

Figure S1. (A) Number of uniquely mapped read pairs per tissue. (B) Percentage of GMAS exons calculated as the total number of GMAS exons divided by the number of testable exons across selected sampled in a tissue. The analysis was done by selecting 58 samples from each tissue randomly, but matching the total number of reads per sample with those in the tissue (brain substantia nigra) that has the least number ($n=58$) of samples.

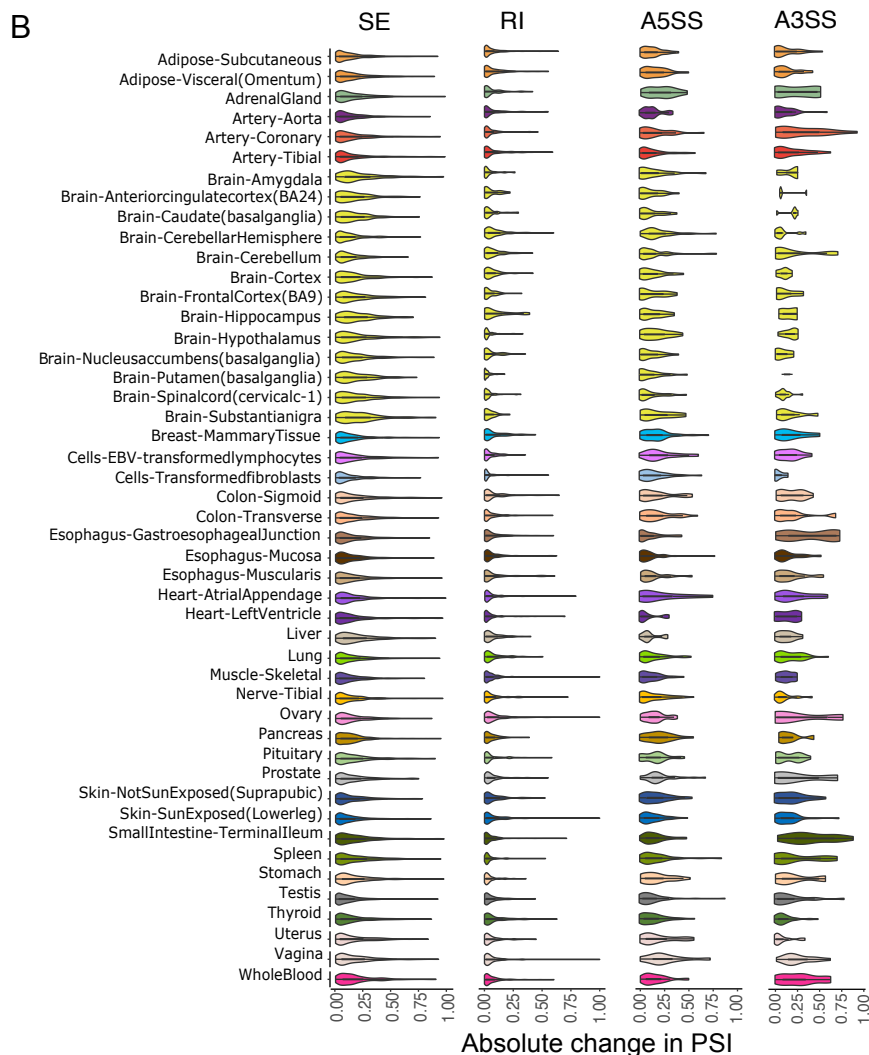
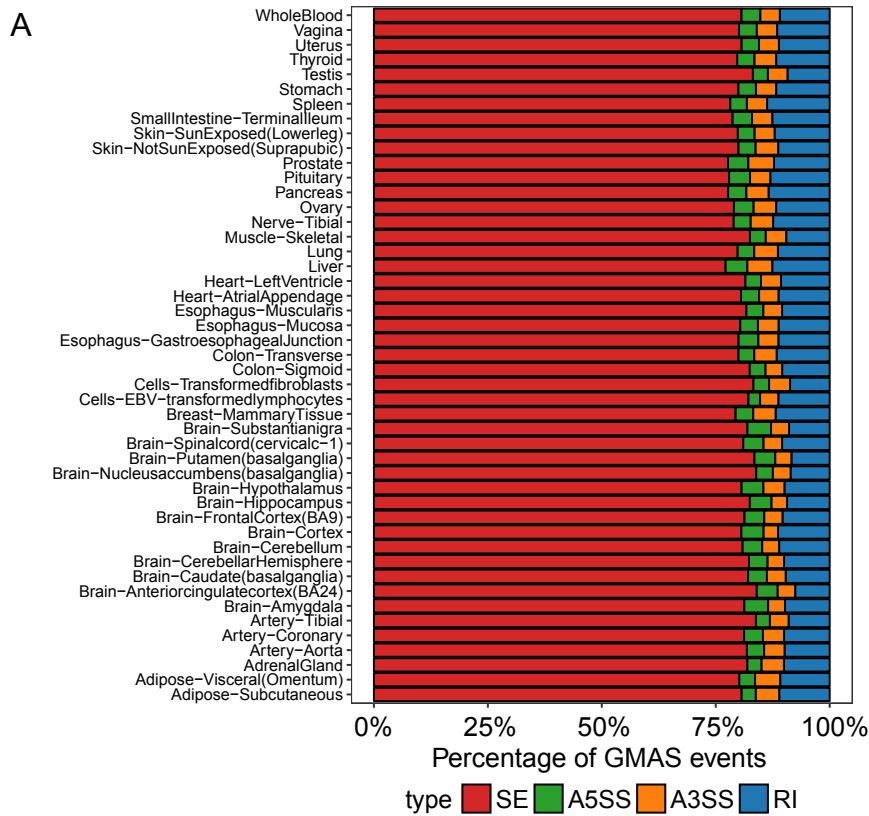


Figure S2. (A) Distribution of GMAS types per tissue. (B) The distribution of changes in PSI of GMAS exons per tissue. For each GMAS exon in each tissue, the mean absolute difference between PSI for individuals with homozygous reference allele and those with homozygous variants was taken. SE: skipped exons; RI: retained introns; A5SS: alternative 5'ss exon; A3SS: alternative 3'ss exon.

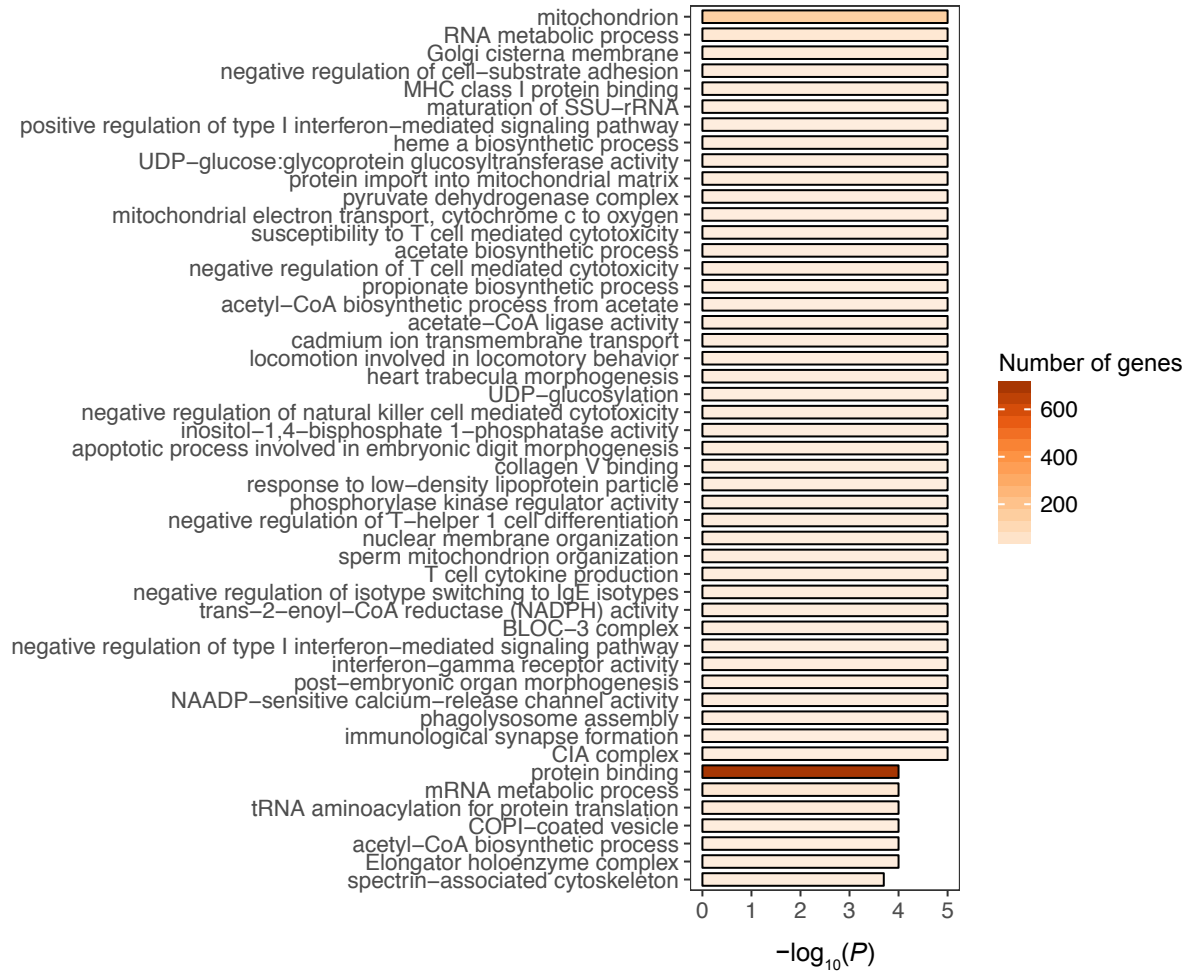


Figure S3. GO terms enriched among genes harboring GMAS exons with low variability across tissues and across individuals (N = 1636).

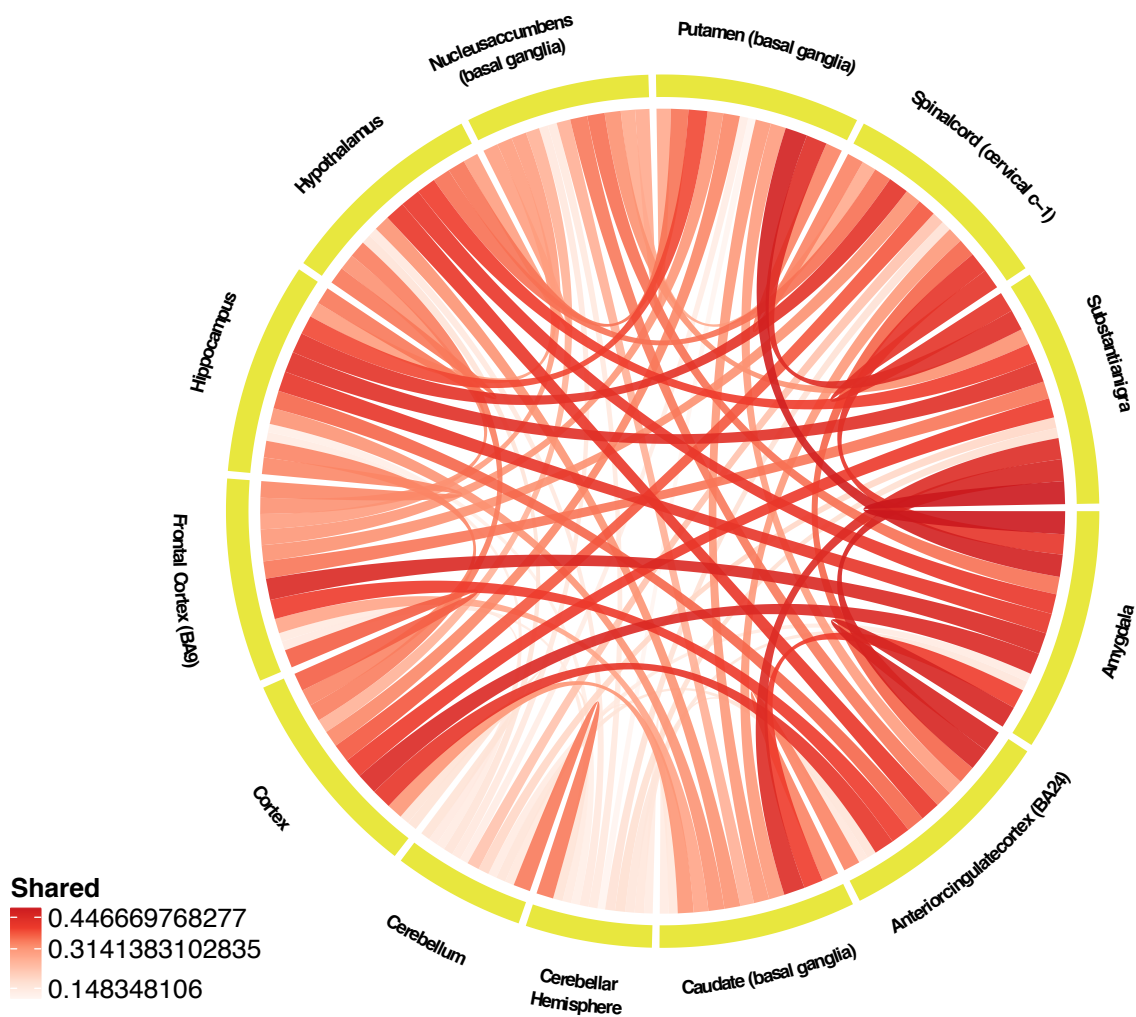


Figure S4. Jaccard index of GMAS patterns between pairs of brain regions (inner links). The color shade and thickness of the links are proportional to the number of shared GMAS exons between the two tissues.

