP | Closest gene | Chr | Position | P-value(AD) | P-value(BIP) | FDR(AD) | condFDR(AD|BIP) |
| 1 | rs6656401 | CR1 | 1 | 207692049 | 7.73E-15 | 5.04E-01 | 6.24E-06 | 8.35E-06 |
| 2 | rs6431219 | BIN1 | 2 | 127862133 | 7.63E-13 | 8.44E-01 | 6.24E-06 | 1.26E-05 |
| 2 | rs12617835 | LOC105373605 | 2 | 127886416 | 7.70E-13 | 3.23E-01 | 6.24E-06 | 5.89E-06 |
| 2 | rs56368748 | LOC105373605 | 2 | 127894098 | 7.16E-11 | 8.57E-01 | 7.25E-06 | 1.55E-05 |
| 3 | rs2878896 | HBEGF | 5 | 139710507 | 9.22E-08 | 9.76E-02 | 1.76E-03 | 2.25E-03 |
| 4 | rs77212406 | HLA-DRB5 | 6 | 32578209 | 6.84E-09 | 1.00E-01 | 2.57E-04 | 2.10E-04 |
| 5 | rs9381563 | CD2AP | 6 | 47432637 | 5.30E-09 | 5.86E-01 | 2.09E-04 | 5.45E-04 |
| 6 | rs11763230 | EPHA1-AS1 | 7 | 143108841 | 2.11E-11 | 4.47E-01 | 6.24E-06 | 7.60E-06 |
| 6 | rs12540656 | EPHA1-AS1 | 7 | 143117919 | 1.17E-08 | 3.46E-01 | 3.80E-04 | 7.72E-04 |
| 7 | rs28834970 | PTK2B | 8 | 27195121 | 3.27E-09 | 7.26E-01 | 1.38E-04 | 4.15E-04 |
| 8 | rs9331896 | CLU | 8 | 27467686 | 9.63E-17 | 2.48E-01 | 6.24E-06 | 4.79E-06 |
| 9 | rs71475924 | NDUFS3 | 11 | 47603006 | 1.44E-06 | 3.28E-03 | 1.50E-02 | 3.23E-03\* |
| 10 | rs1530914 | MS4A4A | 11 | 60028940 | 5.60E-11 | 4.10E-01 | 6.24E-06 | 7.11E-06 |
| 11 | rs659023 | PICALM | 11 | 85824859 | 1.17E-12 | 5.03E-01 | 6.24E-06 | 8.34E-06 |
| 12 | rs11218343 | SORL1 | 11 | 121435587 | 4.98E-11 | 7.19E-01 | 6.24E-06 | 1.11E-05 |
| 13 | rs10143128 | RPS6KL1 | 14 | 75398902 | 1.00E-07 | 3.26E-01 | 1.88E-03 | 4.60E-03 |
| 14 | rs12590654 | SLC24A4 | 14 | 92938855 | 4.10E-08 | 2.16E-01 | 9.71E-04 | 1.72E-03 |
| 15 | rs12597717 | MTSS1L | 16 | 70702758 | 9.85E-06 | 1.25E-04 | 4.78E-02 | 5.57E-03\* |
| 16 | rs8093731 | DSG2 | 18 | 29088958 | 4.63E-08 | 6.46E-01 | 1.06E-03 | 3.47E-03 |
| 17 | rs4147929 | ABCA7 | 19 | 1063443 | 1.70E-09 | 5.04E-01 | 7.68E-05 | 1.81E-04 |
| 18 | rs17878252 | FBXO46 | 19 | 46234155 | 7.87E-08 | 1.38E-01 | 1.56E-03 | 2.37E-03 |
| 19 | rs3865444 | CD33 | 19 | 51727962 | 5.12E-08 | 3.52E-01 | 1.14E-03 | 2.73E-03 |

