

Deciphering Distinct Genetic Risk Factors for FTLD-TDP Pathological Subtypes via Whole-Genome Sequencing

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† In memoriam

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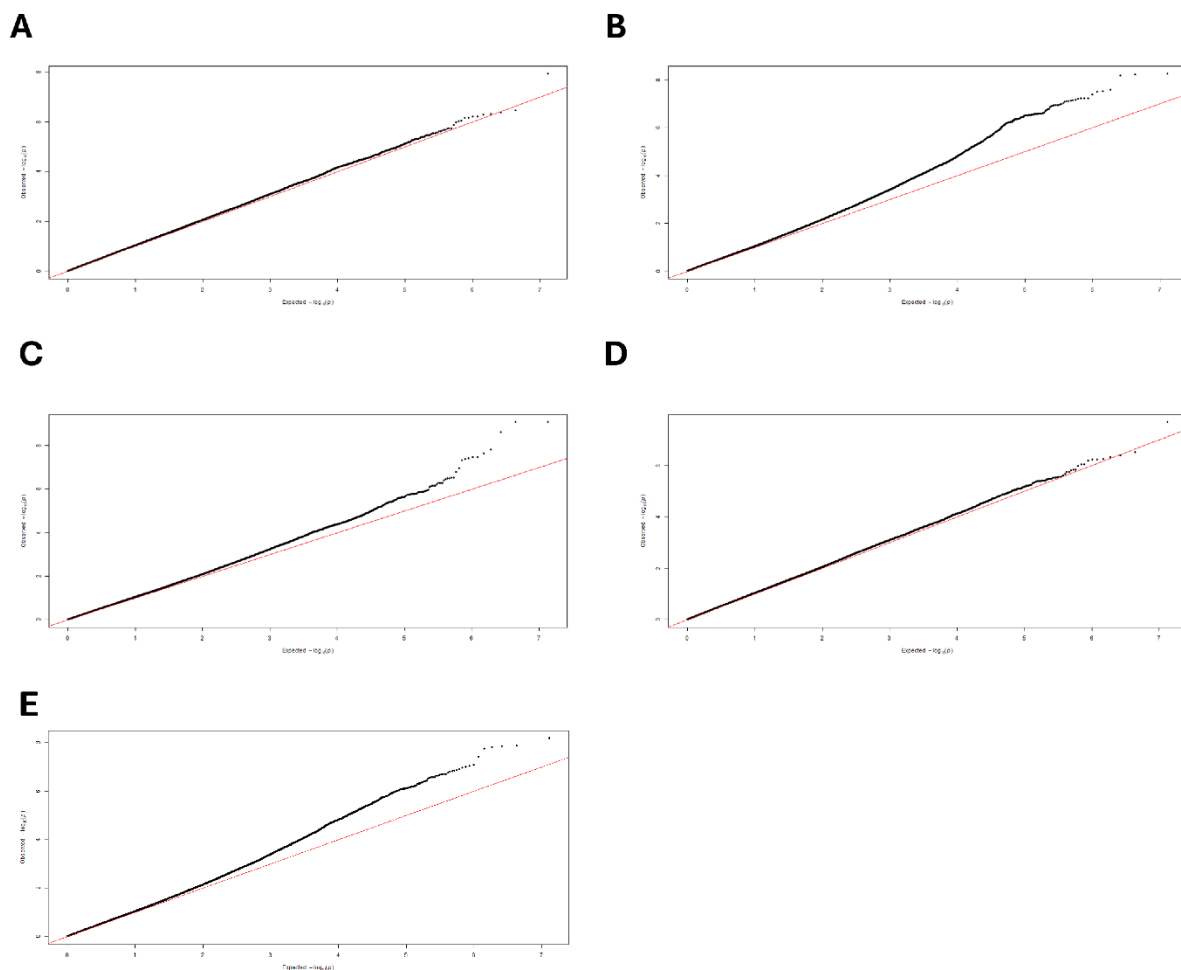
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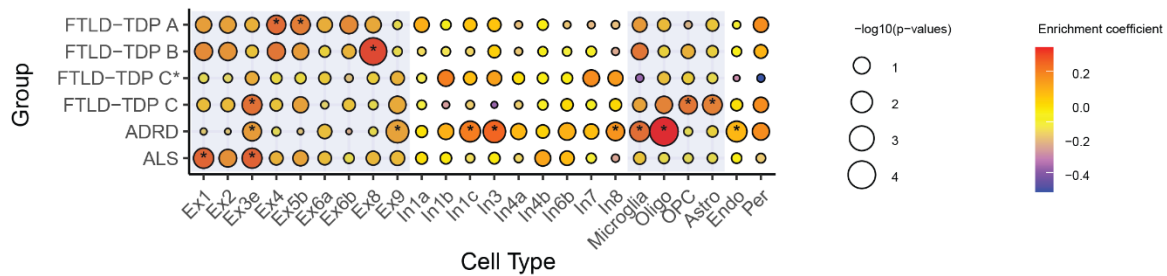
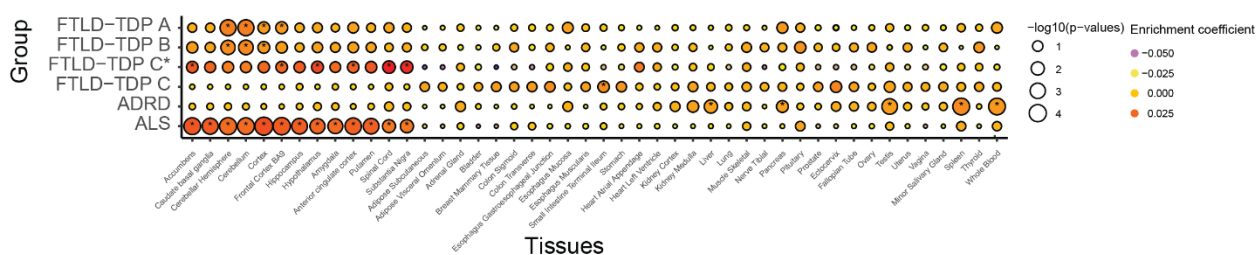
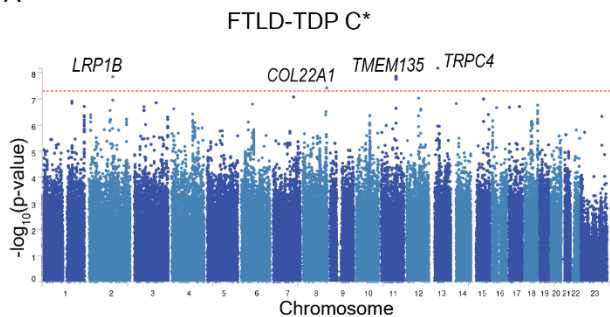
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SUPPLEMENTARY FIGURES