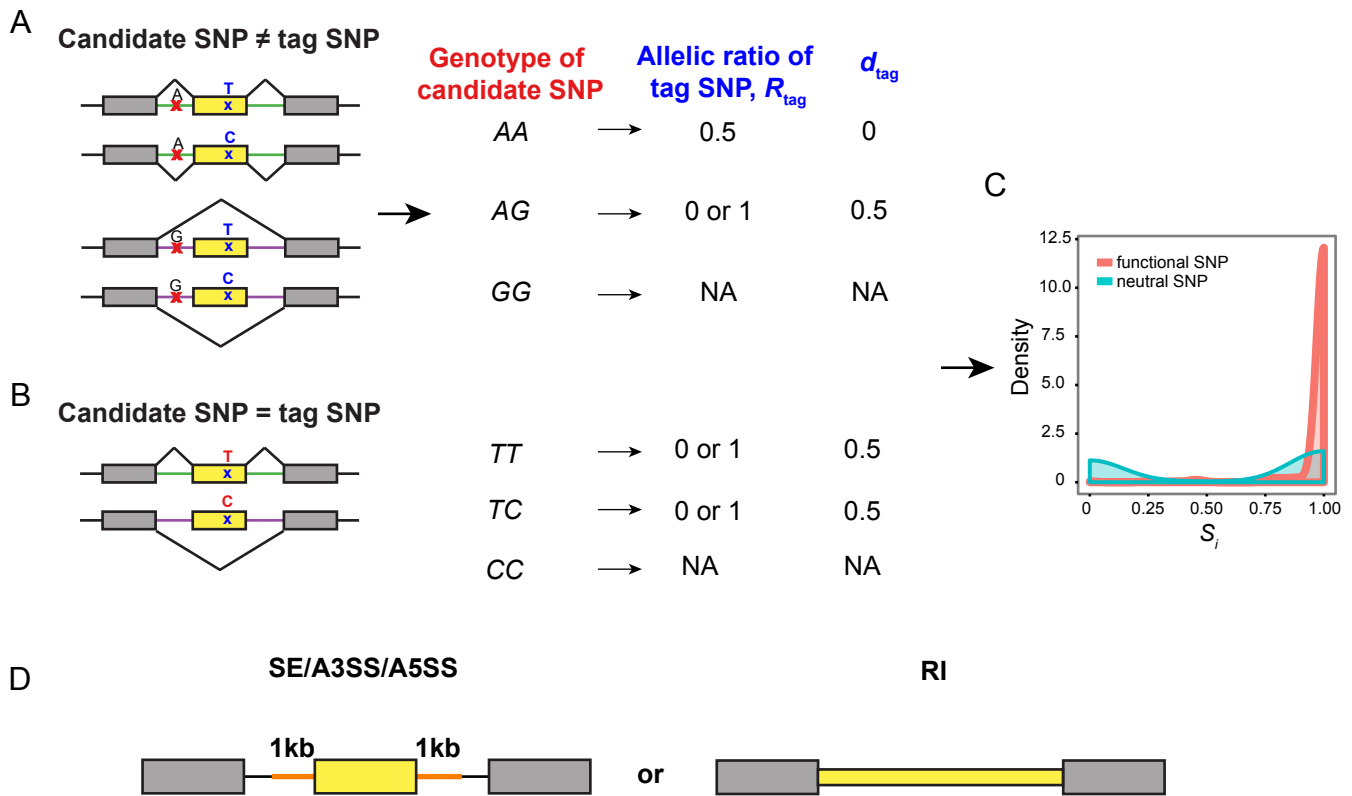
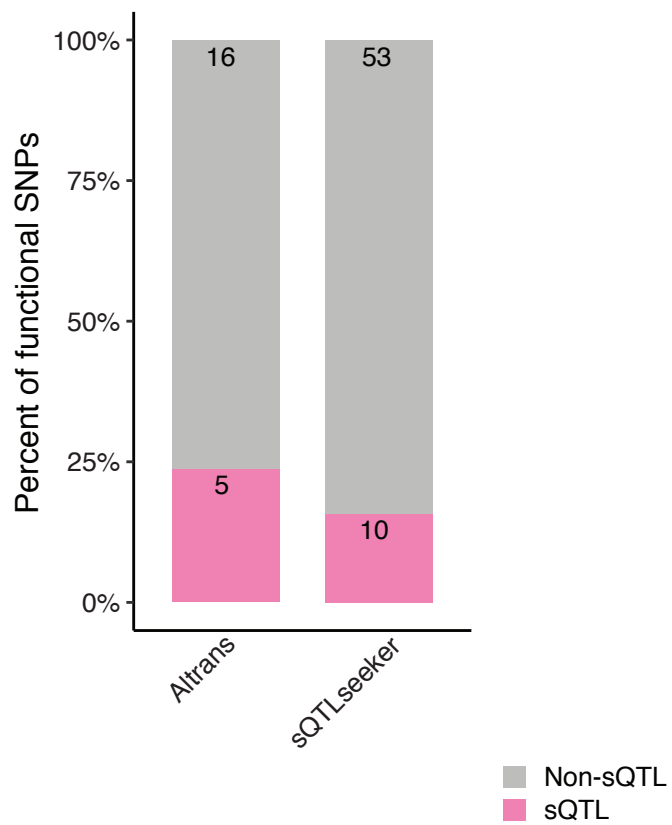


Figure S5. Calculation of concordance scores to predict functional SNPs. (A) A simple example showing a functional candidate SNP that causes complete exon inclusion or exclusion. The allelic ratio of the tag SNP is shown depending on the genotype of the functional SNP. d_{tag} is calculated as $|R_{\text{tag}} - 0.5|$. (B) A simple example showing that the tag SNP is the functional SNP and its alleles induce complete exon inclusion or exclusion. (C) Hypothetic distribution of concordance score S_i for the functional SNPs in (A) and (B). The distribution for neutral SNPs is also shown. (D) The regions within which to search for candidate functional SNPs (yellow boxes). For SE, A3SS, and A5SS events, we also included intronic SNPs within 1kb (orange line) of the target exon.

A



B

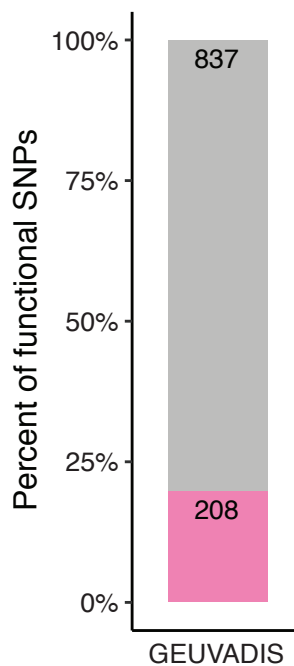


Figure S6. Functional SNPs overlapping known sQTLs. (A) sQTLs identified from GTEx pilot study. (B) sQTLs identified from 1000 Genomes Project.

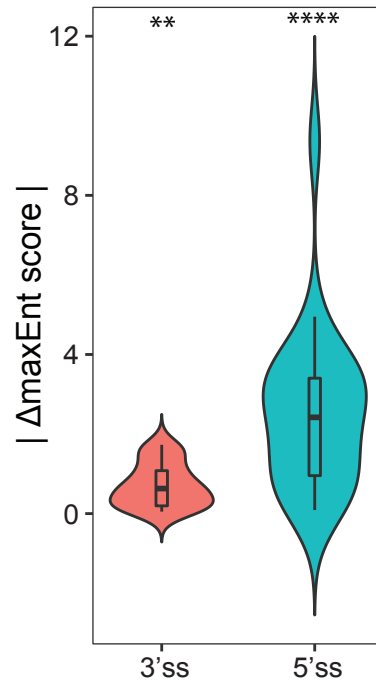


Figure S7. The absolute difference in maxEnt scores between the alternative alleles of predicted functional SNPs located in the 3'ss (Kolmogorov-Smirnov $P = 0.003007$) or 5'ss (Kolmogorov-Smirnov $P = 0.0001128$).

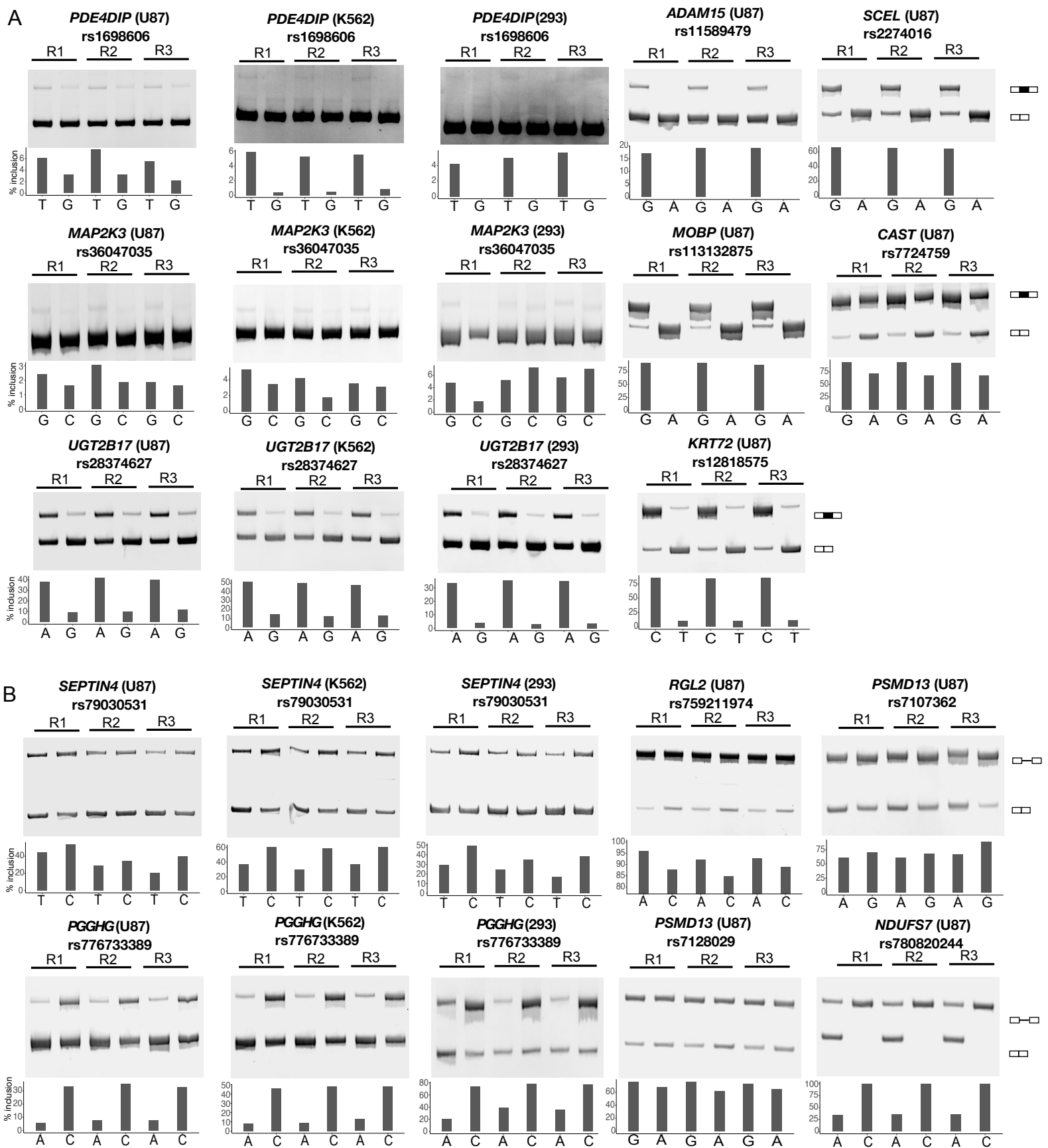


Fig. S8: Experimental support of predicted functional SNPs. Minigene experiments validating predicted functional SNPs for GMAS in triplicates (R1-3). The inclusion levels (% inclusion) of the skipped exons or retained introns were estimated from the band intensities of the PAGE gel. (A) Functional SNPs in *PDE4DIP*, *MAP2K3*, *UGT2B17*, *ADAM15*, *SCEL*, *MOBP*, *CAST* and *KRT72* tested in U87, K562 and HEK293 cells for exon skipping. (B) Functional SNPs in *SEPTIN4*, *PGGHG*, *PSMD13*, *RGL2* and *NDUFS7* tested in U87, K562 and HEK293 cells for intron retention

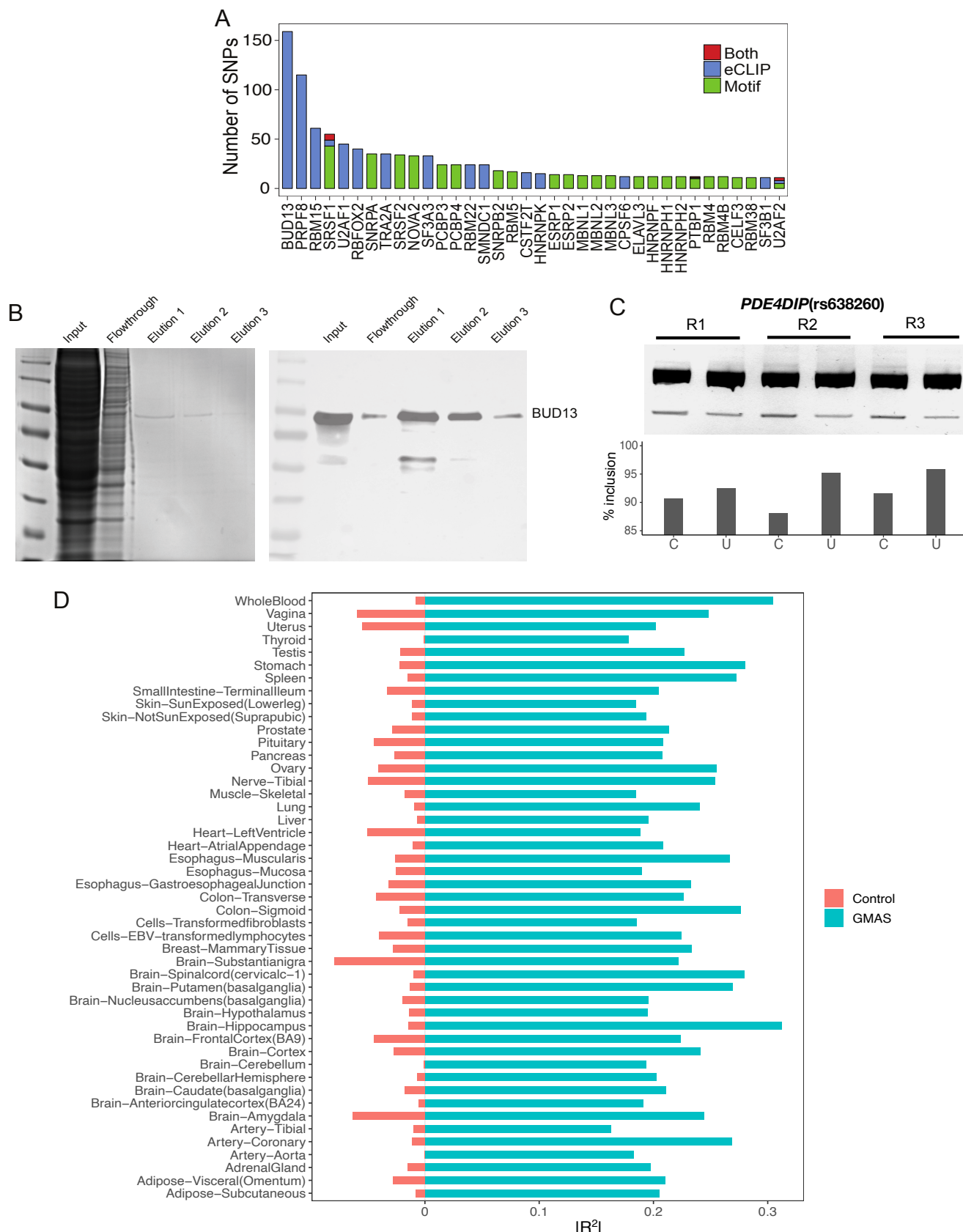


Fig. S9: (A) Number of functional SNPs predicted to alter RNA binding motifs of splicing factors by de novo motif and/or eCLIP overlap analyses. Both: functional SNPs predicted by both methods (B) Purification of recombinant BUD13. Mammalian overexpression of human BUD13 was carried out. pLJM1 3XFlag-Bud13-6HIS lentiviral plasmid was transfected into 293T cells. Stably overexpressed BUD13 was purified using HisTrap purification column and additional Flag affinity purification was performed. Detailed purification conditions are described in Methods. Purified BUD13 proteins were confirmed by SimplyBlue Safe staining (left) and western blot using BUD13 antibody (right). (C) Splicing of a minigene reporter carrying the exon in *PDE4DIP* regulated by rs638260, previously reported in Yang et al. 2019 (PMID: 30902979). (D) *BUD13* expression correlated with GMAS tag SNP allelic ratio. We required GMAS SNPs to overlap with BUD13 eCLIP peaks and randomly sampled an equal number of testable non-GMAS SNPs as control. For all 47 tissues, GMAS events are better correlated with *BUD13* expression levels than controls.

