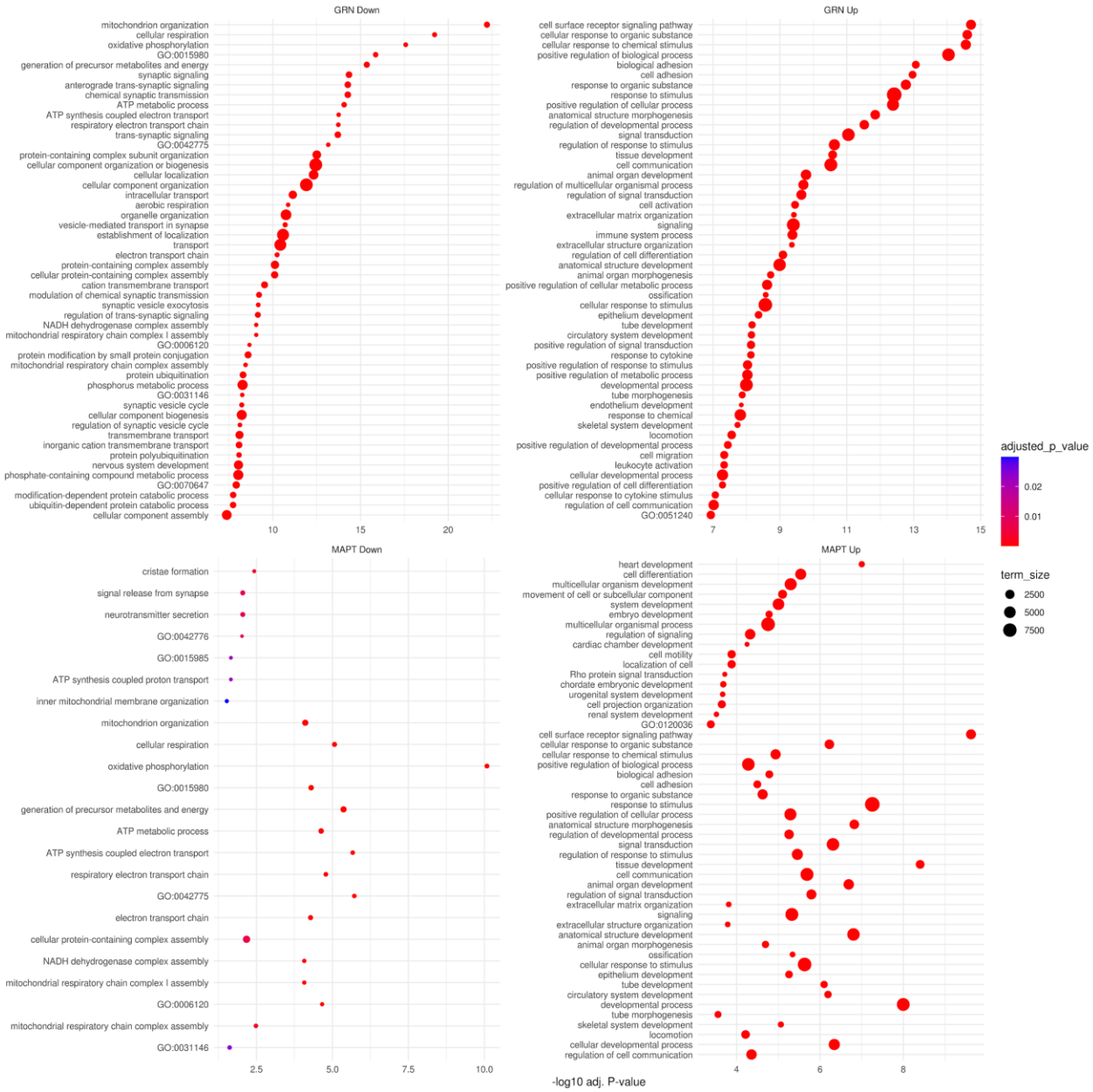
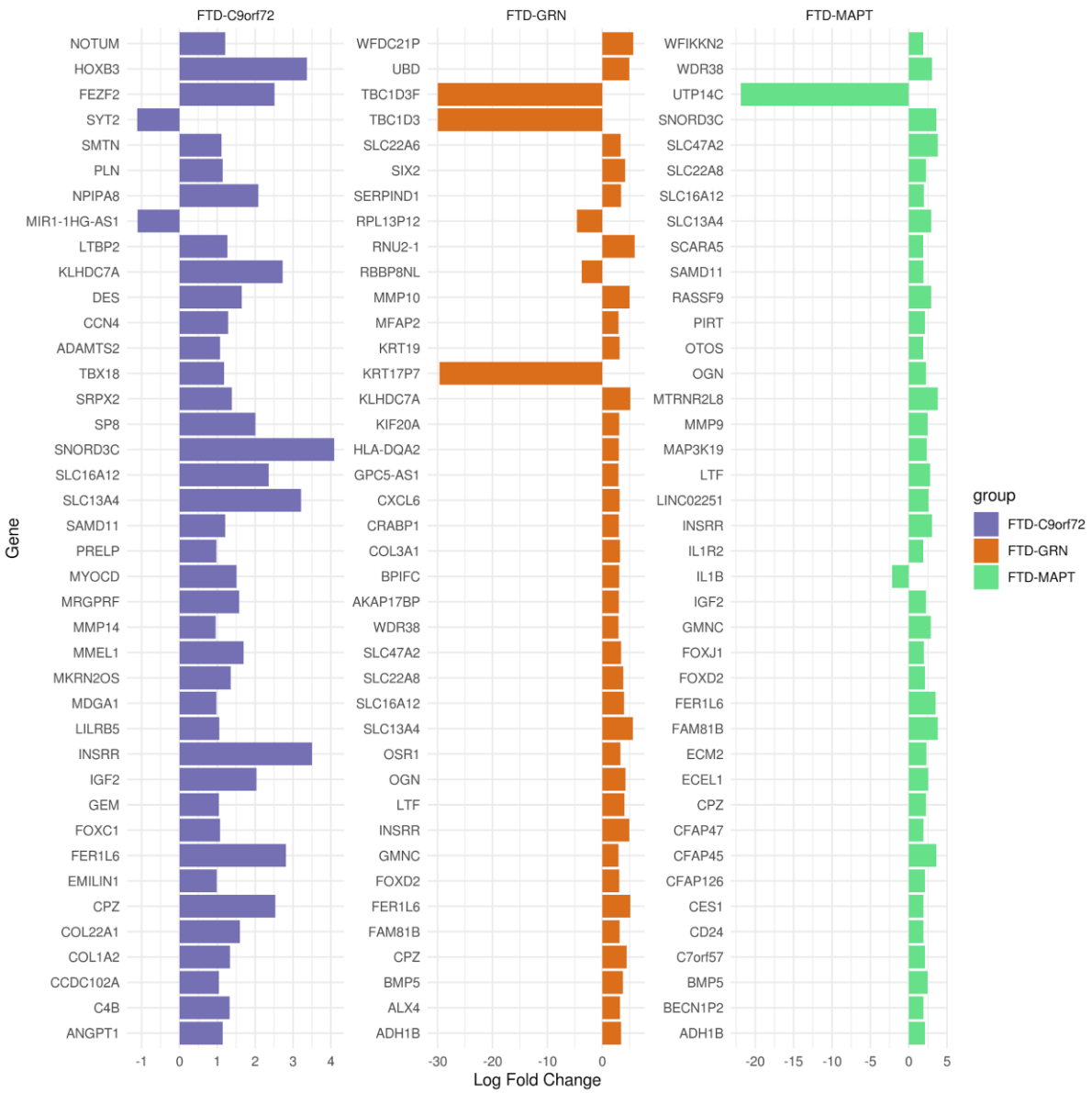
Supplementary Material