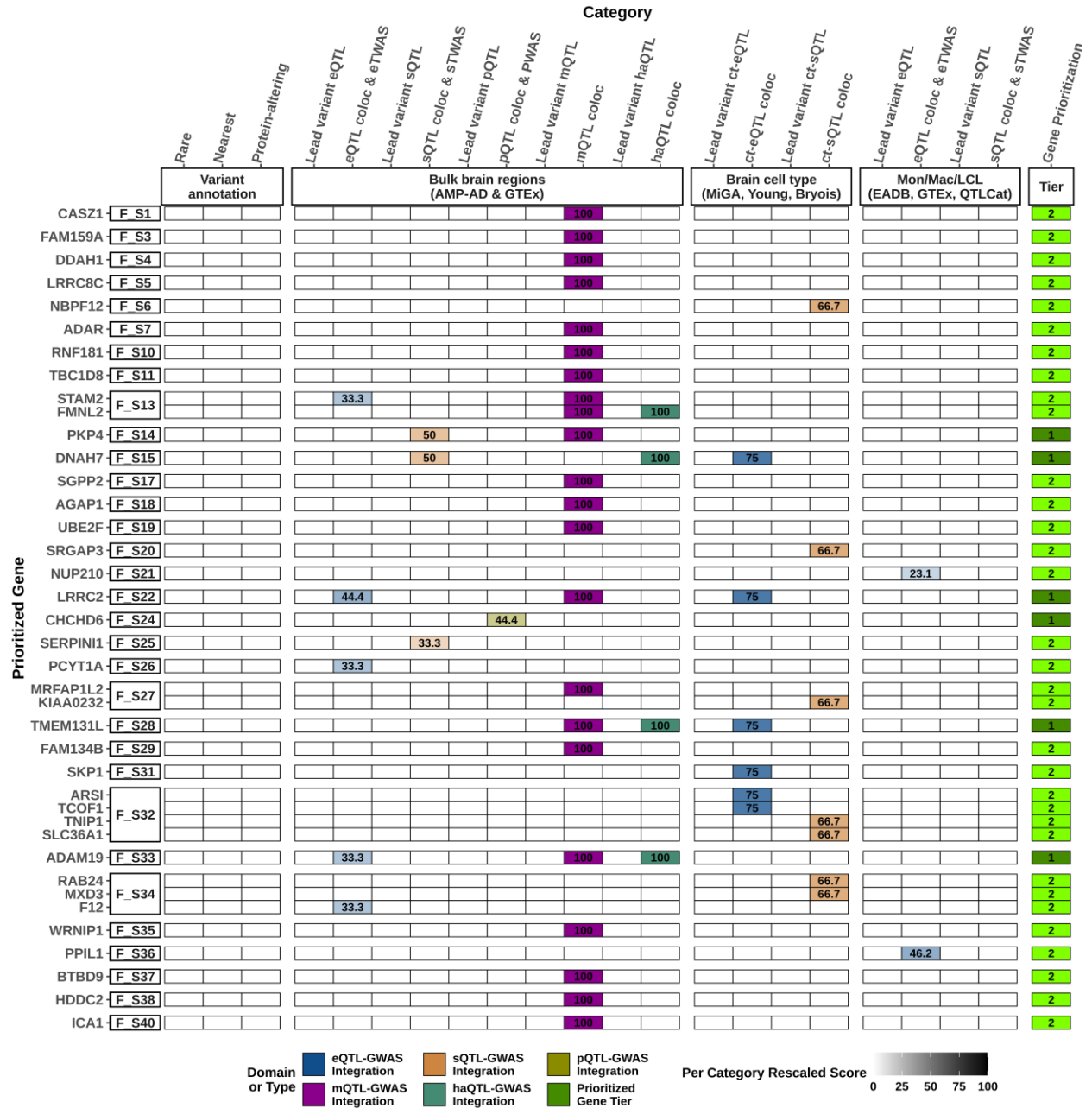
Supplementary Figure 1. Quantile-quantile (QQ) plots of the GWAS performed. **A** QQ plot of the FTLT-TDP All patients versus controls association study (inflation, $\lambda=1.05$). **B** QQ plot of the FTLT-TDP A patients versus controls association study ($\lambda=1.07$). **C** QQ plot of the FTLT-TDP B patients versus controls association study ($\lambda=1.06$). **D** QQ plot of the FTLT-TDP C patients versus controls association study ($\lambda=1.05$). **E** QQ plot of the FTLT-TDP C* patients (FTLT-TDP C without svPPA) versus controls association study ($\lambda=1.08$)



Supplementary Figure 2. Genome wide association study including only pathologically confirmed FTLD-TDP C patients (excluding svPPA patients; FTLD-TDP C*). **A.** Manhattan plot of GWAS comparing FTLD-TDP C* versus controls ($\lambda=1.08$). The red-dotted line represents the genome-wide significance level ($p = 5 \times 10^{-8}$). Association studies was performed using logistic regression with allele dosage as the predictor assuming log-additive allele effects adjusted for relevant covariates. Raw two-sided P are reported as $-\log_{10}(P)$. **B.** Top 5 Gene Ontology terms enriched in FTLD-TDP C*. Hierarchical GO analysis of biological process terms considering genes in genetic loci prioritized for FTLD-TDP C*. **C.** Enrichment of genes in multiple tissues, including 13 brain regions, and based on GTEX data in FTLD subgroups (including FTLD-TDP C*), ADRD and ALS. Color represents the enrichment coefficient, and size indicates two-sided $-\log_{10}$ (FDR adjusted P s) of enrichment obtained by the linear regression model in the MAGMA gene property analysis. **D.** Central nervous system cell type enrichment analyses in FTLD subgroups (including FTLD-TDP C*), ADRD and ALS. Color represents the enrichment coefficient, and size indicates two-sided $-\log_{10}$ (FDR adjusted P s) of enrichment obtained by the linear regression model in the MAGMA gene property analysis. Excitatory neurons and glial cells are highlighted in blue. Excitatory and inhibitory neurons from the PsychENCODE dataset were labeled based on their transcriptional profile from 1 to 8. Asterisks denote brain regions or cell types enriched with FDR $P < 0.05$. Cx, cortex; Ex*, Excitatory neuron, In*, inhibitory neurons; Oligo, oligodendrocytes; OPCs, oligodendrocyte progenitor cells; Astro, astrocytes; Endo, endothelial cells; Per, pericytes. Raw two-sided p-values are represented.