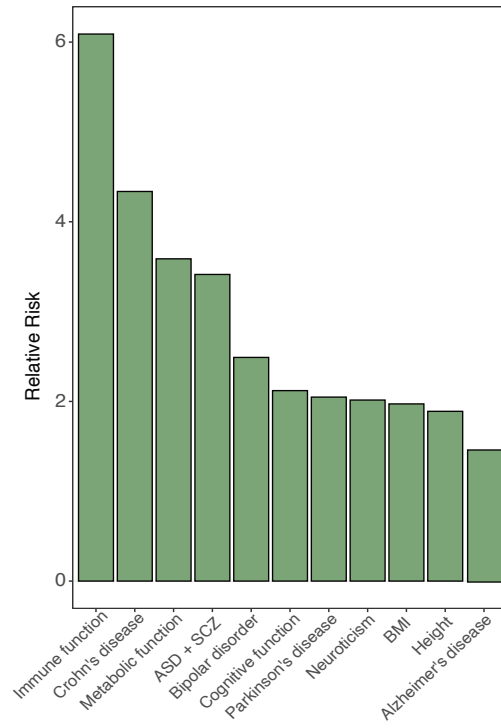
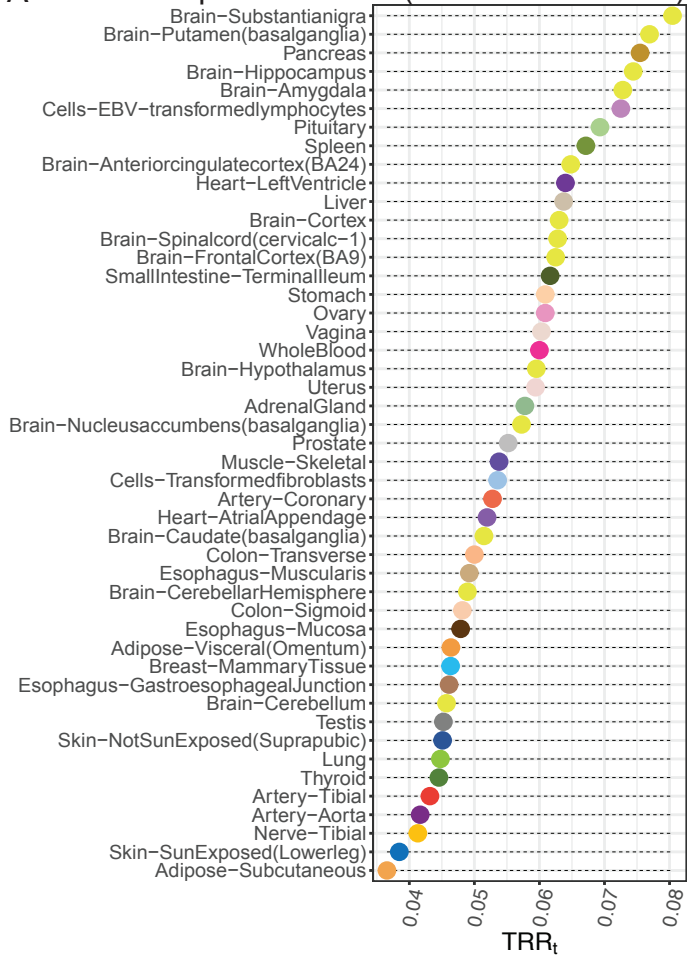
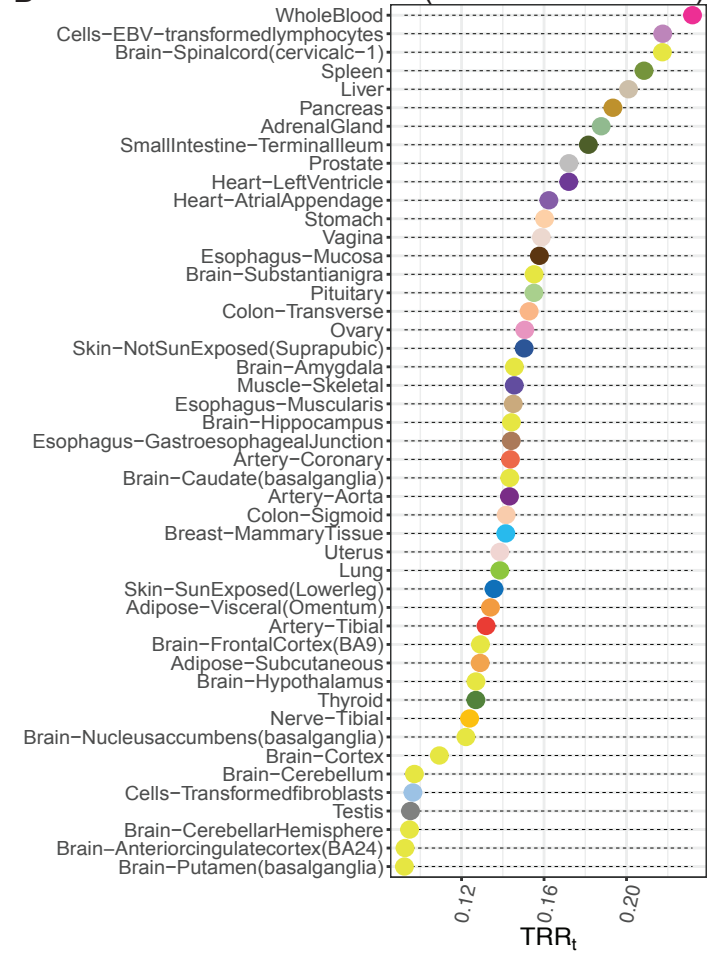


Fig. S10: Relative risk of putative functional SNPs in LD with selected trait/disease.

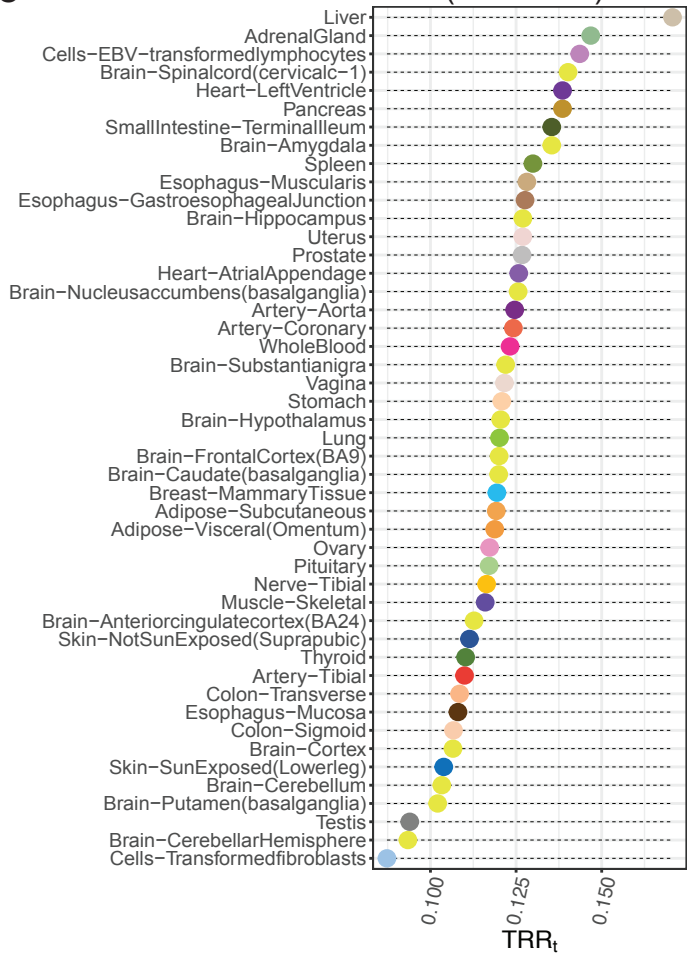
A Bipolar disorder (Putative functional)



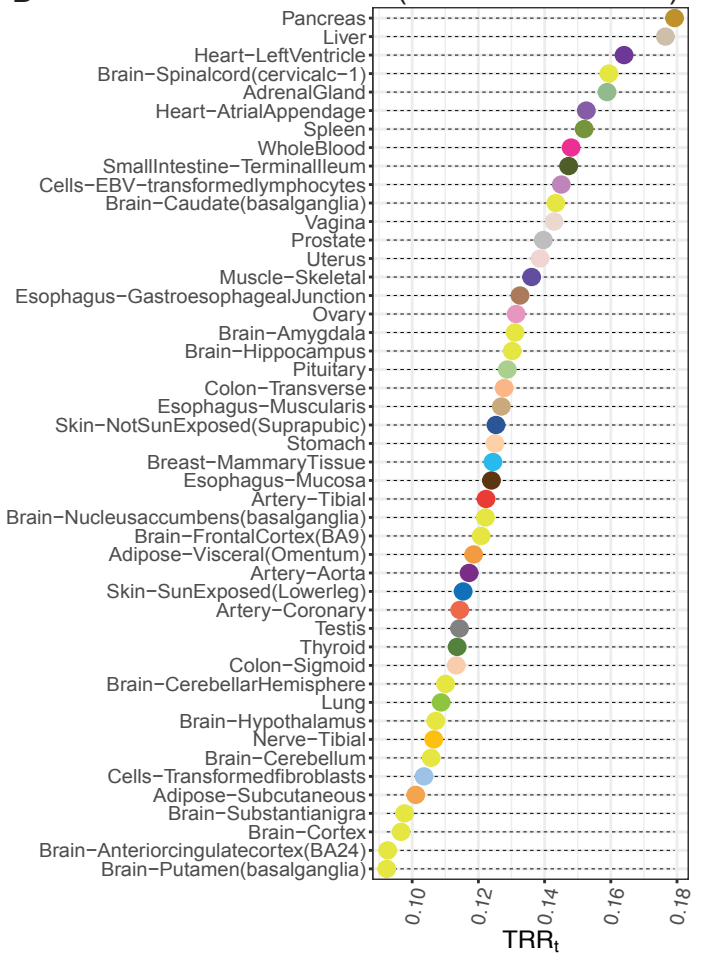
B Immune function (Putative functional)

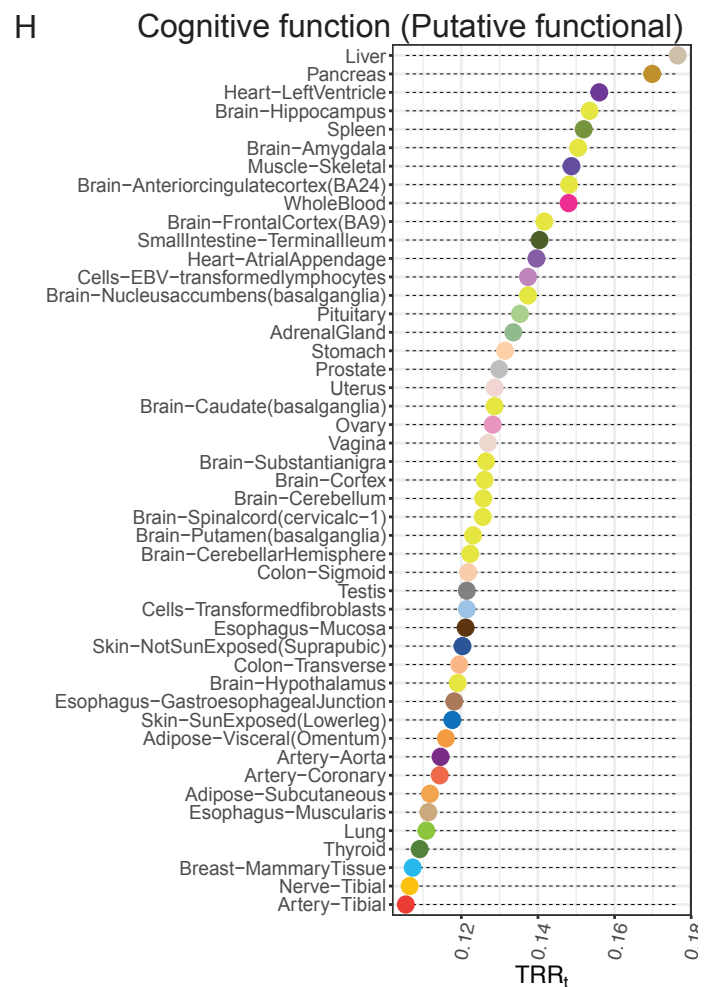
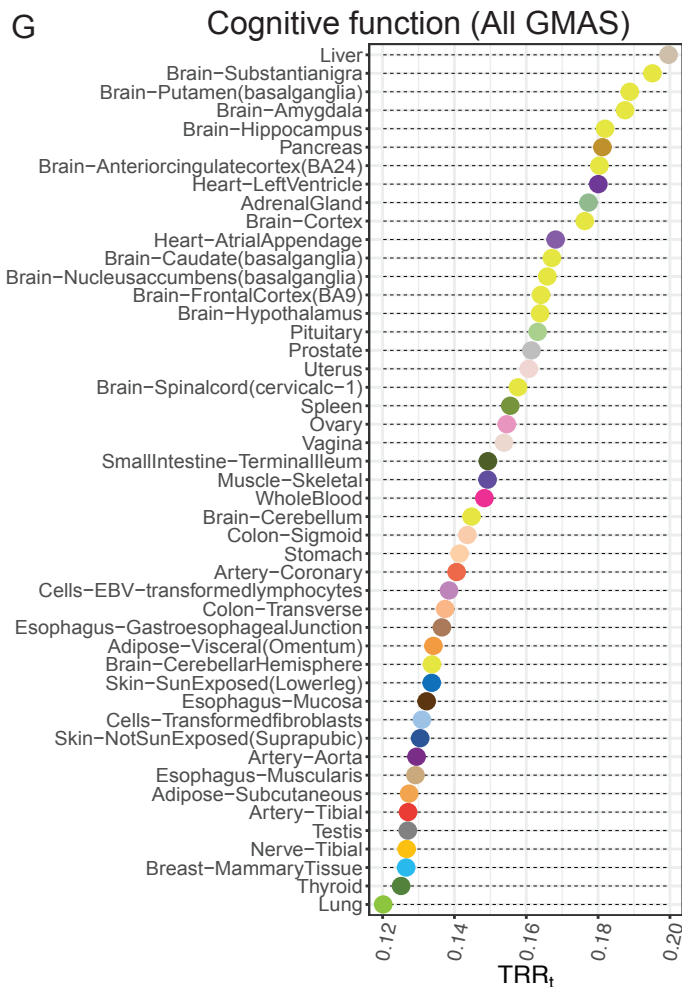
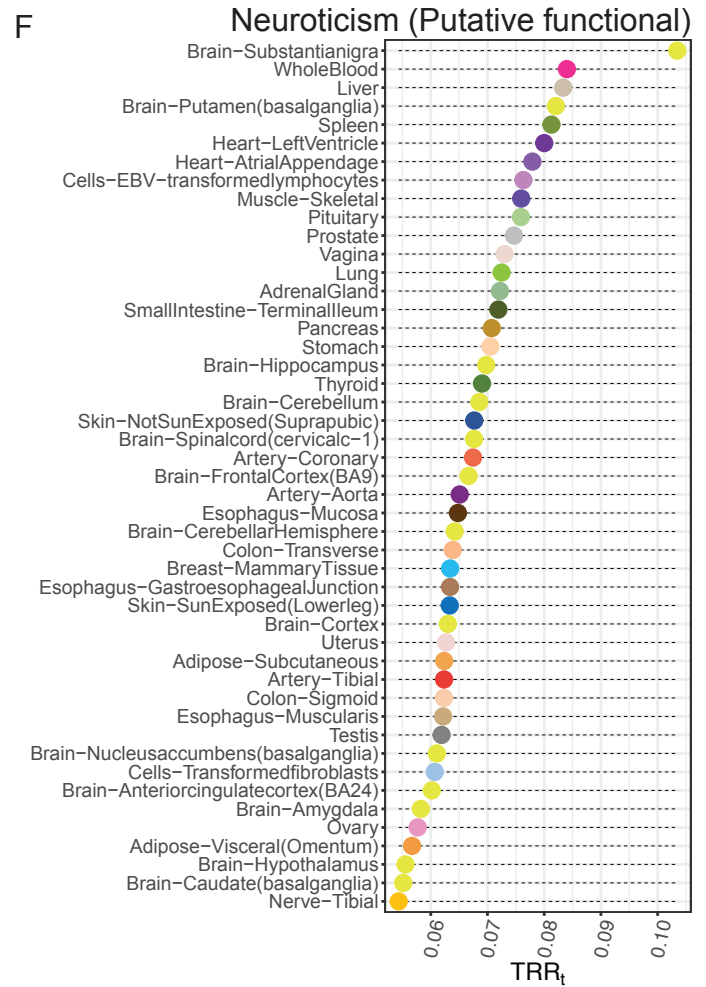
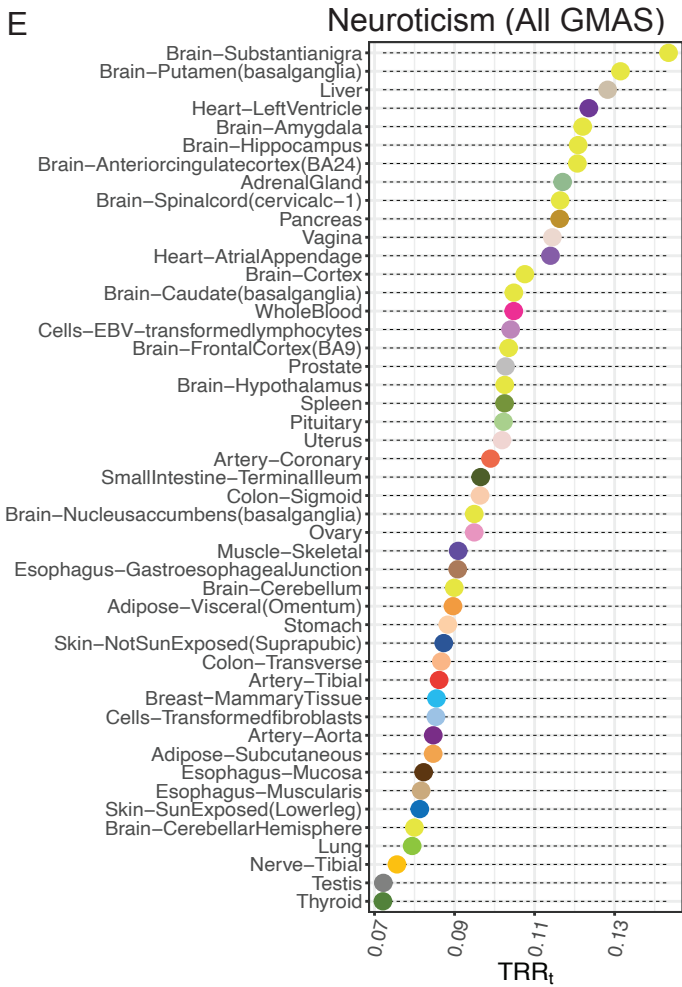


