**Supplementary File**



**Figure S1** Correlation matrix of gene expressions estimated from 13 GTEx brain tissues across all available genes. We here included 11 donators who had complete gene expressions across those tissues. After removing all zero-expressed genes in any donator, we performed the TMM normalization method [[1](#_ENREF_1)] on read counts for the remaining 15,157 genes using the cpm function (with prior count equal to zero and log2 transformation) in the edgeR package [[**2**](#_ENREF_2)]. The correlation matrix was computed in a shrinkage fashion [[3-5](#_ENREF_3)]:  with  the empirical correlation matrix among gene expressions and λ = 0.9.



**Figure S2** Number of missing genes in the TWAS analysis with FUSION across 13 GTEx brain tissues. For example, there are 236 genes having one missing *p*-value, 233 genes having two missing *p*-values; and so forth.



**Figure S3** Estimated statistical power of SCAT when combining two FUSION analyses and one of them is non-significant. Specifically, a two-dimensional vector was generated from a multivariate normal distribution with the mean being (2.5, 0) and the variance matrix being ; and then we produced the p values in terms of the standard normal destitution. That is, here one of the p values obtained from individual FUSION analyses is always non-significant. Here, we clearly find that SCAT encounters a power reduction because redundant p values are combined.



**Figure S4** Estimated statistical power of SCAT under various correlation structures. Here, as done in the simulations in the main text, we obtained p values based on Z values. Specifically, we first obtained the correlation matrix of **Z** values of FUSION (i.e. the **C** matrix) and generated a 13-dimentional multivariate random variable which followed **MVN**(***μ***, **C**); then, we yielded the *p*-value for each marginal random variable by assuming it followed a standard normal distribution. Finally, we combined these *p*-values with SCAT. For a fair comparison, we set each element of***μ*** to be with *T* = 13. Three correlation structures were considered, including the exchangeable structure (**A**), the autoregressive structure (**B**) and the m-dependent structure (**C**). We varied the correlation in these structures to assess the power performance of SCAT.





**Figure S5 (A)** Correlation matrix of *p*-values in -log(10) scale for FUSION from 13 GTEx brain tissues across genes. **(B)** Correlation matrix of Z scores for FUSION from 13 GTEx brain tissues across genes.

(A) (B)



**Figure S6** Upset plot of genes identified by FUSION (i.e. TWAS with single tissue) and SCAT for ALS from 13 GTEx brain tissues across genes. (**A**) the shared genes before the adjustment of multiple comparison; (**B**) the shared genes after the adjustment of multiple comparison. Each bar in the plot represents the number of shared genes discovered in various tissues or detected by SCAT. The Upset plot was created by the R UpSetR package [[6](#_ENREF_6)].

















**Figure S7** LocusZoom plots for eight genes associated with ALS identified by SCAT. Those plots were generated with the online tool at <http://locuszoom.org/> [[7](#_ENREF_7)].