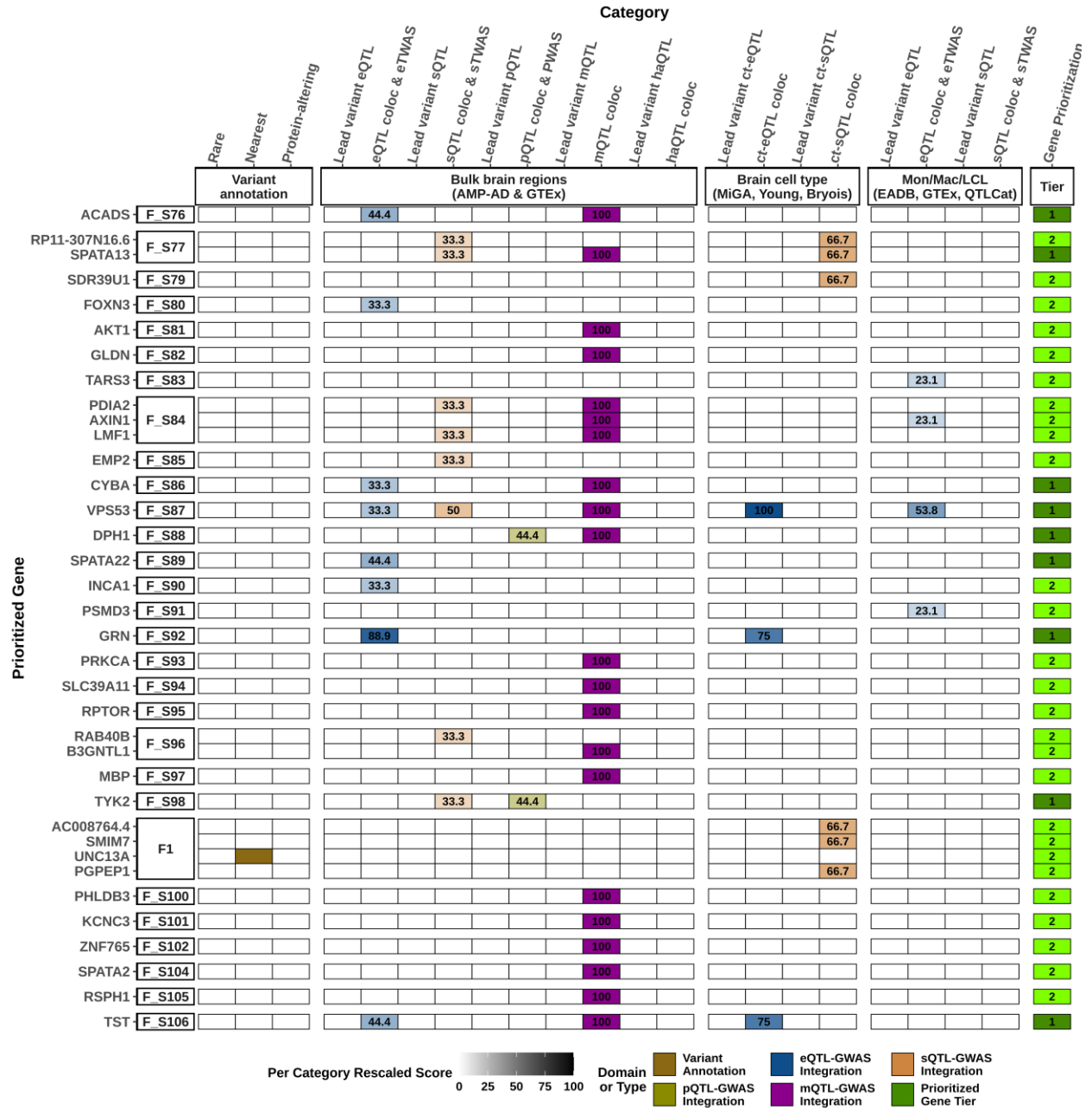
Supplementary Figure 3. Gene prioritization results for FTLT-TDP All. A visual summary of weighted evidence category scores for the prioritized genes within genome-wide significant and subthreshold loci for FTLT-TDP All GWAS. The leftmost squares indicate the locus index numbers which contain additional “_S” patterns for the subthreshold loci, meanwhile others indicate the genome-wide significant loci. The types of evidence for each category are colored according to the six different domains to which they belonged. Weighted scores for each evidence category are rescaled to a 0–100 scale based on the maximum score a candidate gene can obtain from a category (see **Supplementary Data 3**). The darker colors represent higher scores in categories, while tier 1 prioritized genes are displayed in dark green and tier 2 prioritized genes are displayed in light green. Only tier 1 and tier 2 genes are shown for each locus, and all candidate genes considered and scored can be found in **Supplementary Data 4**. MAFs (based on gnomAD v4 non-Finnish European samples) and CADD (v1.7) PHRED scores for rare and/or protein-altering rare variants are labeled in white within the respective squares. eQTL, expression QTL; sQTL, splicing QTL; mQTL, methylation QTL; pQTL, protein-expression QTL; haQTL, histone acetylation QTL; coloc, colocalization; eTWAS, expression transcriptome-wide association study; sTWAS, splicing transcriptome-wide association study; PWAS, proteome-wide association study; Mon. Mac., monocytes and macrophages; LCL, lymphoblastoid cell line; QTLCat, The eQTL Catalogue.



Prioritized Gene

		Category																						
		Rare	Nearest	Protein-altering	Lead variant eQTL	eQTL coloc & eTWAS	Lead variant sQTL	sQTL coloc & sTWAS	Lead variant pQTL	pQTL coloc & pWAS	Lead variant mQTL	mQTL coloc	Lead variant haQTL	haQTL coloc	Lead variant ct-eQTL	ct-eQTL coloc	Lead variant ct-sQTL	ct-sQTL coloc	Lead variant eQTL	eQTL coloc & eTWAS	Lead variant sQTL	sQTL coloc & sTWAS	Gene Prioritization	
		Variant annotation			Bulk brain regions (AMP-AD & GTEx)										Brain cell type (MiGA, Young, Bryois)				Mon/Mac/LCL (EADB, GTEx, QTLCat)				Tier	
PKD1L1	F_S42				44.4					100									23.1				1	
IKZF1	F_S43									100													2	
ABHD11	F_S44															66.7							2	
KEL	F_S46						33.3																2	
RP1L1	F_S47									100													2	
ST18	F_S48									100													2	
RAD54B							33.3																2	
FSBP	F_S49						33.3																2	
KIAA1429							33.3																2	
SAMD12	F_S50									100													2	
ZC3H3	F_S51									100													2	
NUDT2	F_S52				33.3																		2	
SYK																							2	
NFIL3	F_S53									100									30.8				2	
C9orf43	F_S54						50																2	
LCN2										100													2	
C9orf16	F_S55									100													2	
AKR1C2	F_S56									100													2	
PARD3	F_S57									100													2	
AGAP4	F_S58				33.3														23.1		40		1	
USP54	F_S59									100													2	
ZMI21	F_S60									100													2	
DPCD	F_S61									100													2	
PLPP4	F_S62											100											2	
MTG1					44.4		33.3			100													1	
SCART1	F_S64						33.3			100													2	
PIDD1	F_S65				44.4		50			100		100							23.1				1	
NCAM1	F_S66									100													2	
NXPE2	F_S67									100													2	
PUS3	F_S69				33.3														23.1				1	
CRACR2A	F_S71									100													2	
ERP27	F_S72																		23.1				2	
RAPGEF3	F_S73									100													2	
ITGA7										100													2	
RP11-762I7.5	F_S74						33.3																2	
SARNP							33.3																2	
PHLDA1	F_S75									100													2	
UNC119B										100										30.8			2	
ACADS	F_S76				44.4					100													1	