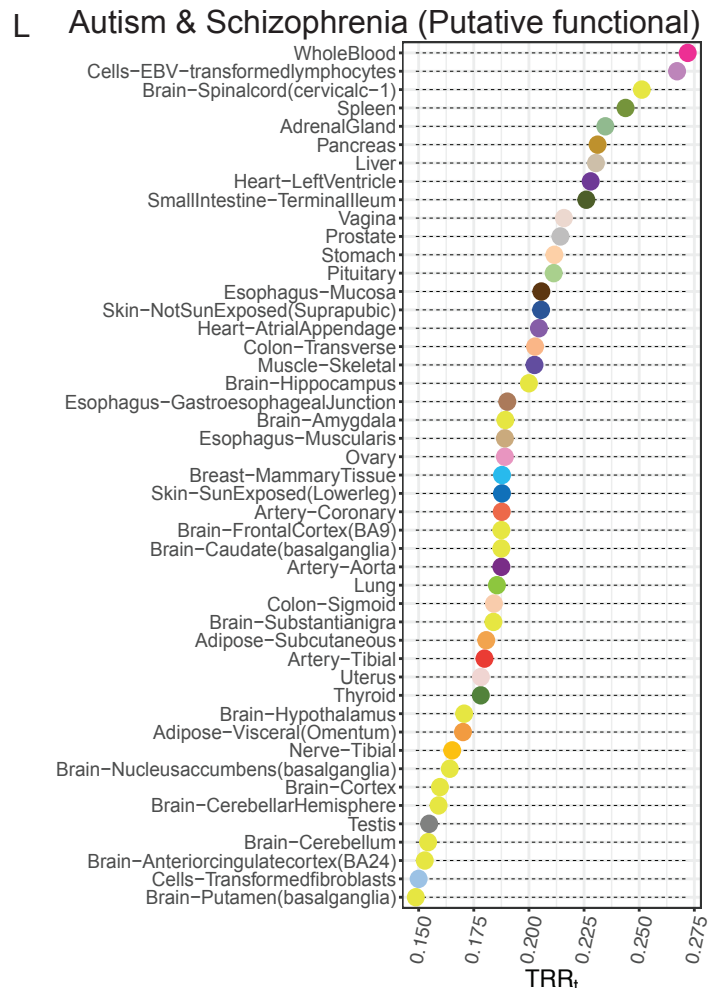
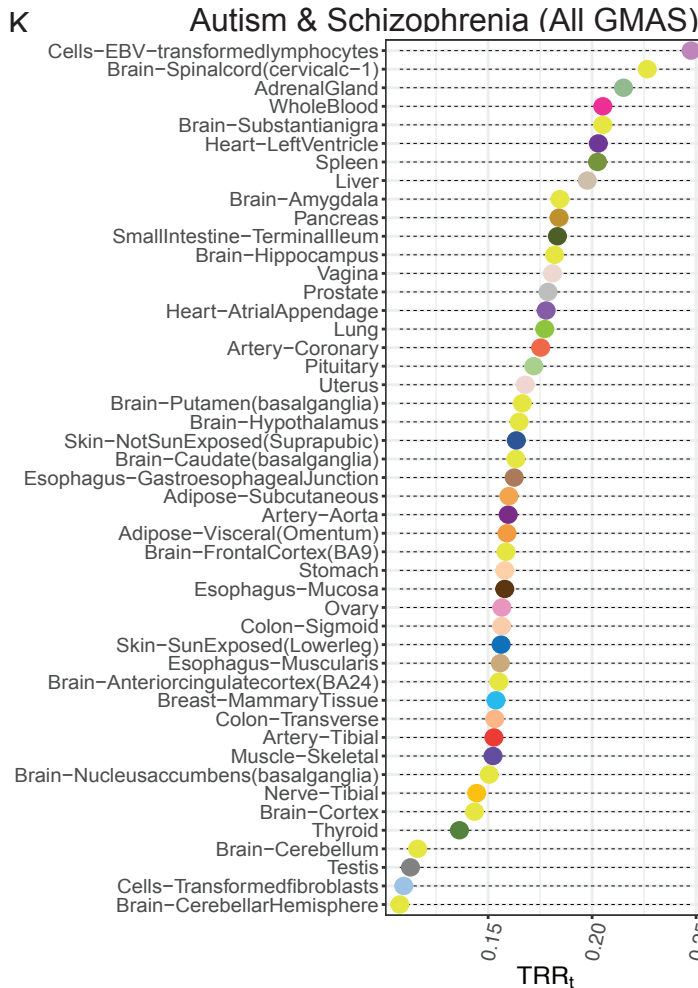
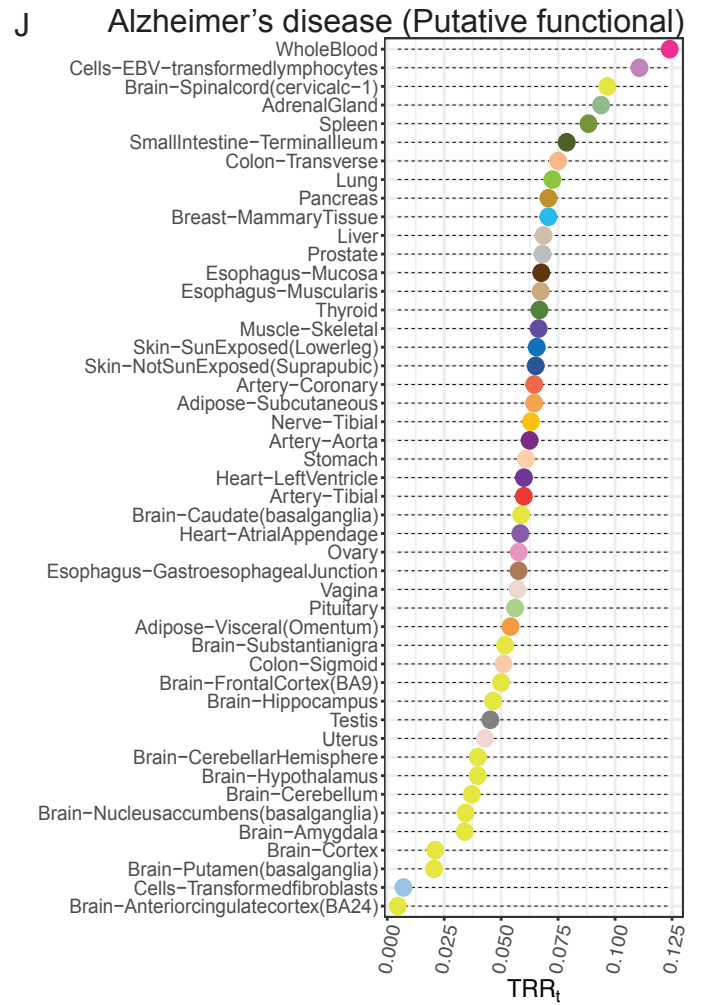
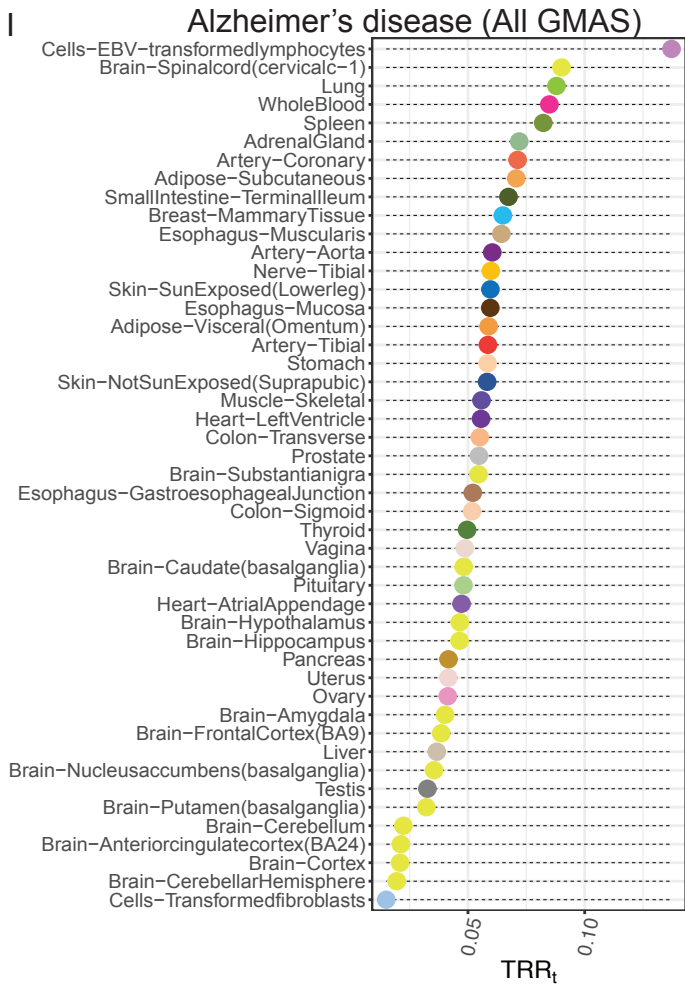
C Metabolic function (All GMAS)