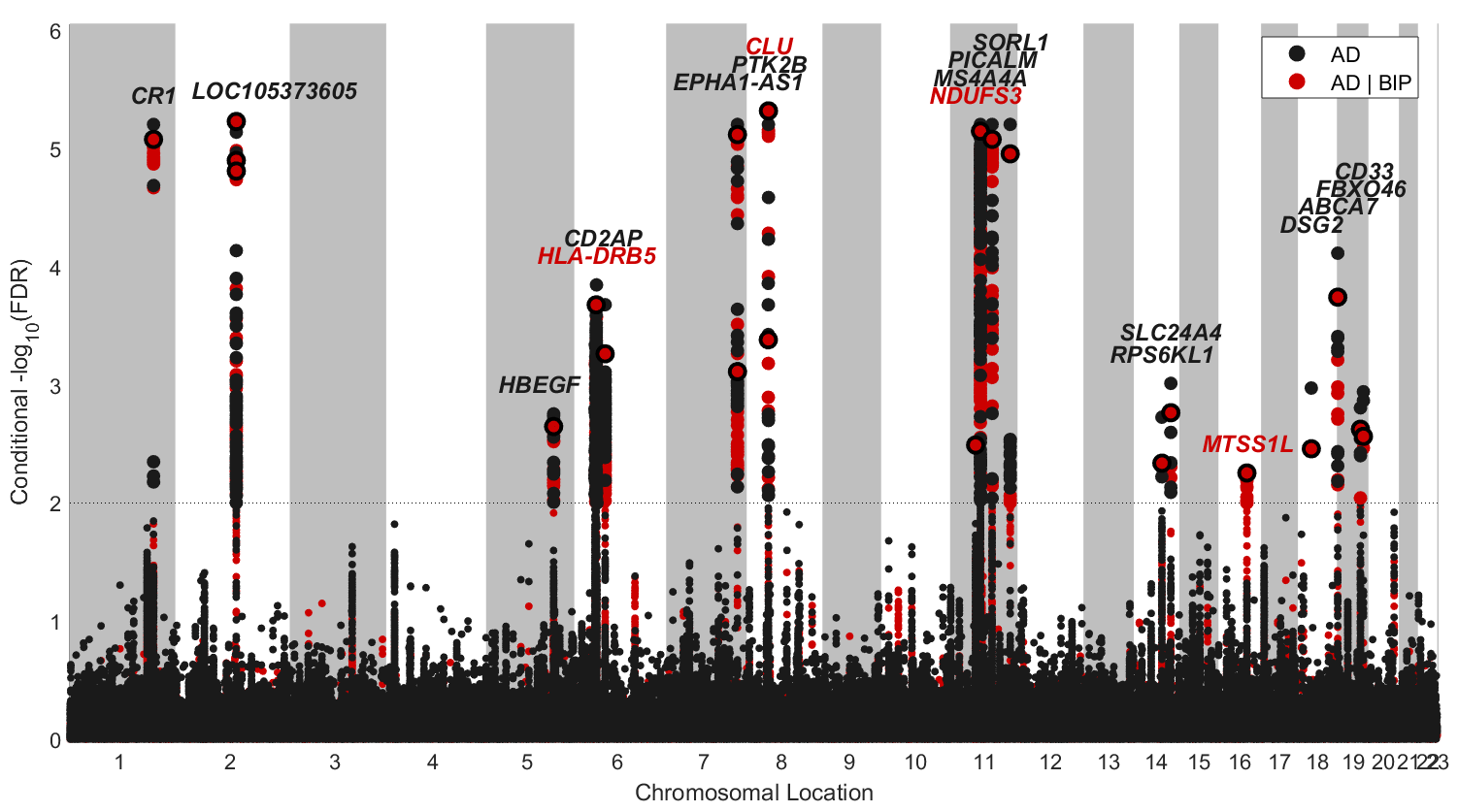
\* loci enriched for associations with BIP (condFDR(AD|BIP) < FDR(AD)) not detected by conventional methods in original GWAS (p-value(AD)>5 x 10-8)

Supplementary table 2: SNPs with related genes associated with bipolar disorder (BIP) conditioned on their association with Alzheimer’s disease (AD) at a conditional false discovery rate <0.01.