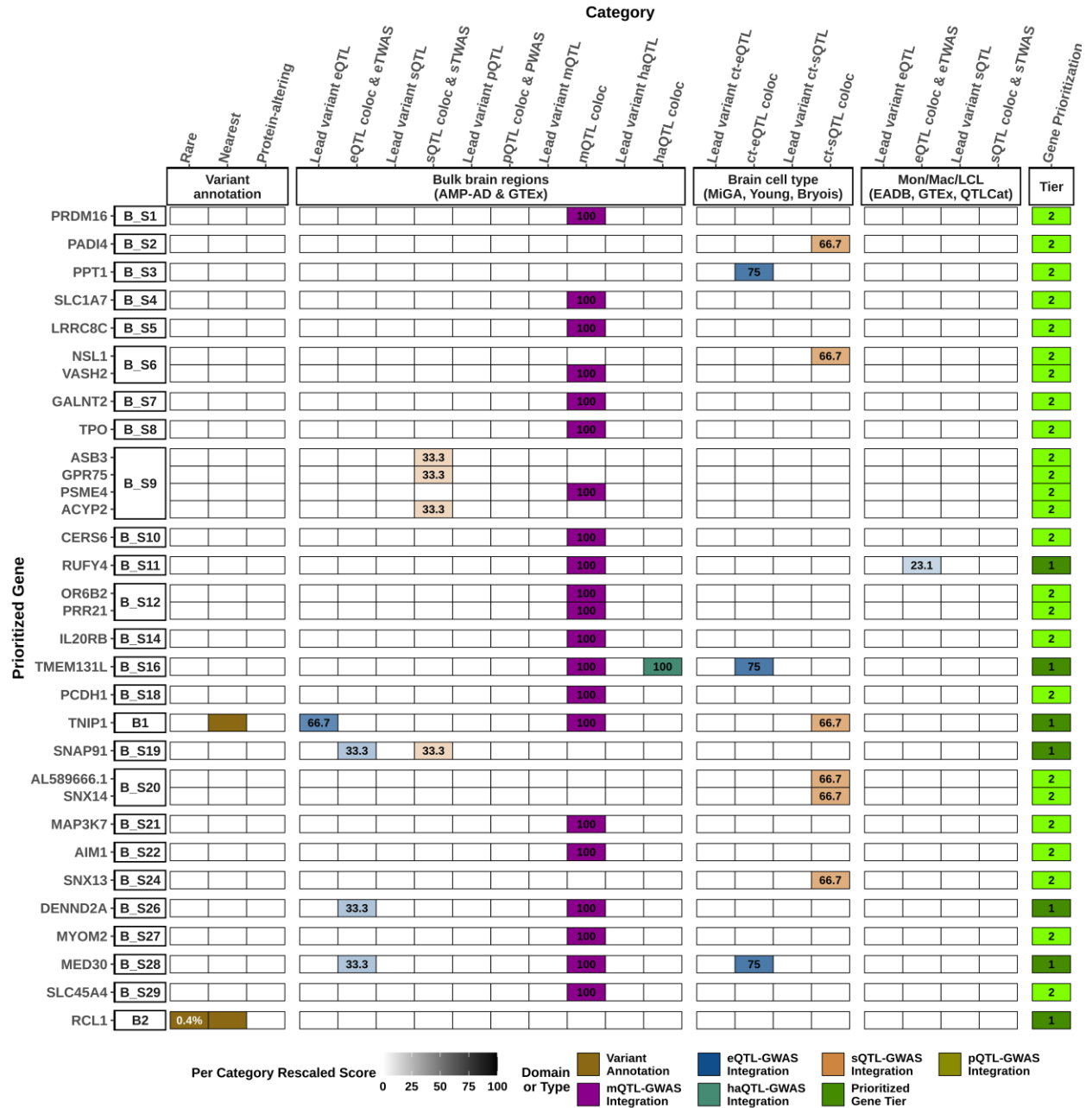




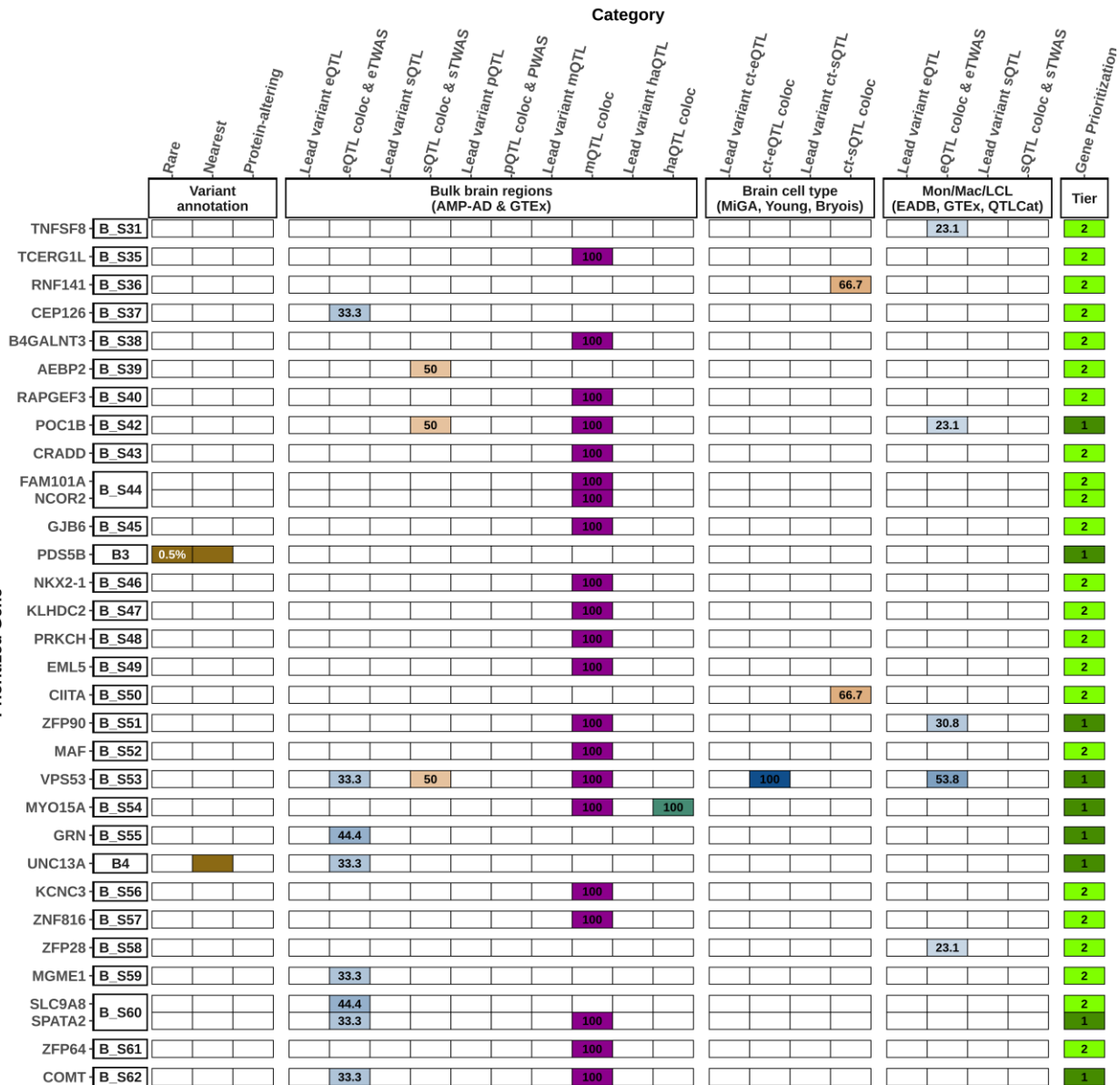
Supplementary Figure 4. Gene prioritization results for FTLD-TDP A. A visual summary of weighted evidence category scores for the prioritized genes within genome-wide significant and subthreshold loci for FTLD-TDP A GWAS. The leftmost squares indicate the locus index numbers which contain additional “_S” patterns for the subthreshold loci, meanwhile others indicate the genome-wide significant loci. The types of evidence for each category are colored according to the six different domains to which they belonged. Weighted scores for each evidence category are rescaled to a 0–100 scale based on the maximum score a candidate gene can obtain from a category (see **Supplementary Data 3**). The darker colors represent higher scores in categories, while tier 1 prioritized genes are displayed in dark green and tier 2 prioritized genes are displayed in light green. Only tier 1 and tier 2 genes are shown for each locus, and all candidate genes considered and scored can be found in **Supplementary Data 4**. MAFs (based on gnomAD v4 non-Finnish European samples) and CADD (v1.7) PHRED scores for rare and/or protein-altering rare variants are labeled in white within the respective squares. eQTL, expression QTL; sQTL, splicing QTL; mQTL, methylation QTL; pQTL, protein-expression QTL; haQTL, histone acetylation QTL; coloc, colocalization; eTWAS, expression transcriptome-wide association study; sTWAS, splicing transcriptome-wide association study; PWAS, proteome-wide association study; Mon. Mac., monocytes and macrophages; LCL, lymphoblastoid cell line; QTLCat, The eQTL Catalogue.