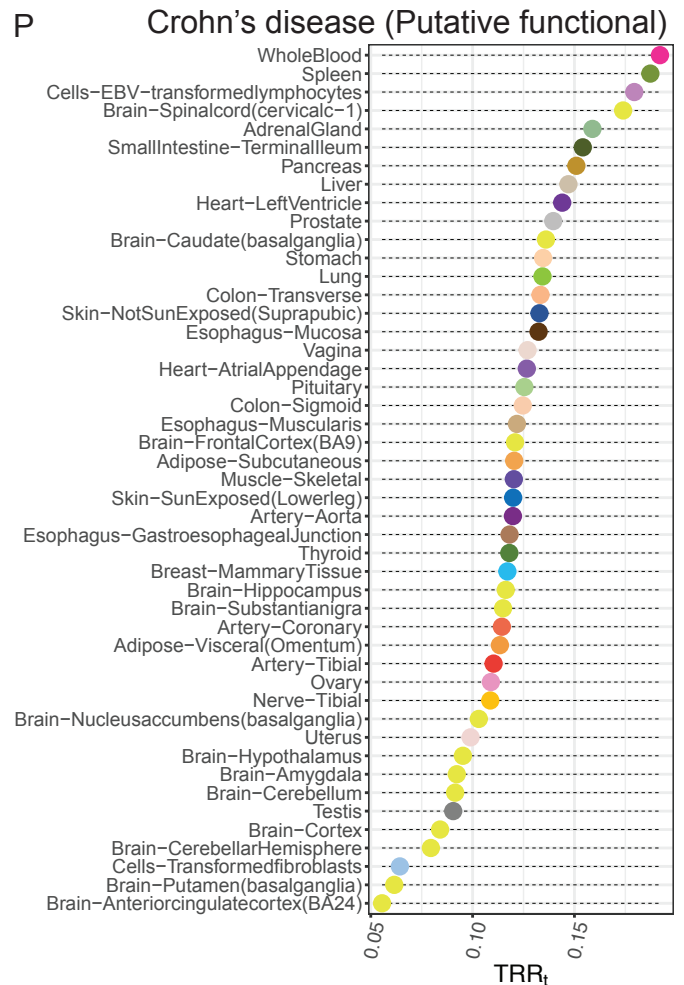
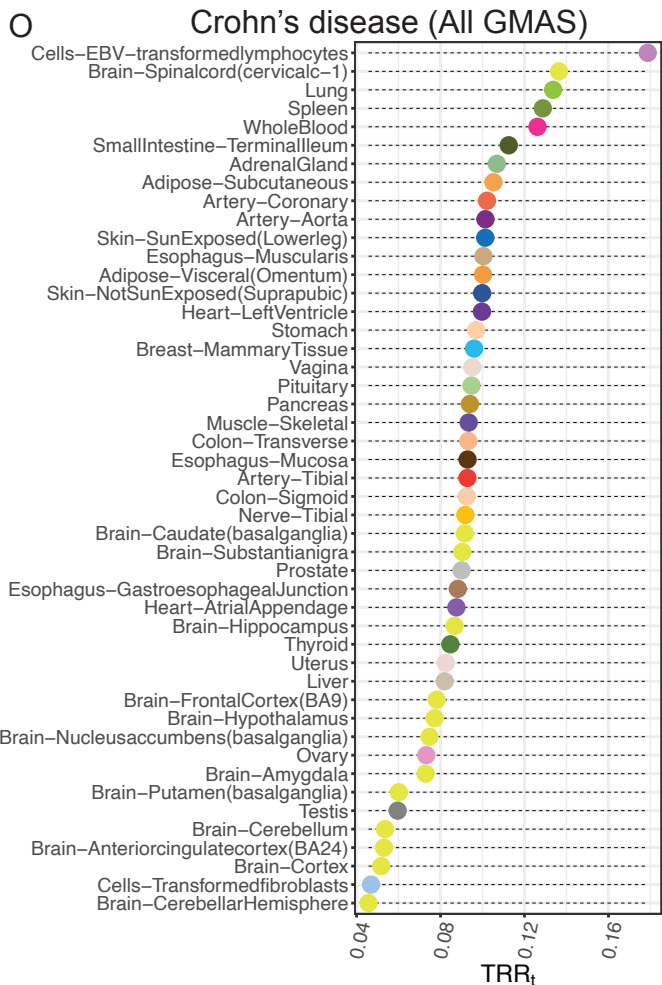
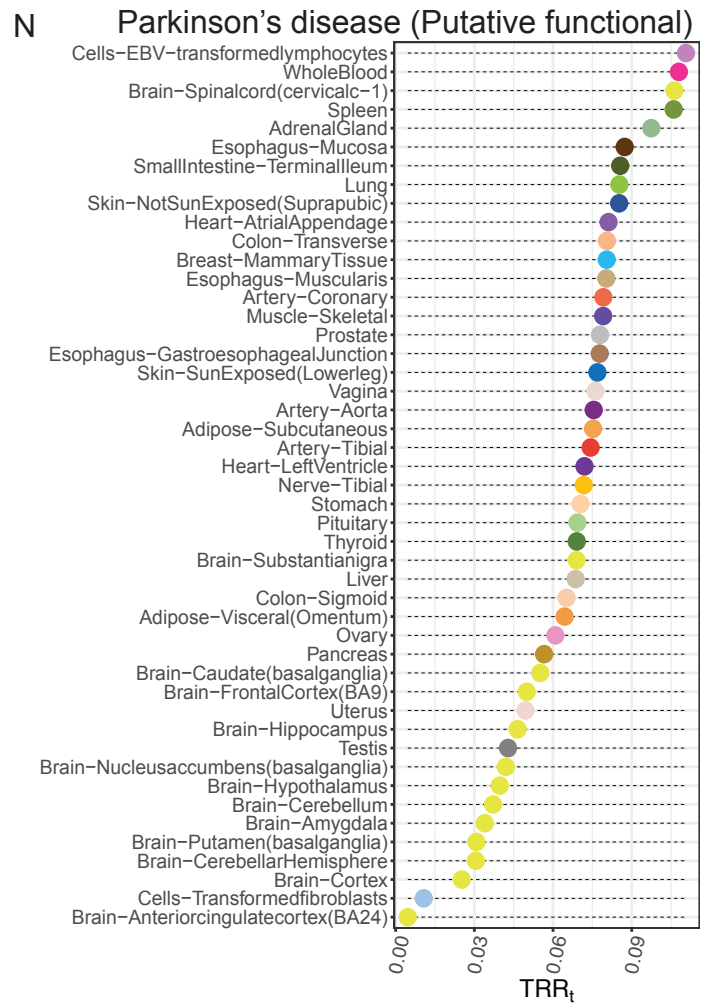
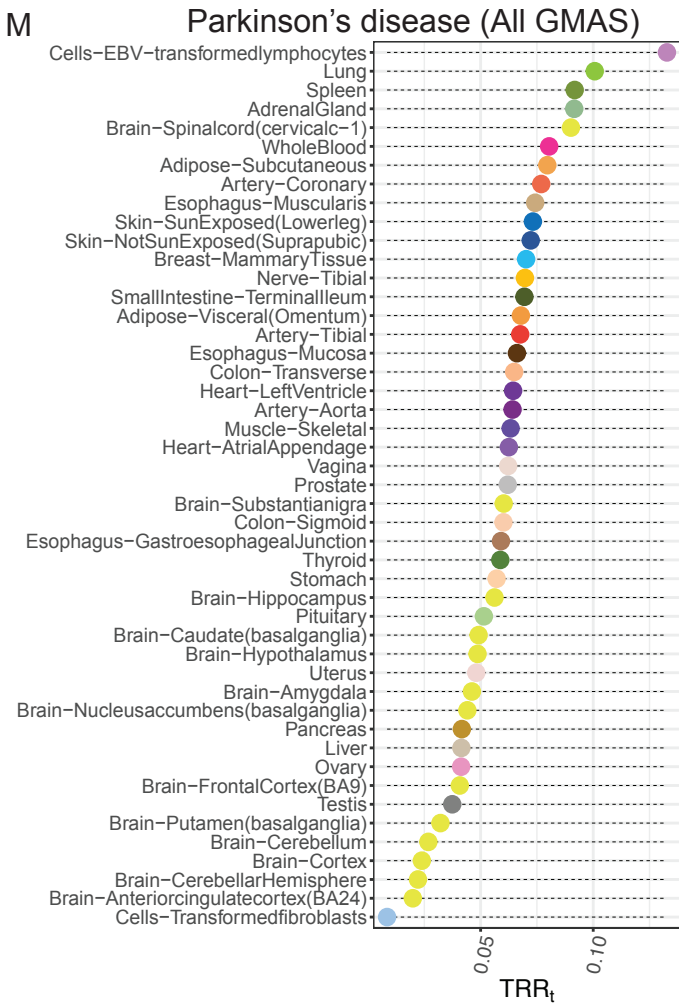


D Metabolic function (Putative functional)









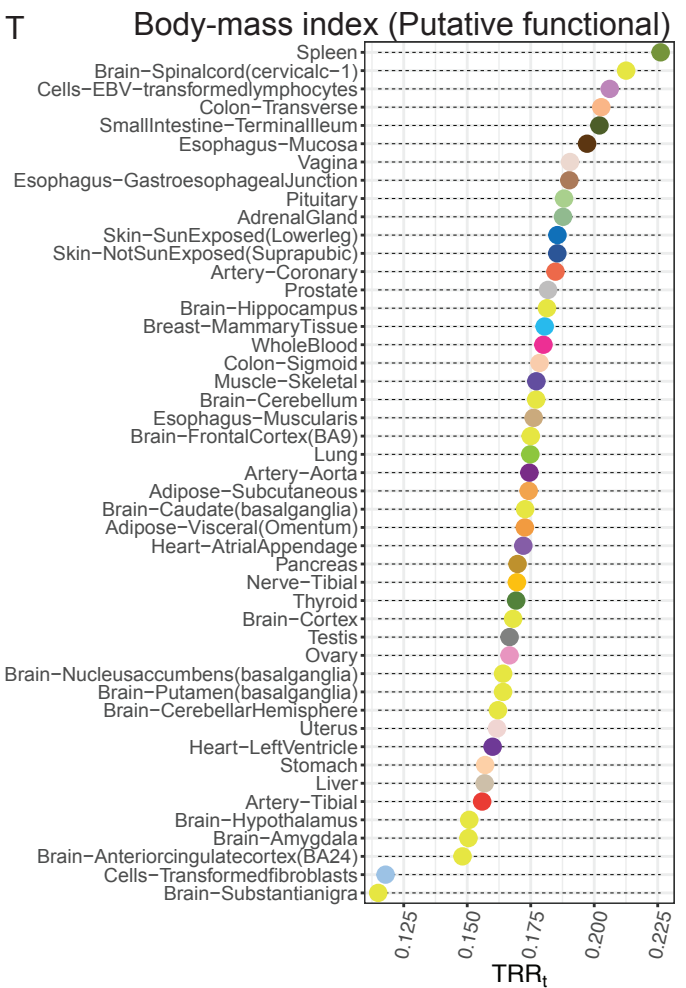
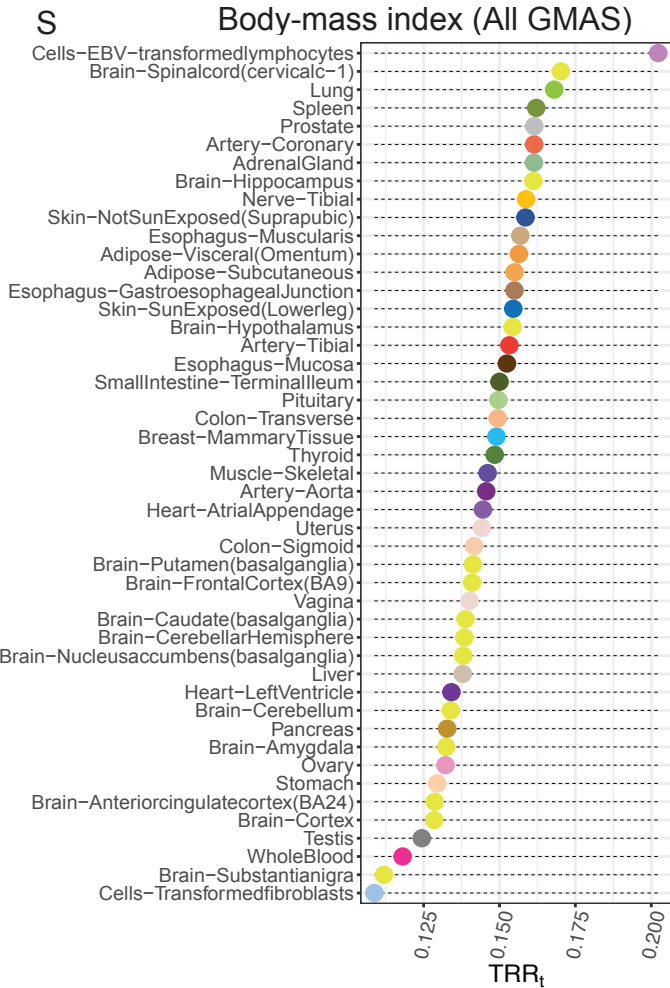
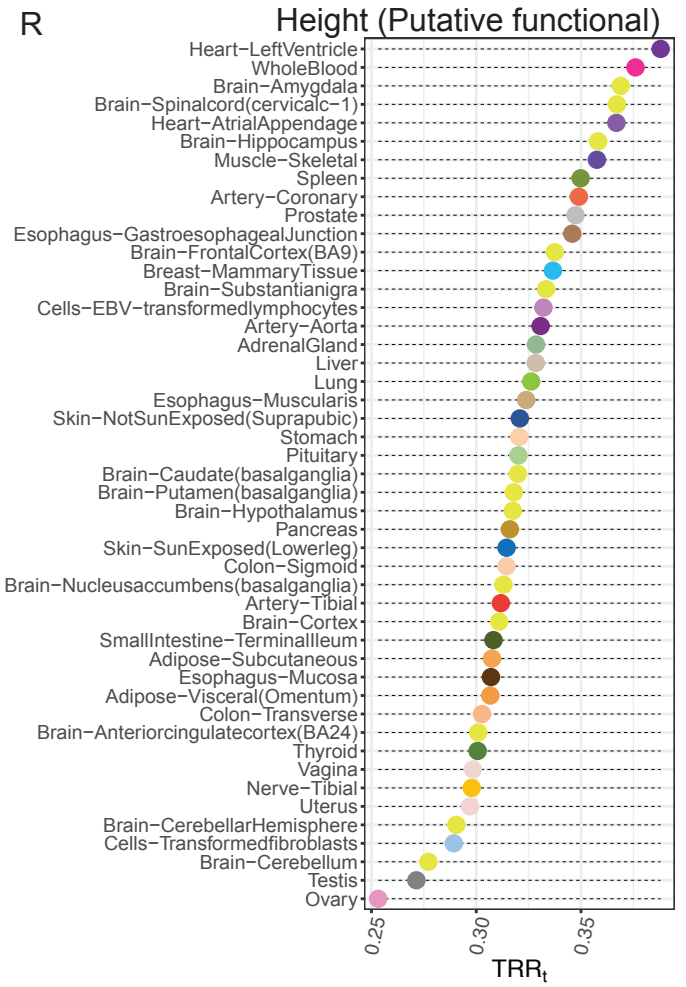
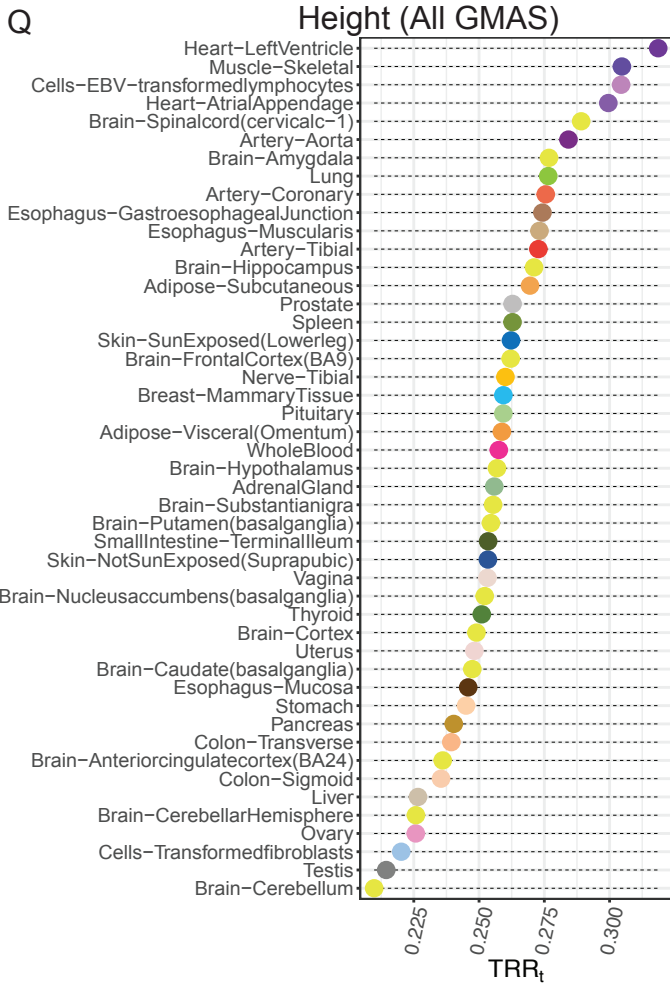
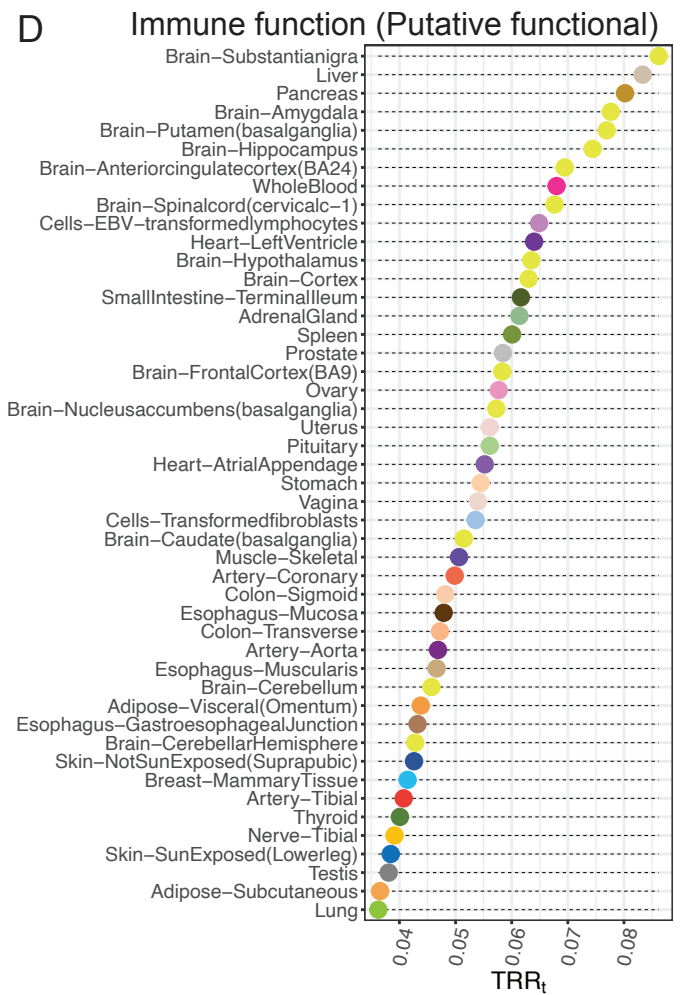
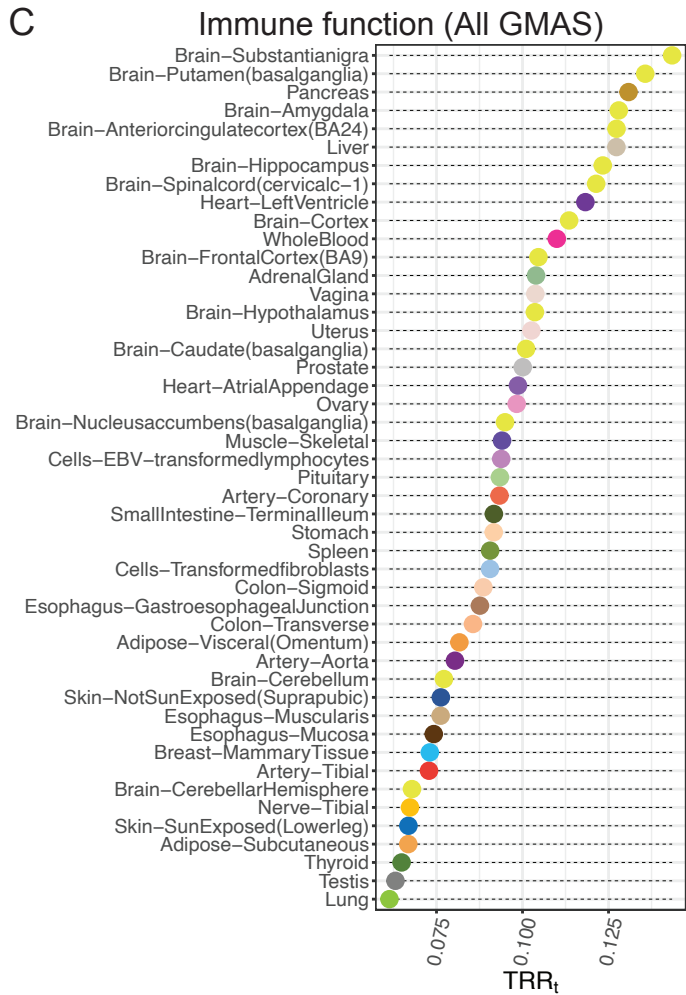
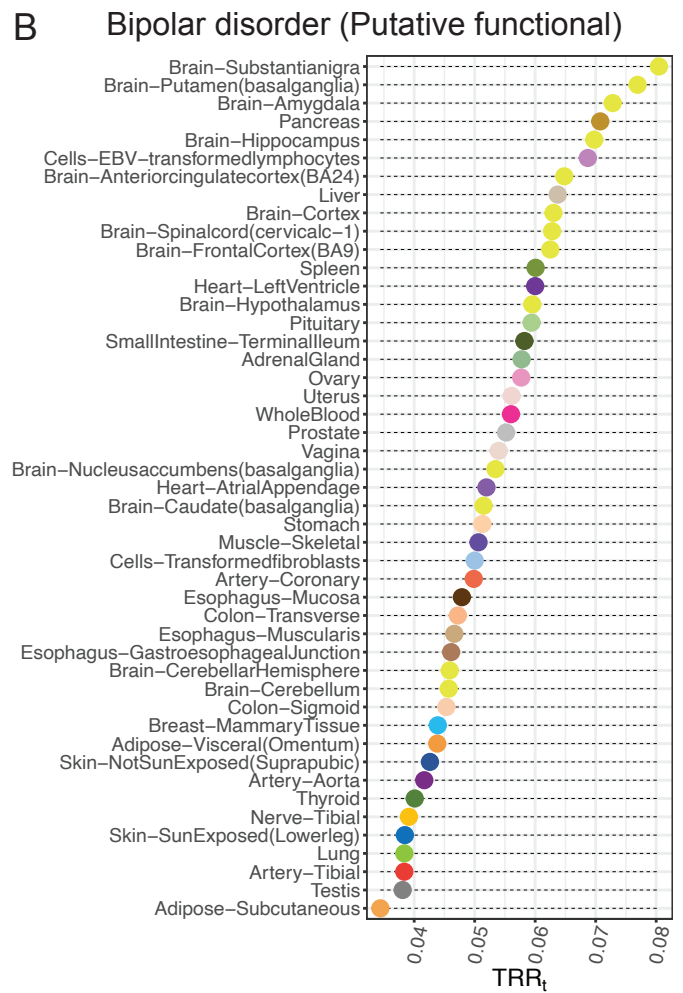
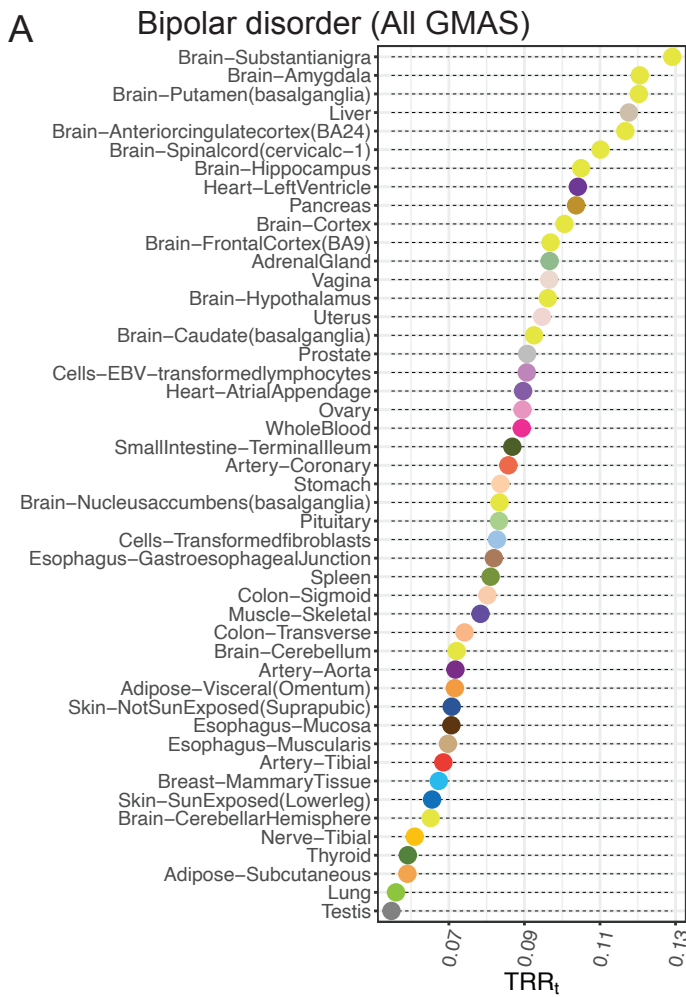
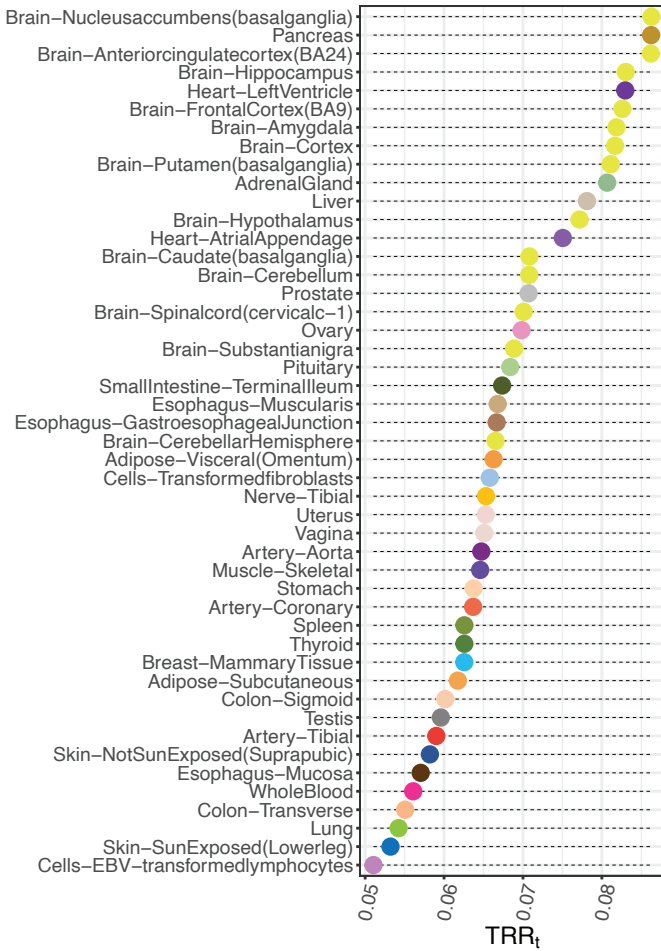