Integrated multi-omics analysis reveals common and distinct dysregulated pathways in genetic subtypes of Frontotemporal Dementia

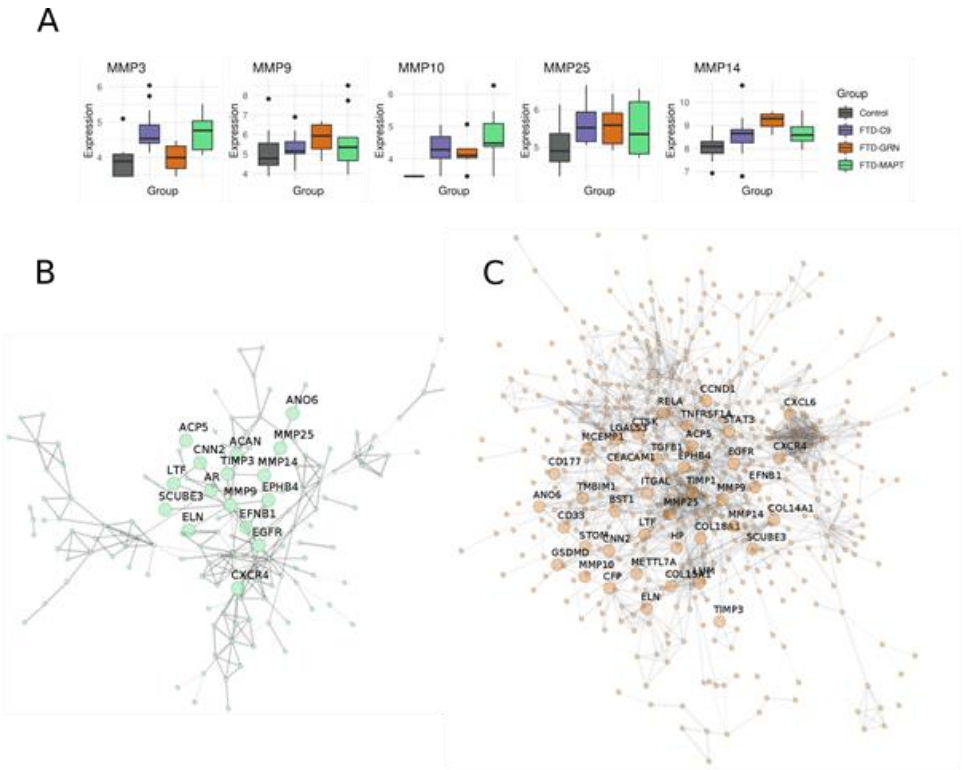
Supplementary Figures



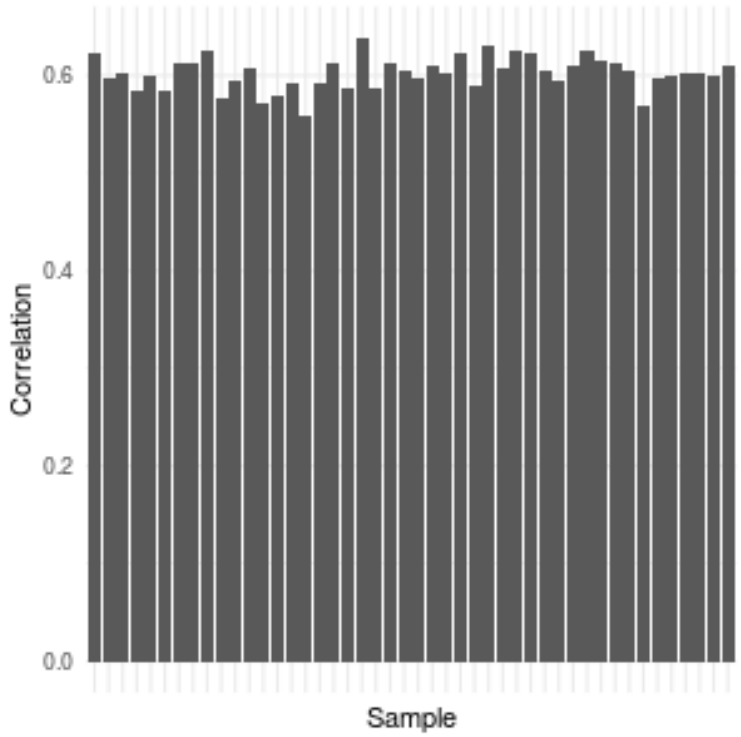
Supplementary Figure S1 GO Biological process enrichment in up- and down-regulated genes for FTD-MAPT and FTD-GRN. Each dot depicts a significantly enriched biological process, the size corresponds to the number of