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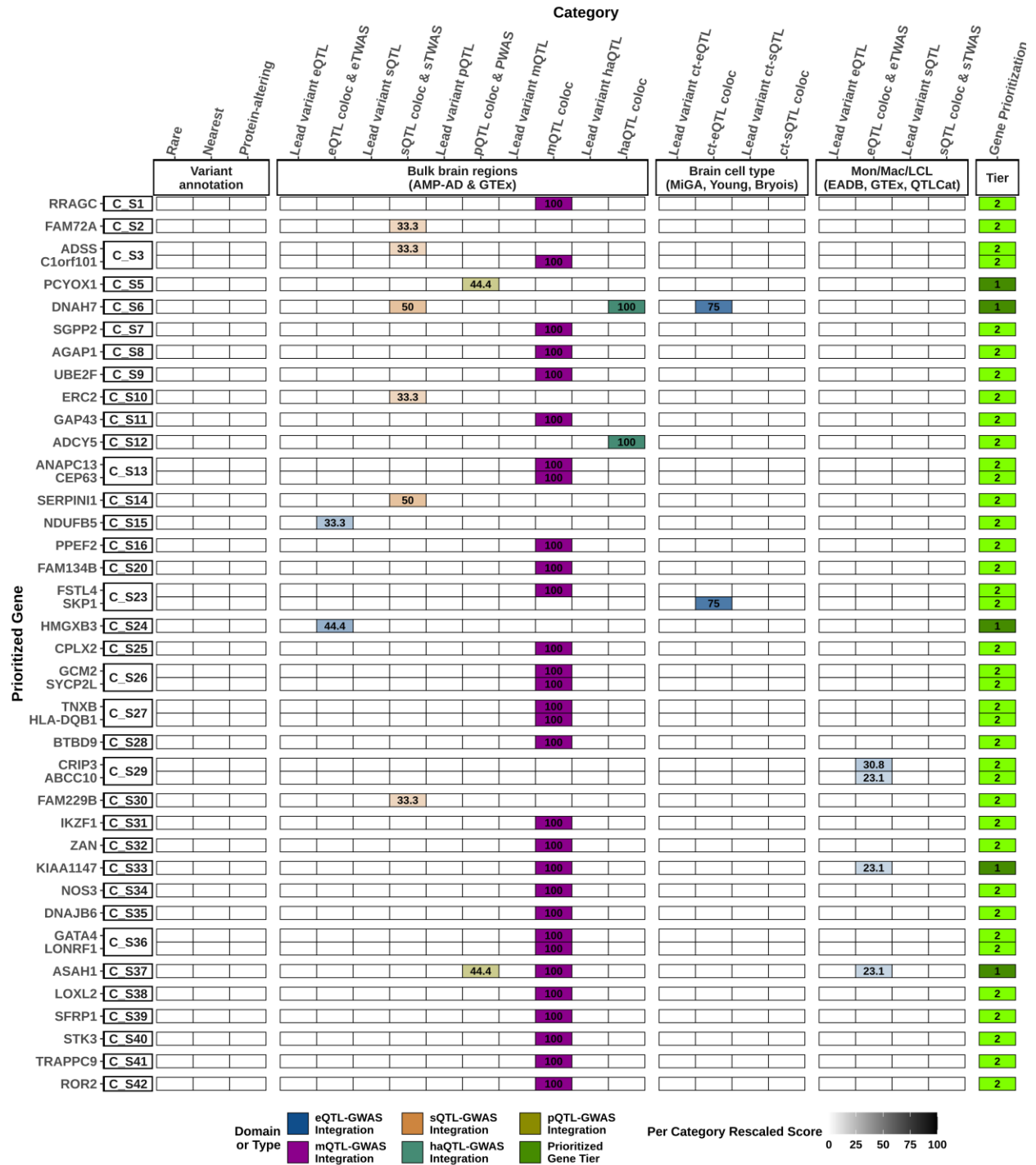
Supplementary Figure 5. Gene prioritization results for FTLD-TDP B. A visual summary of weighted evidence category scores for the prioritized genes within genome-wide significant and subthreshold loci for FTLD-TDP B GWAS. The leftmost squares indicate the locus index numbers which contain additional “_S” patterns for the subthreshold loci, meanwhile others indicate the genome-wide significant loci. The types of evidence for each category are colored according to the six different domains to which they belonged. Weighted scores for each evidence category are rescaled to a 0–100 scale based on the maximum score a candidate gene can obtain from a category (see **Supplementary Data 3**). The darker colors represent higher scores in categories, while tier 1 prioritized genes are displayed in dark green and tier 2 prioritized genes are displayed in light green. Only tier 1 and tier 2 genes are shown for each locus, and all candidate genes considered and scored can be found in **Supplementary Data 4**. MAFs (based on gnomAD v4 non-Finnish European samples) and CADD (v1.7) PHRED scores for rare and/or protein-altering rare variants are labeled in white within the respective squares. eQTL, expression QTL; sQTL, splicing QTL; mQTL, methylation QTL; pQTL, protein-expression QTL; haQTL, histone acetylation QTL; coloc, colocalization; eTWAS, expression transcriptome-wide association study; sTWAS, splicing transcriptome-wide association study; PWAS, proteome-wide association study; Mon. Mac., monocytes and macrophages; LCL, lymphoblastoid cell line; QTLCat, The eQTL Catalogue.



Prioritized Gene



Supplementary Figure 6. Gene prioritization results for FTLD-TDP C. A visual summary of weighted evidence category scores for the prioritized genes within genome-wide significant and subthreshold loci for FTLD-TDP C GWAS. The leftmost squares indicate the locus index numbers which contain additional “_S” patterns for the subthreshold loci, meanwhile others indicate the genome-wide significant loci. The types of evidence for each category are colored according to the six different domains to which they belonged. Weighted scores for each evidence category are rescaled to a 0–100 scale based on the maximum score a candidate gene can obtain from a category (see **Supplementary Data 3**). The darker colors represent higher scores in categories, while tier 1 prioritized genes are displayed in dark green and tier 2 prioritized genes are displayed in light green. Only tier 1 and tier 2 genes are shown for each locus, and all candidate genes considered and scored can be found in **Supplementary Data 4**. MAFs (based on gnomAD v4 non-Finnish European samples) and CADD (v1.7) PHRED scores for rare and/or protein-altering rare variants are labeled in white within the respective squares. eQTL, expression QTL; sQTL, splicing QTL; mQTL, methylation QTL; pQTL, protein-expression QTL; haQTL, histone acetylation QTL; coloc, colocalization; eTWAS, expression transcriptome-wide association study; sTWAS, splicing transcriptome-wide association study; PWAS, proteome-wide association study; Mon. Mac., monocytes and macrophages; LCL, lymphoblastoid cell line; QTLCat, The eQTL Catalogue.



Prioritized Gene		Variant annotation	Category																		Tier		
			Rare	Nearest	Protein-altering	Bulk brain regions (AMP-AD & GTEx)							Brain cell type (MIGA, Young, Bryois)			Mon/Mac/LCL (EADB, GTEx, QTLcat)							
						Lead variant eQTL	eQTL coloc & eTWAS	Lead variant sQTL	sQTL coloc & sTWAS	Lead variant pQTL	pQTL coloc & pWAS	Lead variant mQTL	mQTL coloc	Lead variant haQTL	haQTL coloc	Lead variant ct-eQTL	ct-eQTL coloc	Lead variant ct-sQTL	ct-sQTL coloc	Lead variant eQTL		eQTL coloc & eTWAS	Lead variant sQTL
C9orf43	C_S43						50																2
GARNL3	C_S44											100											2
PARD3	C_S45											100											2
MAT1A	C_S46											100											2
FAM213A	C_S46					44.4																	1
PIDD1	C_S48							50				100											2
PNPLA2	C_S48					33.3						100											2
CALCB	C_S49											100											2
NAT10	C_S50											100											2
ABTB2	C_S50											100											2
AKAP3	C_S51					44.4																	1
PEX5	C_S52					33.3																	2
FAM234B	C_S53					33.3																	2
GSG1	C_S53											100											2
MRPS35	C_S55							50															2
MANSC4	C_S55					33.3																	2
PHLDA1	C_S56											100											2
HAL	C_S57																	23.1					2
PSMD9	C_S58					33.3					44.4												2
WDR66	C_S58					33.3						100											2
BCL7A	C_S58					33.3									75								2
CCDC92	C_S59							50				100			100			23.1					1
SPATA13	C_S60											100											2
LCP1	C_S61											100											2
CHD8	C_S62															66.7							2
ALKBH1	C_S63											100											2
FOXN3	C_S64											100											2
FAN1	C_S65														75								2
CEMP1	C_S66											100											2
LMF1	C_S67							50				100											1
PPL	C_S68					33.3																	2
RMI2	C_S69											100											2
P2RX5	C_S71					44.4						100						53.8					1
INCA1	C_S72					33.3																	2
TBC1D3L	C_S73					33.3												46.2					1
DYNLL2	C_S74							33.3															2
PRKCA	C_S75											100											2
C19orf52	C1	0.5%																					1
DMPK	C_S76							50				100											1
ZNF765	C_S77											100											2
TST	C_S78										44.4				75								1
TCF20	C_S79							33.3															2
FAM19A5	C_S80												100										2