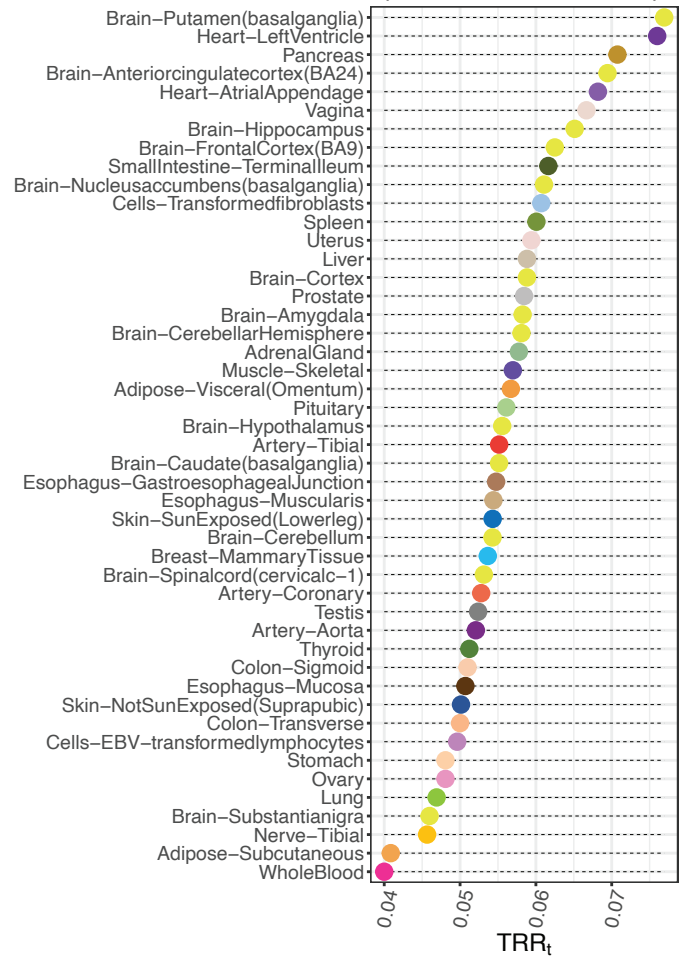
Fig. S11: Functional relevance of GMAS SNPs (A)-(T) Trait relevance ratios of all GMAS SNPs and putative functional SNPs (labeled accordingly) in LD with GWAS SNPs for different traits/diseases.



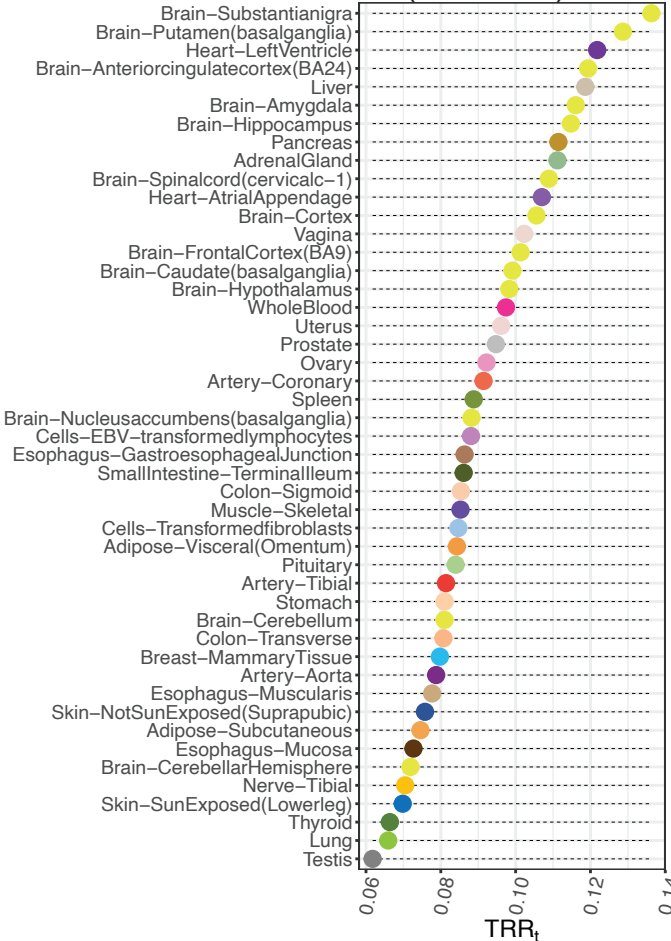
E Metabolic function (All GMAS)



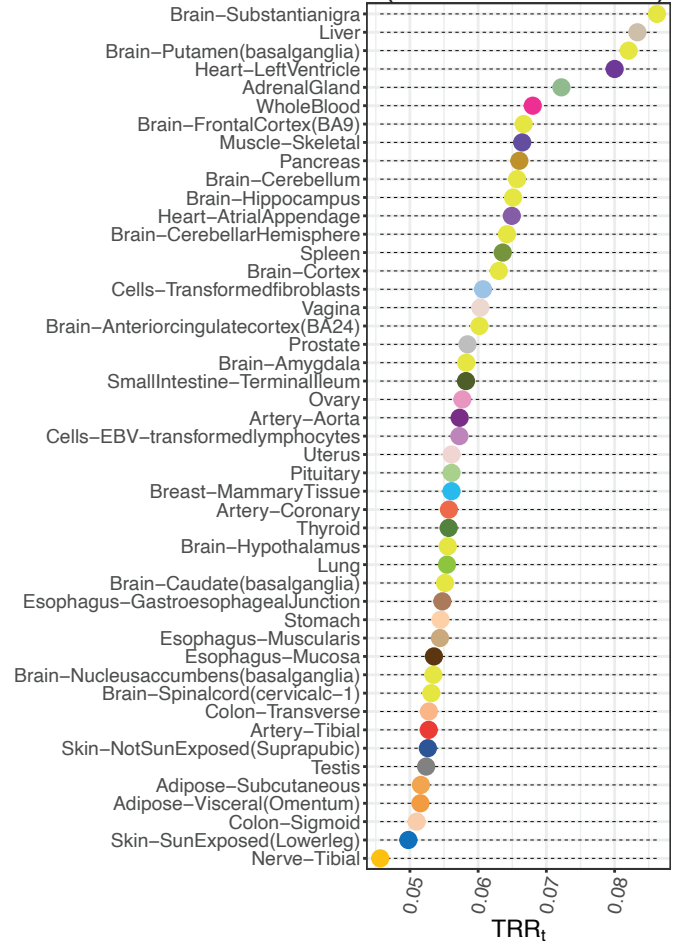
F Metabolic function (Putative functional)