genes belonging to this process. Position on the x-axis corresponds to the negative log10 adjusted P-value.



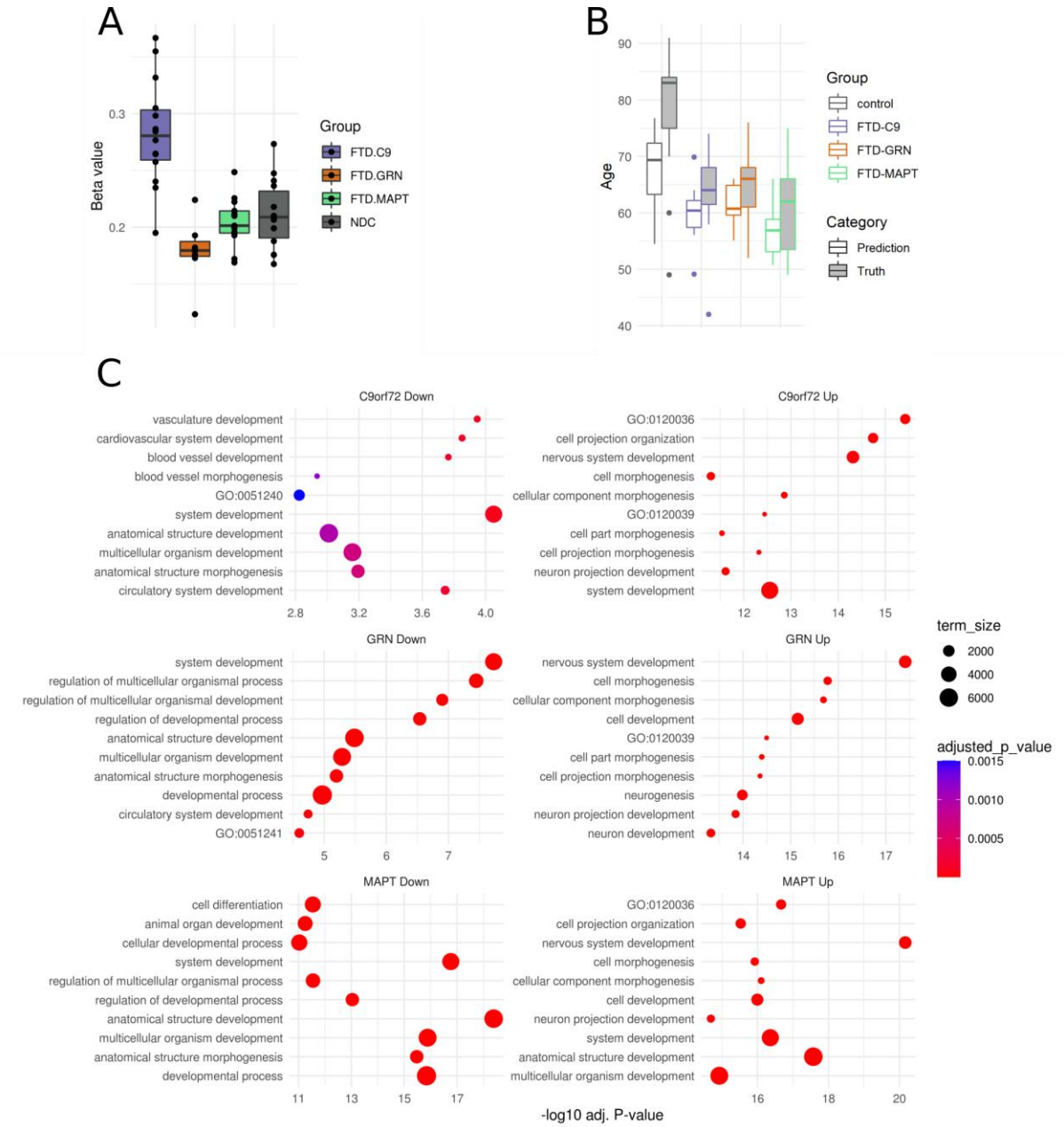
Supplementary Figure S2: Highly dysregulated genes in FTD. Shown are the 40 genes with the largest log fold-changes for each disease group. Each bar represents the log fold change (x-axis) of a specific gene. The different colours correspond to the three disease groups as specified in the legend.