Per Category Rescaled Score

0

25

50

75

100

Domain or Type

Variant Annotation

mQTL-GWAS Integration

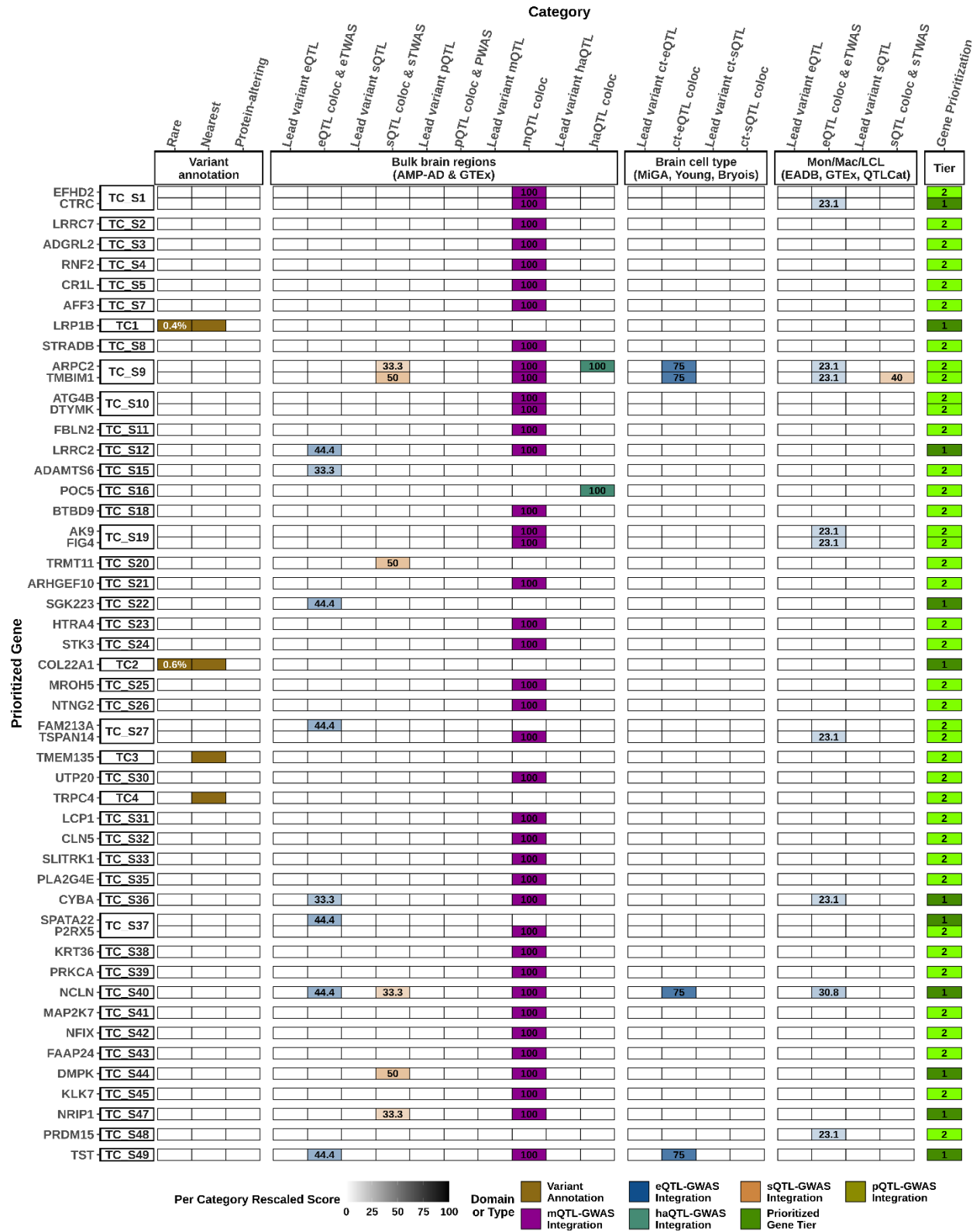
eQTL-GWAS Integration

haQTL-GWAS Integration

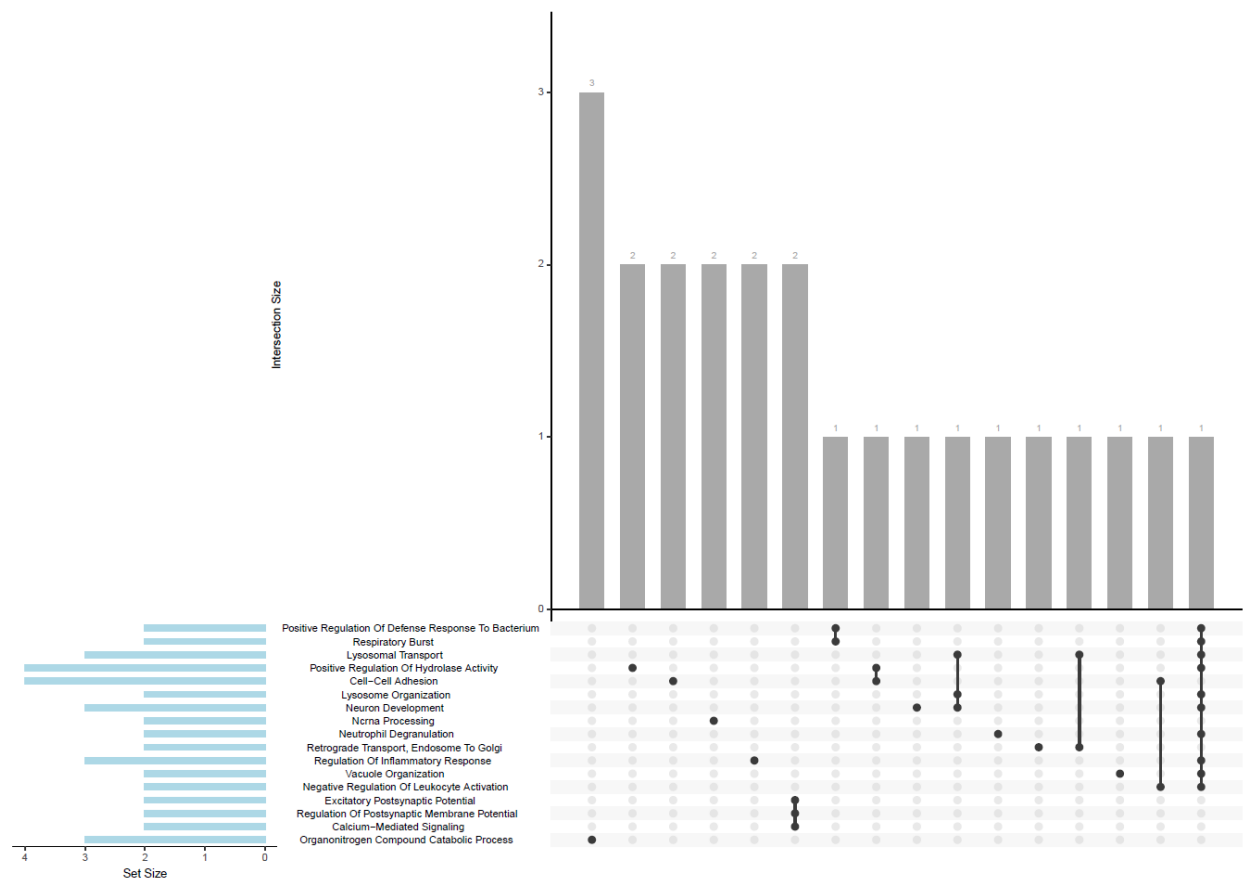
sQTL-GWAS Integration

Prioritized Gene Tier

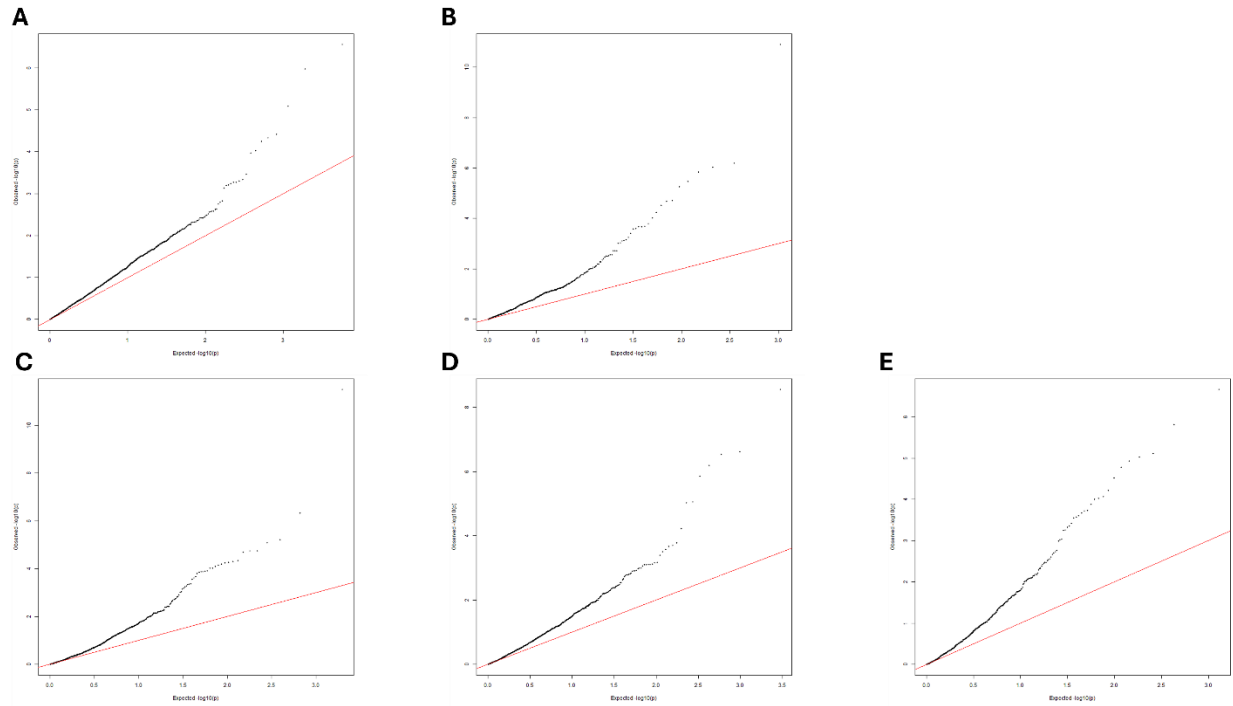
Supplementary Figure 7. Gene prioritization results for FTLD-TDP C*. A visual summary of weighted evidence category scores for the prioritized genes within genome-wide significant and subthreshold loci for FTLD-TDP C* GWAS. The leftmost squares indicate the locus index numbers which contain additional “_S” patterns for the subthreshold loci, meanwhile others indicate the genome-wide significant loci. The types of evidence for each category are colored according to the six different domains to which they belonged. Weighted scores for each evidence category are rescaled to a 0–100 scale based on the maximum score a candidate gene can obtain from a category (see **Supplementary Data 3**). The darker colors represent higher scores in categories, while tier 1 prioritized genes are displayed in dark green and tier 2 prioritized genes are displayed in light green. Only tier 1 and tier 2 