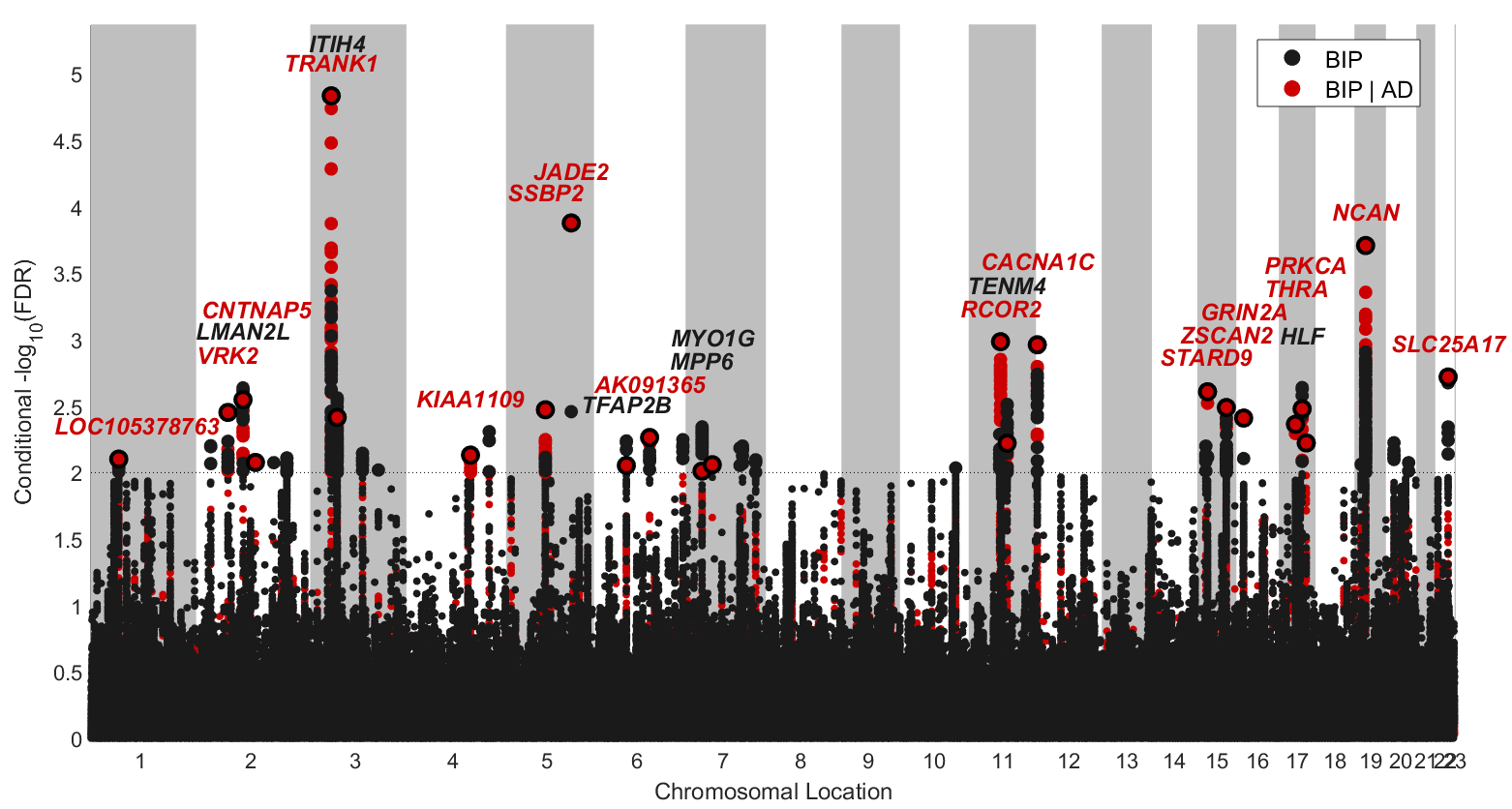
|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Locus no. | SNP | Closest gene | Chr | Position | P-value(BIP) | P-value(AD) | FDR(BIP) | condFDR(BIP|AD) |
| 1 | rs1889778 | LOC105378763 | 1 | 61066279 | 2.32E-07 | 5.49E-02 | 9.85E-03 | 7.91E-03\* |
| 2 | rs57681866 | VRK2 | 2 | 57975714 | 5.00E-08 | 9.21E-02 | 5.81E-03 | 3.53E-03 |
| 3 | rs4619651 | LMAN2L | 2 | 97416153 | 5.97E-09 | 5.12E-01 | 2.30E-03 | 2.83E-03 |
| 4 | rs13011184 | CNTNAP5 | 2 | 125089268 | 9.26E-06 | 5.91E-04 | 3.73E-02 | 8.39E-03\* |
| 5 | rs9834970 | TRANK1 | 3 | 36856030 | 5.53E-14 | 6.68E-01 | 4.28E-04 | 1.46E-05 |
| 6 | rs2071044 | ITIH4 | 3 | 52847601 | 9.10E-09 | 5.01E-01 | 2.74E-03 | 3.84E-03 |
| 7 | rs45605540 | KIAA1109 | 4 | 123141054 | 8.24E-07 | 1.18E-02 | 1.24E-02 | 7.38E-03\* |
| 8 | rs7707981 | SSBP2 | 5 | 80922749 | 2.76E-07 | 1.42E-02 | 1.04E-02 | 3.37E-03\* |
| 9 | rs329319 | JADE2 | 5 | 133906609 | 1.54E-08 | 6.48E-03 | 3.48E-03 | 1.32E-04 |
| 10 | rs55648125 | TFAP2B | 6 | 50816718 | 4.92E-08 | 3.15E-01 | 5.78E-03 | 8.84E-03 |
| 11 | rs2388334 | AK091365 | 6 | 98591622 | 8.62E-08 | 9.36E-02 | 6.99E-03 | 5.45E-03\* |
| 12 | rs12672003 | MPP6 | 7 | 24647222 | 2.87E-08 | 5.72E-01 | 4.65E-03 | 9.74E-03 |
| 13 | rs12538191 | MYO1G | 7 | 44980824 | 1.46E-07 | 1.05E-01 | 8.36E-03 | 8.72E-03 |
| 14 | rs4980532 | RCOR2 | 11 | 63680719 | 8.95E-07 | 5.85E-04 | 1.26E-02 | 1.04E-03\* |
| 15 | rs11237821 | TENM4 | 11 | 79106804 | 1.17E-08 | 6.75E-01 | 3.07E-03 | 6.01E-03 |
| 16 | rs10744560 | CACNA1C | 12 | 2387099 | 2.92E-09 | 3.40E-01 | 1.82E-03 | 1.09E-03 |
| 17 | rs4447398 | STARD9 | 15 | 42904904 | 1.10E-07 | 2.57E-02 | 7.57E-03 | 2.46E-03\* |
| 18 | rs71395455 | ZSCAN2 | 15 | 85153804 | 1.93E-08 | 2.06E-01 | 3.88E-03 | 3.24E-03 |
| 19 | rs11647445 | GRIN2A | 16 | 9926966 | 1.22E-07 | 4.14E-02 | 7.84E-03 | 3.89E-03\* |
| 20 | rs61554907 | THRA | 17 | 38220432 | 4.32E-06 | 3.33E-04 | 2.54E-02 | 4.33E-03\* |
| 21 | rs876720 | HLF | 17 | 53366515 | 8.33E-09 | 4.57E-01 | 2.63E-03 | 3.31E-03 |
| 22 | rs7406066 | PRKCA | 17 | 64313153 | 6.25E-06 | 6.41E-04 | 3.05E-02 | 5.98E-03\* |
| 23 | rs111444407 | NCAN | 19 | 19358207 | 2.40E-10 | 5.61E-01 | 1.24E-03 | 1.96E-04 |
| 24 | rs138321 | SLC25A17 | 22 | 41209304 | 4.69E-09 | 4.09E-01 | 2.11E-03 | 1.91E-03 |