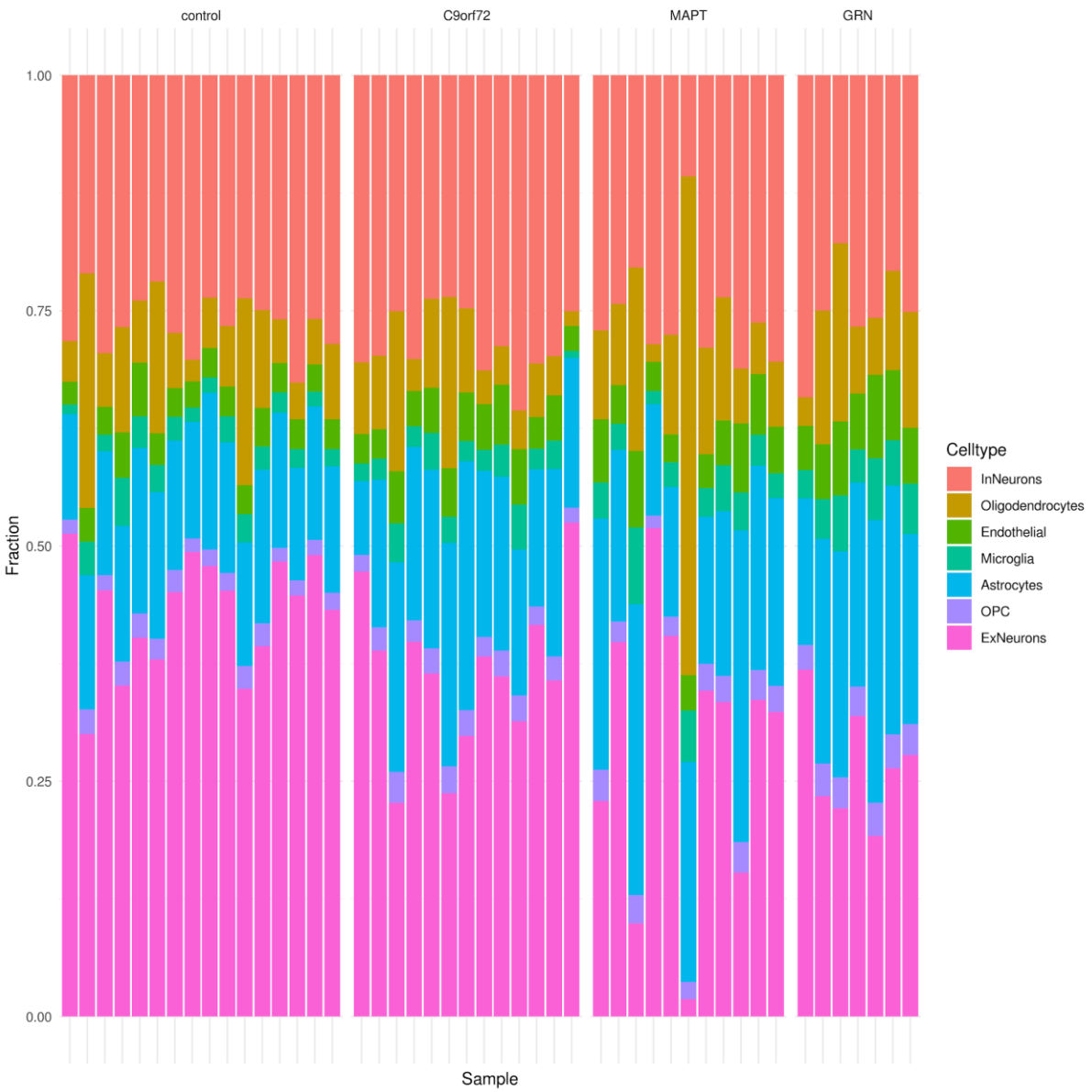
Supplementary Figure 3: MMPs are up-regulated in FTD-GRN and FTD-MAPT. A Box plot of normalized expression values for several up-regulated MMPs. **B** STRING-DB PPI network of genes up-regulated in FTD-MAPT. Disconnected nodes were removed, only connections with a minimum score of 0.7 were kept. MMPs and genes directly connected to them are highlighted. **C** STRING-DB PPI network of up-regulated genes in FTD-GRN (log-fold-change > 0.5). Disconnected nodes were removed and only connections with minimum score were kept. MMPs and genes directly connected to MMPs are highlighted.