genes are shown for each locus, and all candidate genes considered and scored can be found in **Supplementary Data 4**. MAFs (based on gnomAD v4 non-Finnish European samples) and CADD (v1.7) PHRED scores for rare and/or protein-altering rare variants are labeled in white within the respective squares. eQTL, expression QTL; sQTL, splicing QTL; mQTL, methylation QTL; pQTL, protein-expression QTL; haQTL, histone acetylation QTL; coloc, colocalization; eTWAS, expression transcriptome-wide association study; sTWAS, splicing transcriptome-wide association study; PWAS, proteome-wide association study; Mon. Mac., monocytes and macrophages; LCL, lymphoblastoid cell line; QTLCat, The eQTL Catalogue.



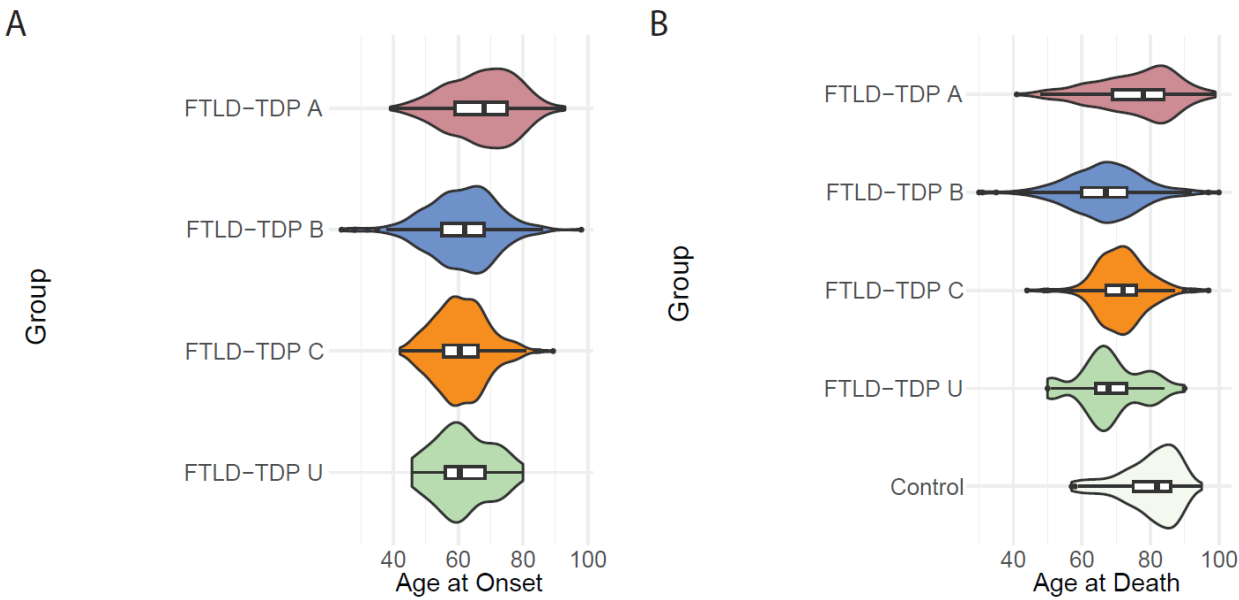
Supplementary Figure 8. Gene overlap between the significant Gene Ontology terms. Upset plot illustrating the overlap of different gene sets in the significant Gene Ontology terms. The vertical bars represent the total number of unique genes in each set, while the intersections indicate the number of genes shared among the sets. The horizontal axis lists the Gene Ontology terms sets, with each bar corresponding to the number of genes present in that specific intersection.