**Table S1** Association studies for ALS in terms of the GWAS catalog

|  |  |  |
| --- | --- | --- |
| year | reported genes | Reference |
| 2007 | *KIAA1727, SUSD1, ZFP64* | [[8](#_ENREF_8)] |
| 2007 | *ITPR2* | [[9](#_ENREF_9)] |
| 2007 | *DPP6* | [[10](#_ENREF_10)] |
| 2008 | *DPP6, LIPC, ITPR2* | [[11](#_ENREF_11)] |
| 2009 | *DPP6* | [[12](#_ENREF_12)] |
| 2009 | *ATXN1,B4GALT6,CNTN4, CSNK1G3,DISC1,EFEMP1,KIFAP3,NT5C1A,RBMS1, SCN7A,SELL,**SEMA6A,SLC39A11,ZNF746* | [[13](#_ENREF_13)] |
| 2009 | *IFNK, MOBKL2B, C9orf72* | [[14](#_ENREF_14)] |
| 2010 | *IFNK, MOBKL2B, C9orf72, SOD1* | [[15](#_ENREF_15)] |
| 2010 | *intergenic* | [[16](#_ENREF_16)] |
| 2010 | *LOC100506746, OR52K1* | [[17](#_ENREF_17)] |
| 2013 | *C9orf72,CPNE4,KIAA0513,LAMA3,PIGL, CENPV,STK36, TTLL4, ZNF142**UNC13A,ANKS1B,ARAP2,ARHGEF2,CNOT2,IFRD1,JMJD2A,NRXN3,**PCSK5,PTPRF,ST3GAL3* | [[18](#_ENREF_18)] |
| 2013 | *CAMK1G,SUSD2, CABIN1, GGT5* | [[19](#_ENREF_19)] |
| 2013 | DYRK2, CAND1,EGR1, REEP2,SEC16B,BOD1L,CREB5,LRRC3, C21orf29,TBC1D1,CPNE4,HDAC4, ASB1,PPP2R2D,UNC13A | [[18](#_ENREF_18)] |
| 2013 | *ANKRD29,SALM1,UNC13A* | [[20](#_ENREF_20)] |
| 2013 | *ABCC12,ABCG1,ACCN1,ADAMTS18,ADAMTSL1,ADAMTSL3,AGXT2L1,ALCAM,ALDH3A1,**ANK3,ANXA3, SB13,ATP2B2,AUTS2,BEND7,BMPR1B,BRUNOL4,C16orf74,C18orf58,C20orf173,**C21orf131,C22orf34,C3orf56,C5orf15,C6orf132,C9orf27,CALN1,CD2AP,CEP250,CHD2,**CHODL,CNTLN,CNTN5,CRBN,CSMD1,CSNK1A1L,CTNND2,CX3CR1,CXCR4,DACH1,**DISC1,DKFZp434E1119,DOCK4,DPF1,EPB41,ERBB4,ERG,FAM119A,FAM167A,FAM19A1,**FAM5C,FANK1,FAT3,FBXO15,FGF9,FLI1,FYN,GLRX5,GNA14,GPR133,HADH,HOXC13,**HOXD10,IFT74,INPP4B,INPP5B,INTS6,IQCF5,ITGA9,KC6,KCNMB2,KCTD16,KIAA0182,**KIAA0947,KIAA1680,LAMA2,LDHC,LOC100128095, PCML,LOC100129986,LOC100130298,**LOC100286951,LOC100287135,LOC100287172,LOC100287306,LOC100287580,LOC100288911**,LOC100289178,LOC100289459,LOC152118,LOC387820,LOC400750,LOC645314,LOC645321,**LOC727677,LOC728755,LOC729204,LPIN2,LRRC8C,LRRTM4,MACROD2,MAP3K7,MASP1,**MAT2B,MGLL,MRAS,MSC,MYO18B,NEDD4L,NEUROG2,NFASC,NFATC2,NKAIN3,NOG,**NR3C2,NTRK3,NUDT12,OLFM4,PAX3,PDGFRL,PFKP,PLIN,PPP2R5D,PROCR,PRR20,PTH2R,**PVT1,RAB3GAP2,RAB9P1,RBM19,RGS6,RNF165,RNF19A,RP1L1,RPS6KA1,RTCD1,RYR3,SDC1,**SEC16B,SLC10A2,SLC25A12,SLC28A3,SLC5A8,SLCO2A1,SLITRK1,SMARCA2,SNORD114-31,**SNX19,SP4,SREBF2,SSTR4,ST6GALNAC5,STON1,STOX1,SYNPO2,SYT16,TAPT1,TBC1D1,TBXAS1,**TFAP2A,THRB,TLL1,TMEM132B,TMEM132E,TMPRSS2,TP53I11,TRPM8,TSPAN9,TTC15,TYRP1,**WAPAL,WWC2,ZFYVE26,ZNF28,ZNF354A,ZNF700* | [[21](#_ENREF_21)] |
| 2014 | SQLE, NSMCE2, KIAA0196,C9orf72,CENPV,SQLE, KIAA0196, NSMCE2,TXNDC6,UNC13A | [[22](#_ENREF_22)] |
| 2015 | C9orf72 | [[23](#_ENREF_23)] |
| 2016 | KALRN | [[24](#_ENREF_24)] |
| 2016 | C21orf2,C9orf72,MOBP,SARM1,SCFD1,TBK1,UNC13A | [[25](#_ENREF_25)] |
| 2017 | c9orf72,MOBP,SARM1,UNC13A | [[26](#_ENREF_26)] |
| 2018 | ATXN3,C21orf2,C9orf72,KIF5A,LOC101927815,PMP22,SCFD1,TBK1,TNIP1,UNC13A | [[27](#_ENREF_27)] |
| 2019 | C9orf72 | [[28](#_ENREF_28)] |

The results were overviewed in terms of the GWAS catalog at <https://www.ebi.ac.uk/gwas> (until 2020-02-02).

**Table S2** Basic information for the eight genes associated with ALS identified by SCAT

|  |  |  |  |
| --- | --- | --- | --- |
| gene | chromosome | position | gene type |
| low | up |
| *FAM66D* | 8 | 11,973,284 | 12,008,698 | antisense |
| *C9orf72* | 9 | 27,546,544 | 27,573,864 | protein coding |
| *TRIP11* | 14 | 92,432,335 | 92,507,241 | protein coding |
| *RP11-529H20.6* | 14 | 92,511,119 | 92,516,990 | sense overlapping |
| *ATXN3* | 14 | 92,524,896 | 92,572,965 | protein coding |
| *SCFD1* | 14 | 31,091,318 | 31,205,018 | protein coding |
| *JUP* | 17 | 39,775,692 | 39,943,183 | protein coding |
| *SLC9A8* | 20 | 48,429,250 | 48,508,779 | protein coding |

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