Supplementary Figure S4 Sample-wise correlation of RNA-seq and CAGE-seq gene expression. Gene expression was measured with RNA-seq and CAGE-seq. Shown is the sample-wise Pearson's correlation coefficient of normalized and variance stabilized counts. CAGE-seq data was transformed to gene expression by assigning counts of CAGE-seq peak clusters to the promoter of the closest gene with a maximal distance of 2,000 base pairs.



Supplementary Figure S5: Pathway enrichment of genes proximal to differentially methylated sites. A Group-wise Beta methylation values of the CpG site ‘cg01589155’ at the C9orf72 locus. **B** Predicted and true age of patients using the Wenda algorithm and the methylation data. **C** The top 10 most significantly enriched biological processes are shown for genes close to hypermethylated (“Up”) or hypomethylated (“Down”) CpG sites for all disease groups.



Supplementary Figure S6 Sample-wise cell composition from deconvolution analysis. Each bar depicts one sample of the RNA-seq data from the frontal lobe. The height of each coloured bar represents the fraction of the corresponding cell type predicted for this sample. The bars are split according to the groups control, FTD-C9orf72, FTD-MAPT, and FTD-GRN.

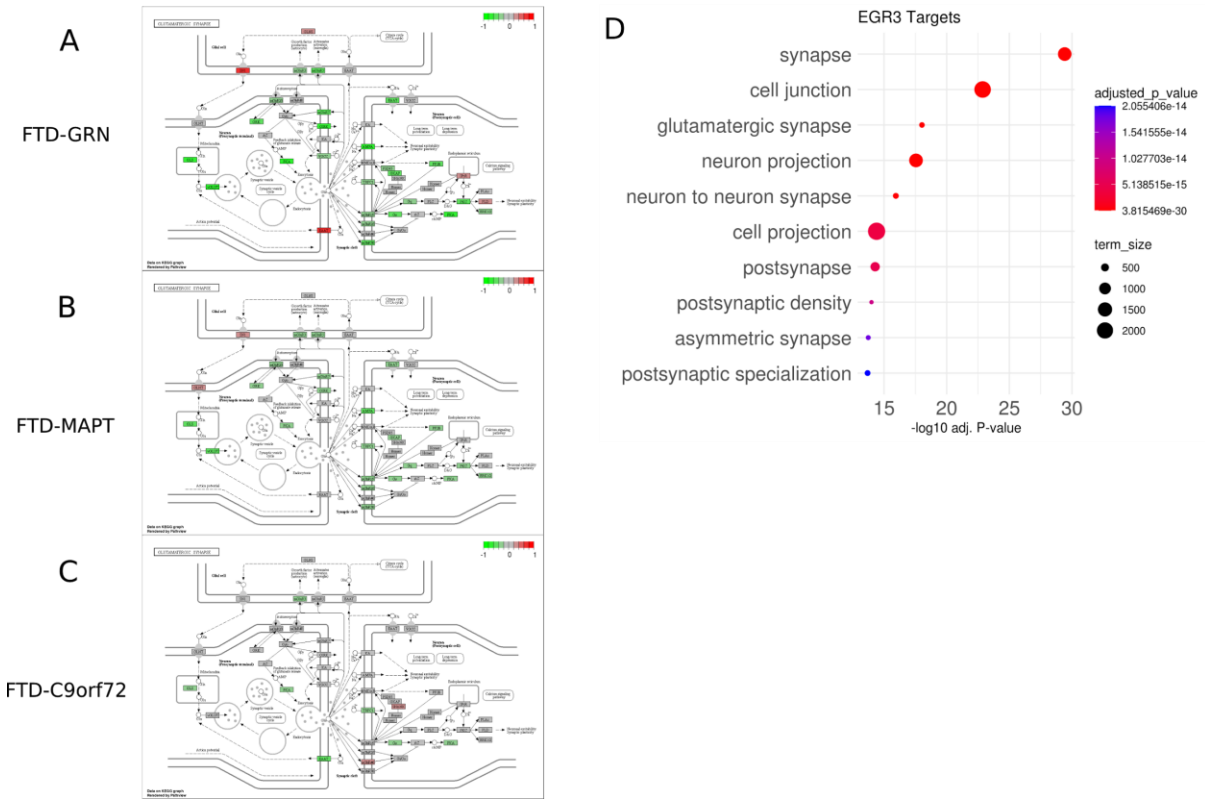


Figure S7: The glutamatergic synapse pathway in FTD (KEGG). A, B, C Shown are the average log fold-changes of genes corresponding to nodes in the KEGG pathway for FTD-GRN, FTD-MAPT and FTD-C9orf72, respectively. Genes were not filtered for significant differential expression. **D** Pathway enrichment (g:Profiler) for predicted targets of the EGR3 transcription factor. Shown is the enrichment for GO cellular compartments. Node size corresponds to term size, color to the P-value adjusted for multiple testing.

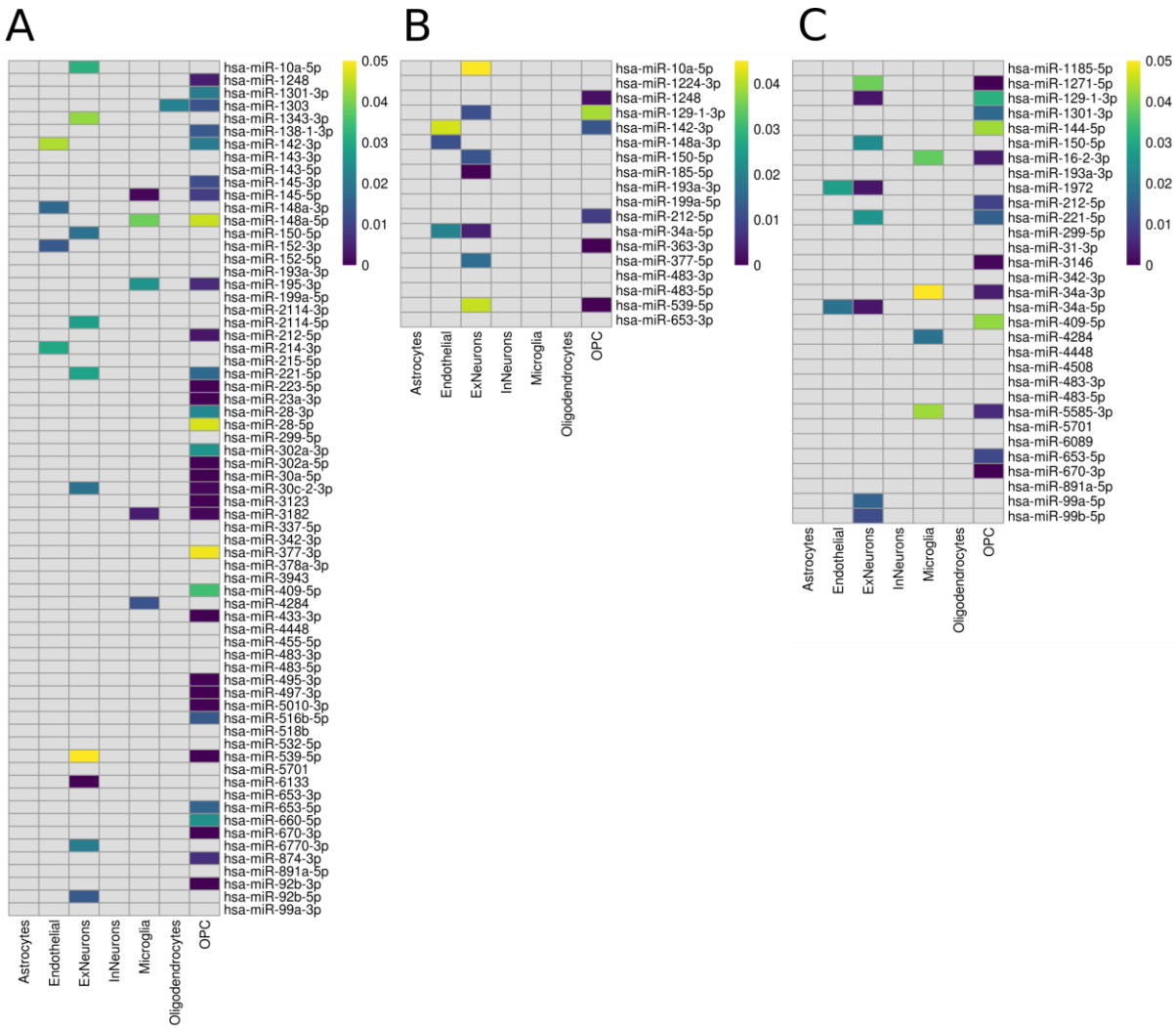


Figure S8: EWCE analysis of miRNA targets. A, B, C EWCE P-value of predicted targets of DE miRNAs in FTD-MAPT, FTD-GRN and FTD-C9orf72, respectively. Insignificant enrichment (P-value > 0.05) is marked as grey.