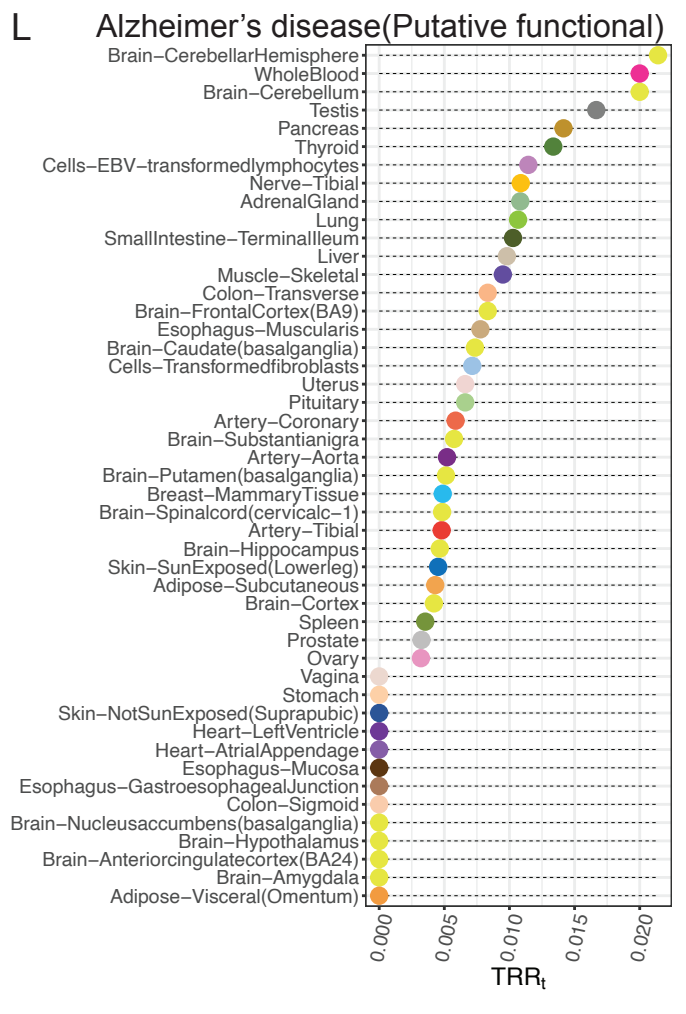
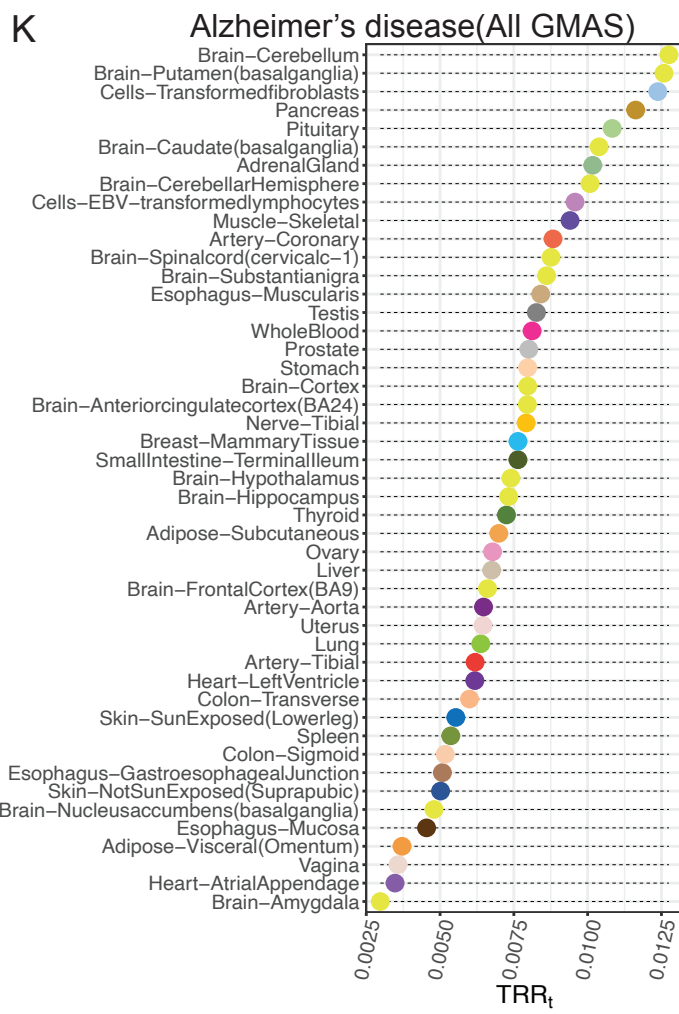
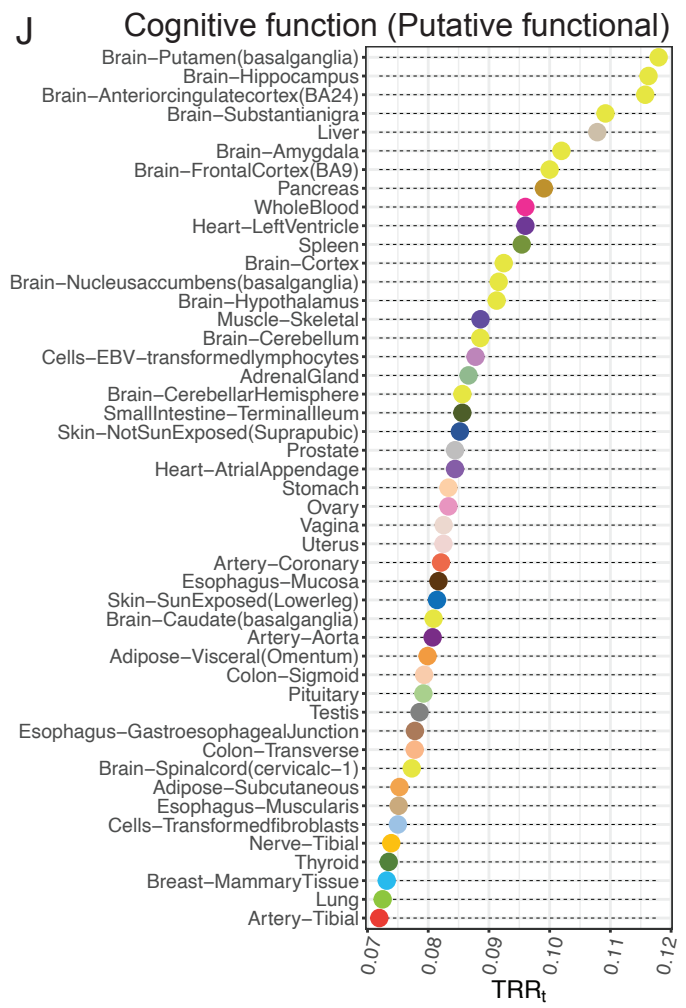
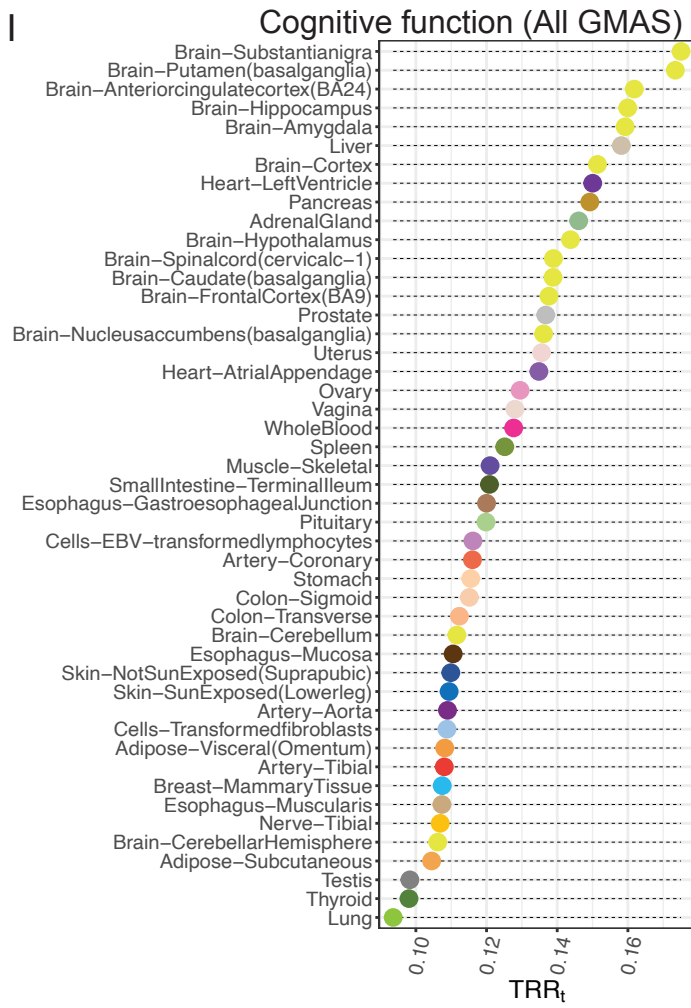


G Neuroticism (All GMAS)

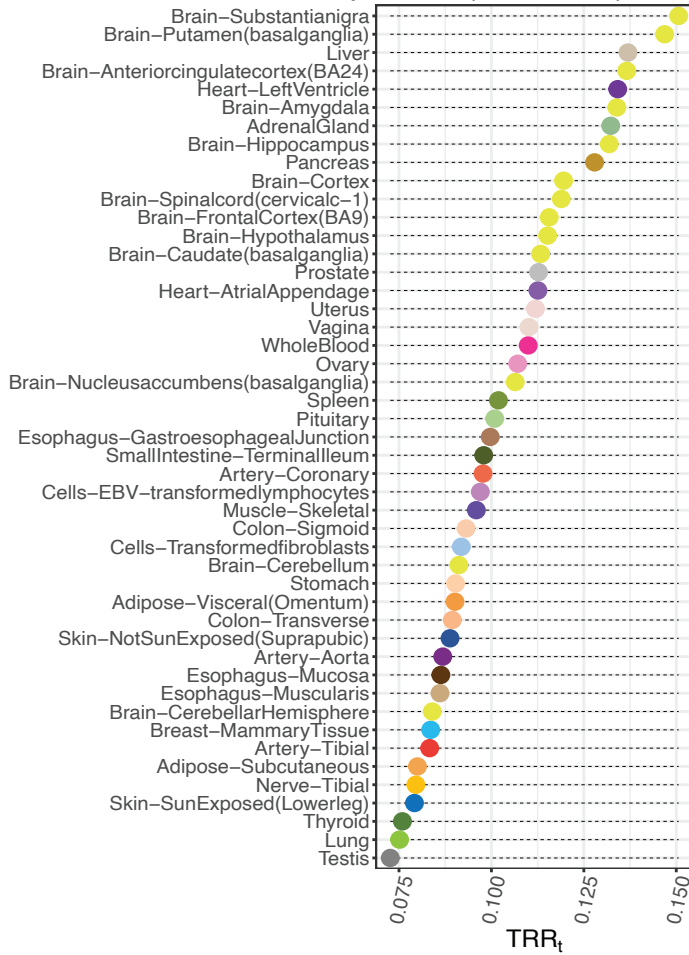


H Neuroticism (Putative functional)

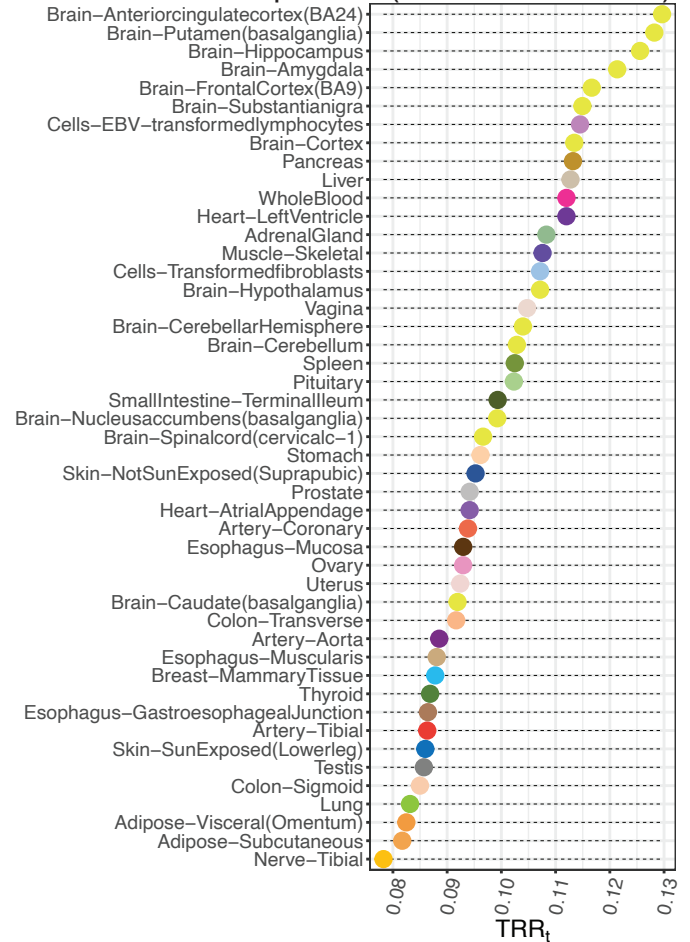




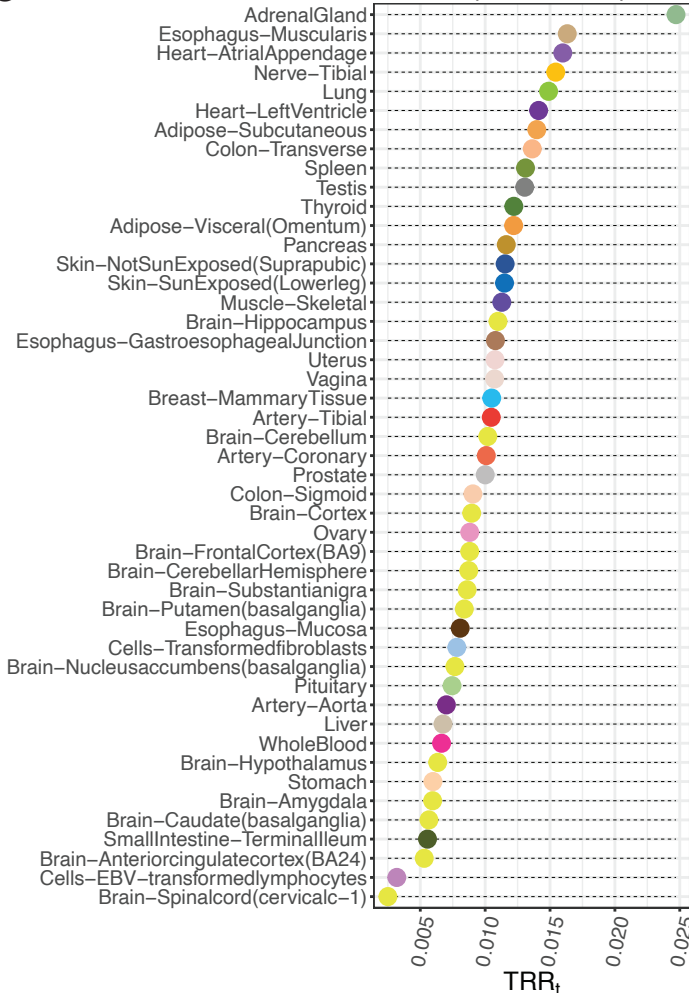
M Autism & Schizophrenia (All GMAS)