\* loci enriched for associations with AD (condFDR(BIP|AD) < FDR(BIP)) not detected by conventional methods in original GWAS (p-value(BIP)>5 x 10-8)

# Supplementary figures



Supplementary figure 1: Conditional Manhattan plot of loci associated with Alzheimer’s disease at a conditional false discovery rate (condFDR) <0.01.



Supplementary figure 2: Conditional Manhattan plot of loci associated with bipolar disorder (BIP) at a conditional false discovery rate (condFDR) <0.01.

../results/MARK2.pdf

Supplementary figure 3: Expression of the MARK2 gene in different parts of the developing and adult human brain obtained from the Human Brain Transcriptome atlas[[1]](#footnote-1) (Kang et al., 2011) (NCX neocortex, HIP hippocampus, AMY amygdala, STR striatum, MD mediodorsal nucleus of the thalamus, CBC cerebellar cortex).

../results/VAC14.pdf

Supplementary figure 4: Expression of the VAC14 gene in different parts of the developing and adult human brain obtained from the Human Brain Transcriptome atlas[[2]](#footnote-2) (Kang et al., 2011) (NCX neocortex, HIP hippocampus, AMY amygdala, STR striatum, MD mediodorsal nucleus of the thalamus, CBC cerebellar cortex).

# Supplementary references

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Bulik-Sullivan, B., Finucane, H. K., Anttila, V., Gusev, A., Day, F. R., Loh, P.-R., et al. (2015a). An atlas of genetic correlations across human diseases and traits. *Nat. Genet.* 47, 1236–1241.

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Kang, H. J., Kawasawa, Y. I., Cheng, F., Zhu, Y., Xu, X., Li, M., et al. (2011). Spatio-temporal transcriptome of the human brain. *Nature* 478, 483–489.

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1. <http://hbatlas.org> [↑](#footnote-ref-1)
2. <http://hbatlas.org> [↑](#footnote-ref-2)