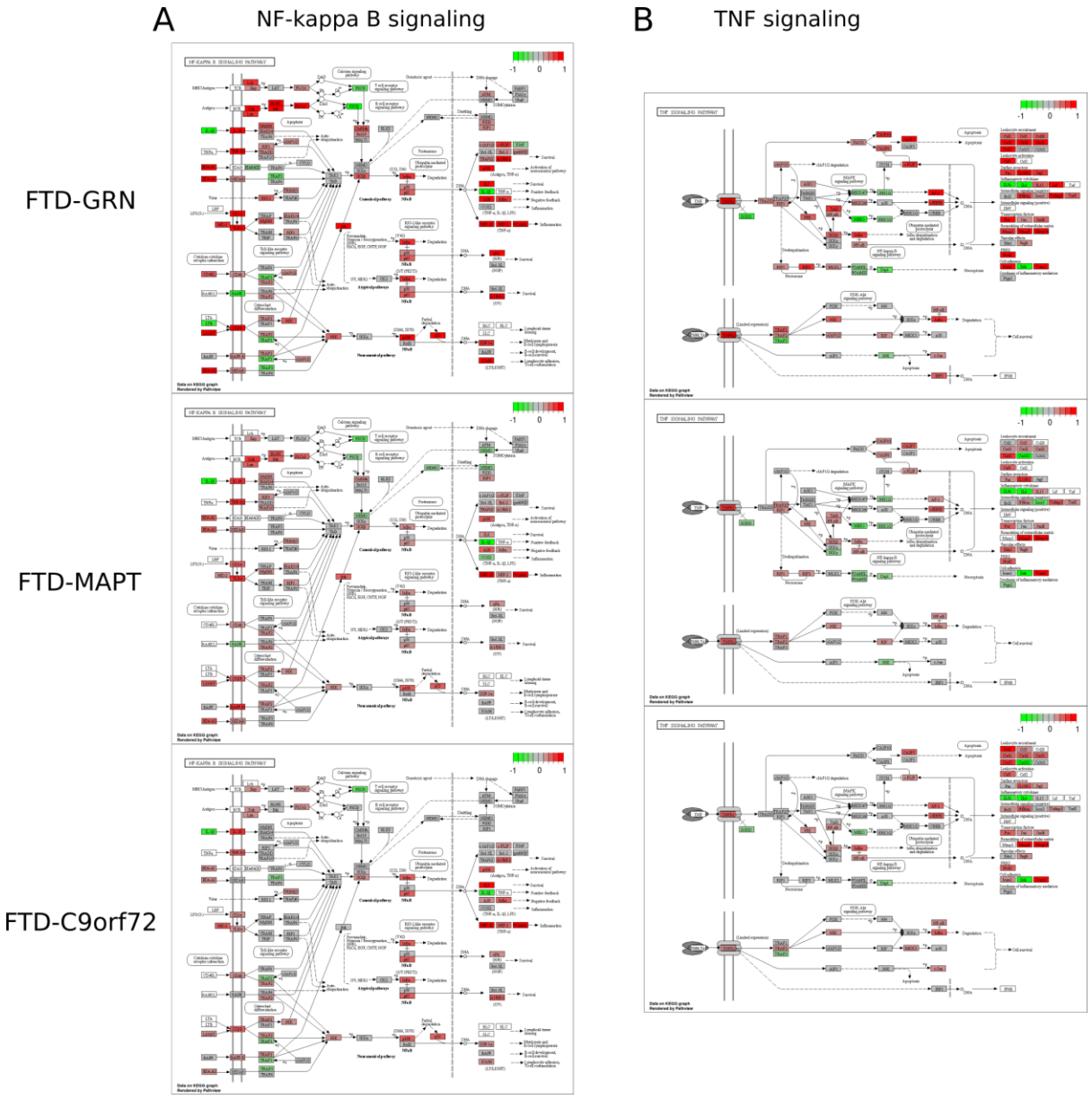


Figure S9: Fold-changes of genes in immune system pathways. A Fold-changes of genes of the NF-kappa B signaling pathways. **B** Fold-changes of genes of the TNF-signaling pathway.

Supplementary Tables

Supplementary Table S1: **Average characteristics of samples from GFM**. The average metrics for each sample group are shown with the standard deviation in brackets. PMI corresponds to time after death until sample collection in minutes. The other metrics are age at death, pH-value, RNA integrity number (RIN) and the number of males (M) and females (F) in the respective group. These numbers were calculated across all samples.