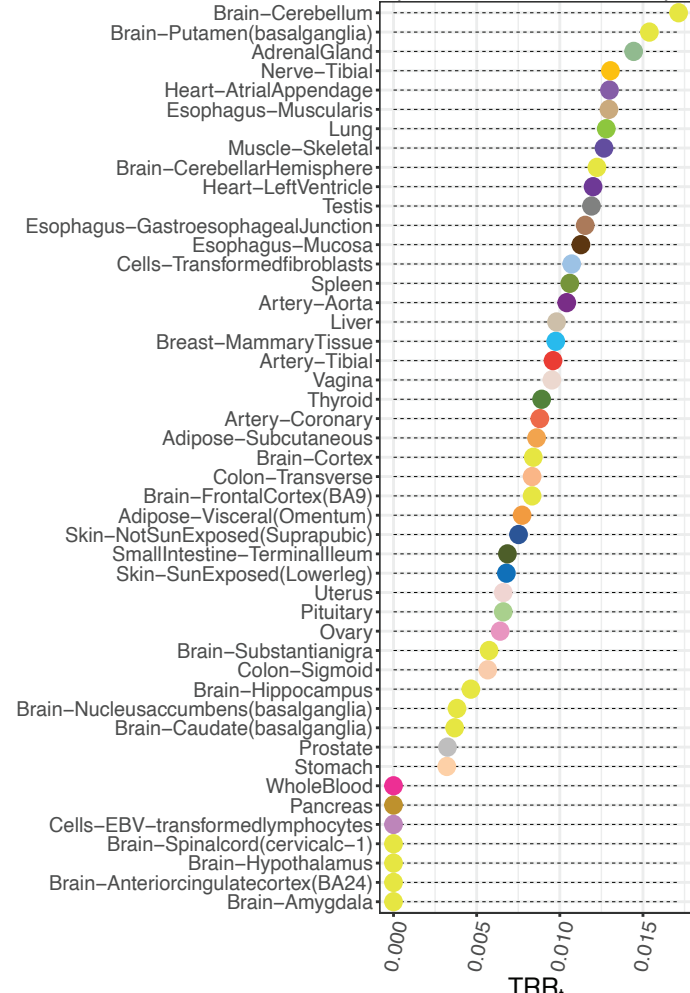
N Autism & Schizophrenia (Putative functional)

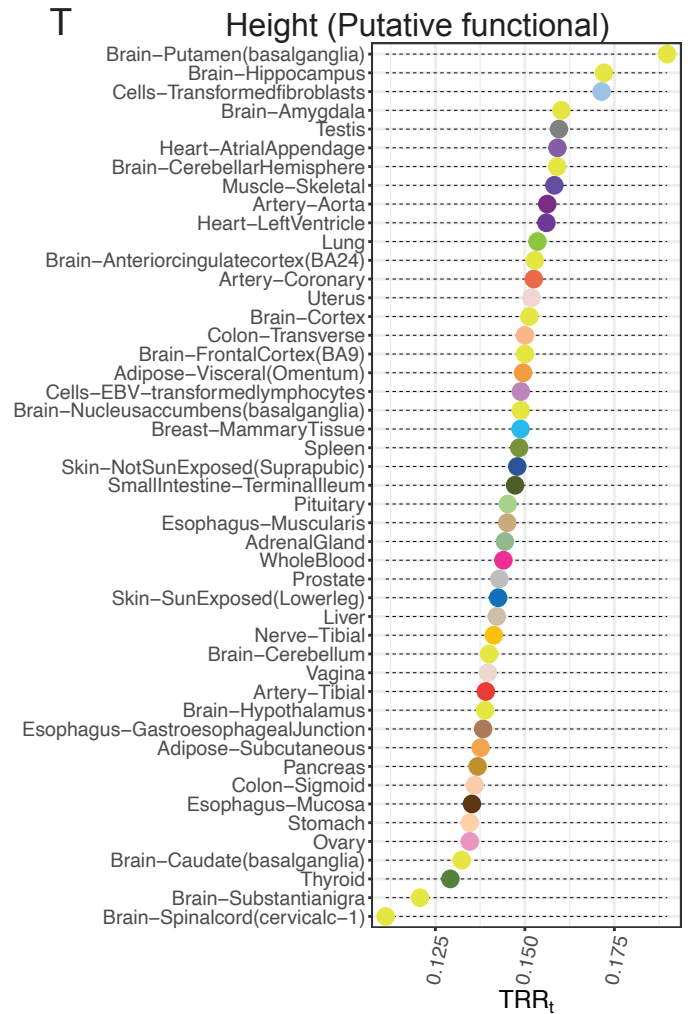
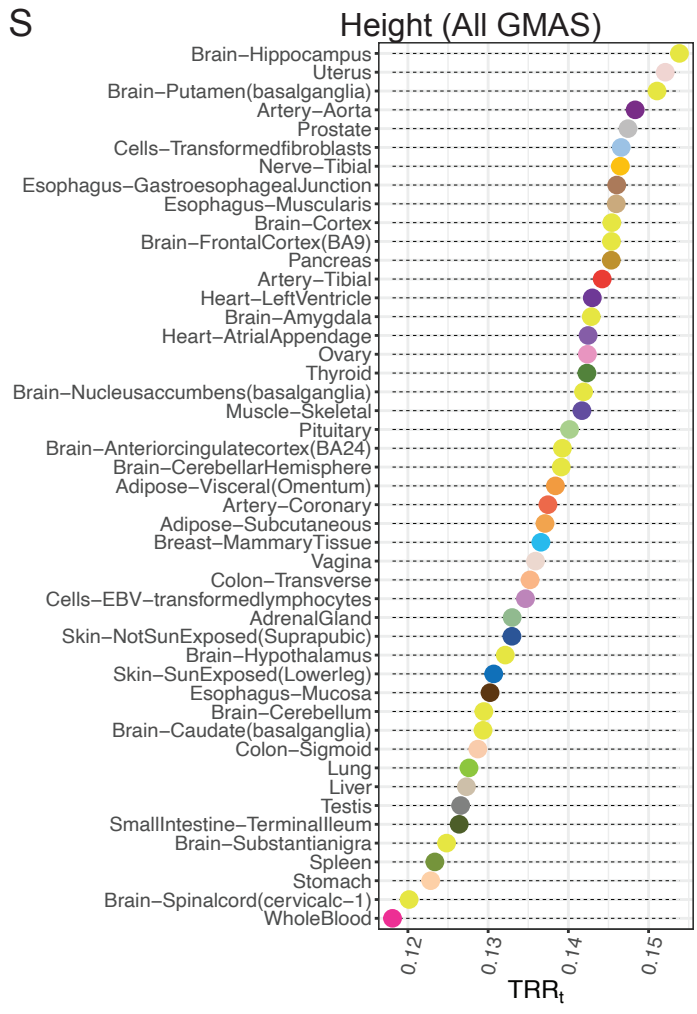
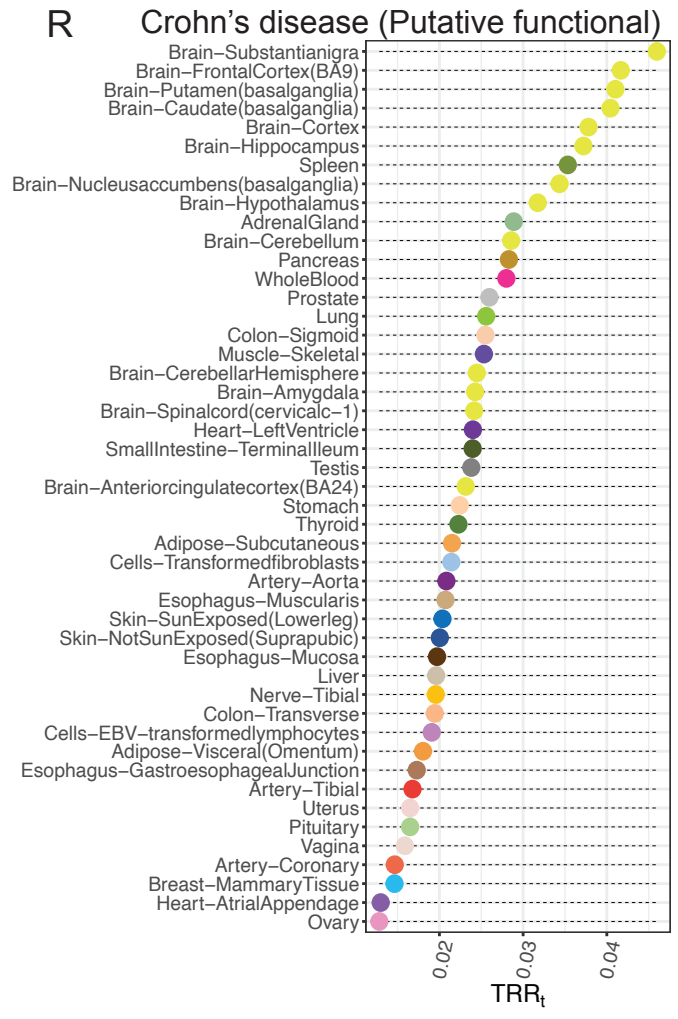
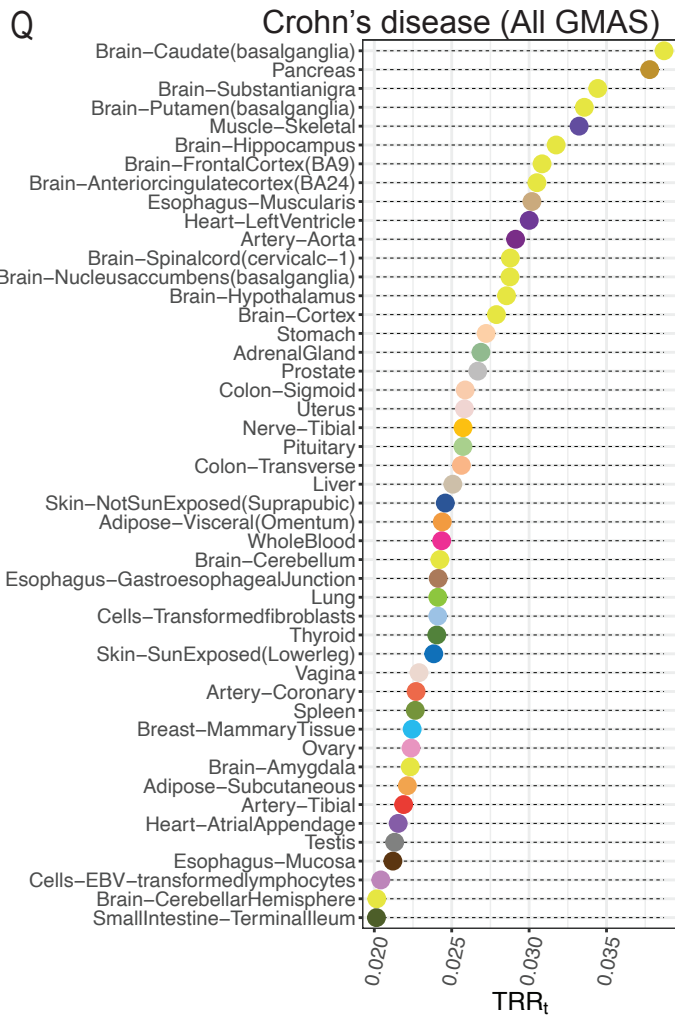


O Parkinson's disease (All GMAS)



P Parkinson's disease (Putative functional)





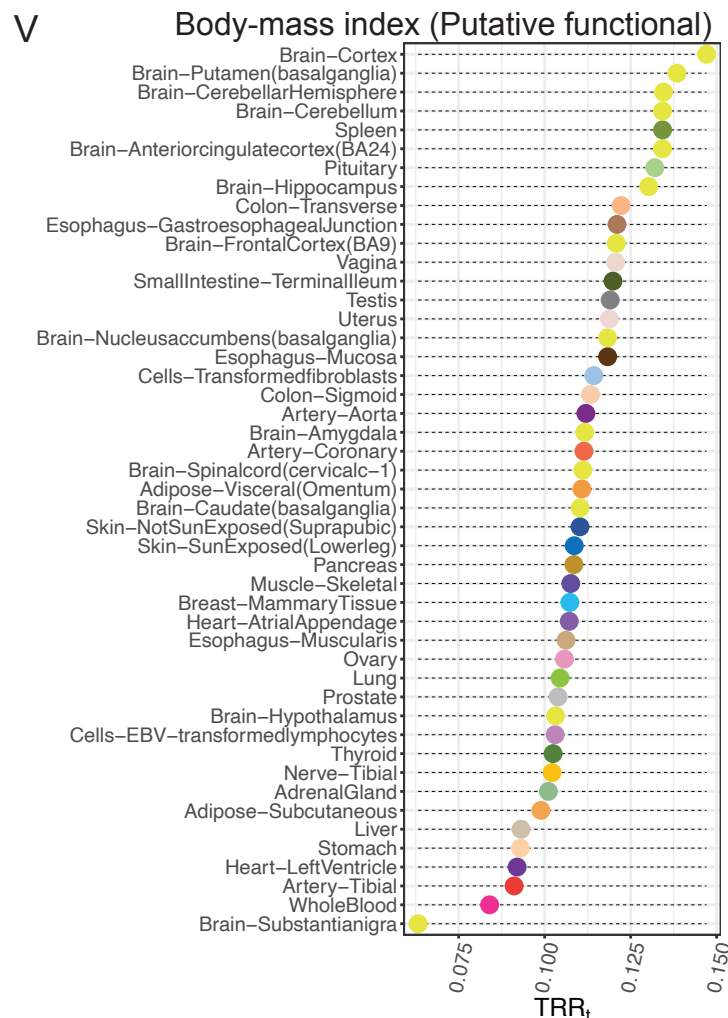
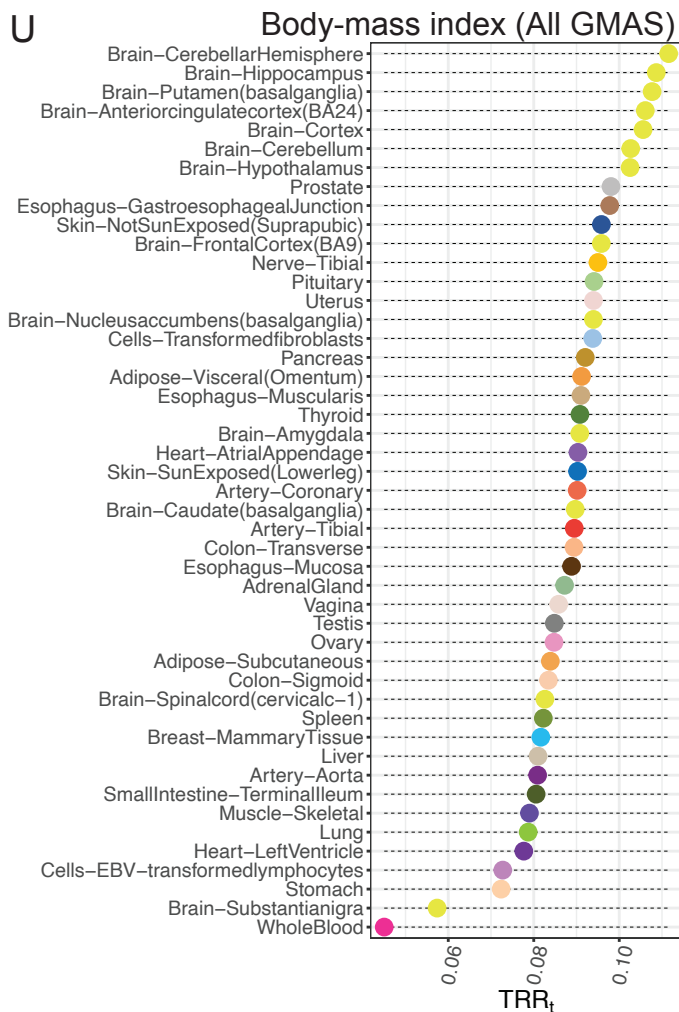


Fig. S12: Functional relevance of relevance SNPs after controlling for tissue-specific gene expression. (A)-(V) Trait relevance ratios of all GMAS SNPs and putative functional SNPs (labeled accordingly) in LD with GWAS SNPs for different traits/diseases.