Supplementary Figure 9. Quantile-quantile (QQ) plot of the multiple association studies performed on rare variants. **A** QQ plot of the FTLD-TDP All patients versus controls association study (inflation, $\lambda=1.35$). **B** QQ plot of the FTLD-TDP A patients versus controls association study ($\lambda=2.18$). **C** QQ plot of the FTLD-TDP B patients versus controls association study ($\lambda=1.49$). **D** QQ plot of the FTLD-TDP C patients versus controls association study ($\lambda=1.51$). **E** QQ plot of the FTLD-TDP C* patients versus controls association study ($\lambda=1.70$).



Supplementary Figure 11. Age at onset and age at death distribution. Violin plots showing age at onset (**A**) and age at death (**B**) are represented as well as box plots for each patient/control groups.



SUPPLEMENTARY NOTES

ADSP Acknowledgment:

The Alzheimer's Disease Sequencing Project (ADSP) is comprised of two Alzheimer's Disease (AD) genetics consortia and three National Human Genome Research Institute (NHGRI) funded Large Scale Sequencing and Analysis Centers (LSAC). The two AD genetics consortia are the Alzheimer's Disease Genetics Consortium (ADGC) funded by NIA (U01 AG032984), and the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) funded by NIA (R01 AG033193), the National Heart, Lung, and Blood Institute (NHLBI), other National Institute of Health (NIH) institutes and other foreign governmental and non-governmental organizations. The Discovery Phase analysis of sequence data is supported through UF1AG047133 (to Drs. Schellenberg, Farrer, Pericak-Vance, Mayeux, and Haines); U01AG049505 to Dr. Seshadri; U01AG049506 to Dr. Boerwinkle; U01AG049507 to Dr. Wijsman; and U01AG049508 to Dr. Goate and the Discovery Extension Phase analysis is supported through U01AG052411 to Dr. Goate, U01AG052410 to Dr. Pericak-Vance and U01AG052409 to Drs. Seshadri and Fornage.

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The ADGC cohorts include: Adult Changes in Thought (ACT) (U01 AG006781, U19 AG066567), the Alzheimer's Disease Research Centers (ADRC) (P30 AG062429, P30 AG066468, P30 AG062421, P30 AG066509, P30 AG066514, P30 AG066530, P30 AG066507, P30 AG066444, P30 AG066518, P30 AG066512, P30 AG066462, P30 AG072979, P30 AG072972, P30 AG072976, P30 AG072975, P30 AG072978, P30 AG072977, P30 AG066519,

P30 AG062677, P30 AG079280, P30 AG062422, P30 AG066511, P30 AG072946, P30 AG062715, P30 AG072973, P30 AG066506, P30 AG066508, P30 AG066515, P30 AG072947, P30 AG072931, P30 AG066546, P20 AG068024, P20 AG068053, P20 AG068077, P20 AG068082, P30 AG072958, P30 AG072959), the Chicago Health and Aging Project (CHAP) (R01 AG11101, RC4 AG039085, K23 AG030944), Indiana Memory and Aging Study (IMAS) (R01 AG019771), Indianapolis Ibadan (R01 AG009956, P30 AG010133), the Memory and Aging Project (MAP) (R01 AG17917), Mayo Clinic (MAYO) (R01 AG032990, U01 AG046139, R01 NS080820, RF1 AG051504, P50 AG016574), Mayo Parkinson's Disease controls (NS039764, NS071674, 5RC2HG005605), University of Miami (R01 AG027944, R01 AG028786, R01 AG019085, IIRG09133827, A2011048), the Multi-Institutional Research in Alzheimer's Genetic Epidemiology Study (MIRAGE) (R01 AG09029, R01 AG025259), the National Centralized Repository for Alzheimer's Disease and Related Dementias (NCRAD) (U24 AG021886), the National Institute on Aging Late Onset Alzheimer's Disease Family Study (NIA- LOAD) (U24 AG056270), the Religious Orders Study (ROS) (P30 AG10161, R01 AG15819), the Texas Alzheimer's Research and Care Consortium (TARCC) (funded by the Darrell K Royal Texas Alzheimer's Initiative), Vanderbilt University/Case Western Reserve University (VAN/CWRU) (R01 AG019757, R01 AG021547, R01 AG027944, R01 AG028786, P01 NS026630, and Alzheimer's Association), the Washington Heights-Inwood Columbia Aging Project (WHICAP) (RF1 AG054023), the University of Washington Families (VA Research Merit Grant, NIA: P50AG005136, R01AG041797, NINDS: R01NS069719), the Columbia University Hispanic Estudio Familiar de Influencia Genetica de Alzheimer (EFIGA) (RF1 AG015473), the University of Toronto (UT) (funded by Wellcome Trust, Medical Research Council, Canadian Institutes of Health Research), and Genetic Differences (GD) (R01 AG007584). The CHARGE cohorts are supported in part by National Heart, Lung, and Blood Institute (NHLBI) infrastructure grant HL105756 (Psaty), RC2HL102419 (Boerwinkle) and the neurology working group is supported by the National Institute on Aging (NIA) R01 grant AG033193.

The CHARGE cohorts participating in the ADSP include the following: Austrian Stroke Prevention Study (ASPS), ASPS-Family study, and the Prospective Dementia Registry-Austria (ASPS/PRODEM-Aus), the Atherosclerosis Risk in Communities (ARIC) Study, the Cardiovascular Health Study (CHS), the Erasmus Rucphen Family Study (ERF), the

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The FUS cohorts include: the Alzheimer's Disease Research Centers (ADRC) (P30 AG062429, P30 AG066468, P30 AG062421, P30 AG066509, P30 AG066514, P30 AG066530, P30 AG066507, P30 AG066444, P30 AG066518, P30 AG066512, P30 AG066462, P30 AG072979, P30 AG072972, P30 AG072976, P30 AG072975, P30 AG072978, P30 AG072977, P30 AG066519, P30 AG062677, P30 AG079280, P30 AG062422, P30 AG066511, P30 AG072946, P30 AG062715, P30 AG072973, P30 AG066506, P30 AG066508, P30 AG066515, P30 AG072947, P30 AG072931, P30 AG066546, P20 AG068024, P20 AG068053, P20 AG068077, P20 AG068082, P30 AG072958, P30 AG072959), Alzheimer's Disease Neuroimaging Initiative (ADNI) (U19AG024904), Amish Protective Variant Study (RF1AG058066), Cache County Study (R01AG11380, R01AG031272, R01AG21136, RF1AG054052), Case Western Reserve University Brain Bank (CWRUBB) (P50AG008012), Case Western Reserve University Rapid Decline (CWRURD) (RF1AG058267, NU38CK000480), CubanAmerican Alzheimer's Disease Initiative (CuAADI) (3U01AG052410), Estudio Familiar de Influencia Genetica en Alzheimer (EFIGA) (5R37AG015473, RF1AG015473, R56AG051876), Genetic and Environmental Risk Factors for Alzheimer Disease Among African Americans Study (GenerAAtions) (2R01AG09029, R01AG025259, 2R01AG048927), Gwangju Alzheimer and Related Dementias Study (GARD) (U01AG062602), Hillblom Aging Network (2014-A-004-NET, R01AG032289, R01AG048234), Hussman Institute for Human Genomics Brain Bank (HIHGBB) (R01AG027944, Alzheimer's Association "Identification of Rare Variants in Alzheimer Disease"), Ibadan Study of Aging (IBADAN) (5R01AG009956), Longevity Genes Project

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