	Age	**PMI**	**pH**	**RIN**	**M / F**
FTD-MAPT	61.2 (8.5)	362.8 (107.3)	6.4 (0.2)	6.6 (1.1)	8 / 9
FTD-GRN	63.4 (8.0)	357.4 (152.1)	6.3 (0.2)	5.9 (1.0)	4 / 7
FTD-C9orf72	62.3 (9.1)	337.6 (147.6)	6.4 (0.3)	6.4 (1.0)	7 / 10
Control	79.7 (11.5)	370.2 (62.5)	6.6 (0.3)	7.7 (1.3)	6 / 10

Supplementary Table S2: Post-mortem human brain datasets analysed in this study with respective number of total samples and samples per group.

Dataset	**samples**	**FTD-GRN**	**FTD-MAPT**	**FTD-C9orf72**	**controls**
RNA-seq	47	7	11	13	16
CAGE-seq	49	8	12	13	16
smRNA-seq	47	8	13	13	13
Methylation	48	7	13	14	14

Supplementary Table S3: P-value statistics from comparisons of cell fractions of different cell types in the disease groups against controls.

FTD-MAPT	**FTD-GRN**	**FTD-C9orf72**	**Cell type**
0.618	0.545	0.122	**InNeurons**
0.342	0.571	0.505	**Oligodendrocytes**
0.013	0.0005	0.009	**Endothelial**
0.037	0.0005	0.475	**Microglia**
0.007	0.0005	0.010	**Astrocytes**
0.016	1.467e-06	0.016	**OPC**
0.010	8.996e-05	0.016	**ExNeurons**

Supplementary Table S4 HumanBase FTD-GRN down modules.

Module	Top terms (max 5)	Genes	Terms
M1	mitochondrion organization, NADH dehydrogenase complex assembly, mitochondrial respiratory chain complex I assembly, mitochondrial respiratory chain complex assembly, generation of precursor metabolites and energy	538	201
M2	monovalent inorganic cation transport, potassium ion transmembrane transport, regulation of cation transmembrane transport, cellular potassium ion transport, potassium ion transport	577	85
M3	protein polyubiquitination, dephosphorylation, protein modification by small protein removal, peptidyl-serine modification, regulation of proteasomal protein catabolic process	791	151
M4	respiratory chain complex IV assembly, cytochrome complex assembly, cellular respiration, energy derivation by oxidation of organic compounds, mitochondrion organization	28	15
M5	epithelial cilium movement involved in determination of left/right asymmetry, epithelial cilium movement, striated muscle contraction, motile cilium assembly, inner dynein arm assembly	287	8
M6	epithelial cell migration, tissue migration, epithelium migration, ameboidal-type cell migration, epithelium development	3	5
M7	mitochondrion organization	21	1

Supplementary Table S5: HumanBase FTD-MAPT down modules.

Module	Top terms (max 5)	Genes	Terms
M1	NADH dehydrogenase complex assembly, mitochondrial respiratory chain complex I assembly, mitochondrial respiratory chain complex assembly, cellular respiration, mitochondrion organization	49	49
M2	protein stabilization, regulation of protein stability	2	2
M3	regulation of RNA splicing, nucleocytoplasmic transport, nuclear transport, RNA splicing	3	4
M4	positive regulation of heterotypic cell-cell adhesion,	53	50

	negative regulation of lipid catabolic process, negative regulation of catabolic process, regulation of heterotypic cell-cell adhesion, regulation of lipid catabolic process		
M5	carboxylic acid transport, organic acid transport, microtubule organizing center organization, establishment of organelle localization, organic anion transport	13	10

Supplementary Table S6: HumanBase FT-GRN up modules.

Module	Top terms (max 5)	Genes	Terms
M1	neutrophil migration, neutrophil chemotaxis, granulocyte migration, granulocyte chemotaxis, leukocyte migration	293	135
M2	response to hormone, response to prostaglandin D, cellular response to prostaglandin D stimulus, endocytosis, canonical Wnt signaling pathway	250	334
M3	symbiont process, viral process, regulation of symbiosis, encompassing mutualism through parasitism, positive regulation of I-kappaB kinase/NF-kappaB signaling, regulation of viral process	308	360
M4	endothelial cell differentiation, I-kappaB kinase/NF-kappaB signaling, endothelium development, cellular response to tumor necrosis factor, regulation of endothelial cell differentiation	276	170
M5	endocrine system development, adrenal gland development, urogenital system development, renal system development, epithelium development	197	246
M6	T cell activation via T cell receptor contact with antigen bound to MHC molecule on antigen presenting cell, T cell activation involved in immune response, leukocyte cell-cell adhesion, lymphocyte activation involved in immune response, lymphocyte activation	19	30
M7	bicellular tight junction assembly, apical junction assembly, cell-cell junction assembly, cell junction assembly, cell-cell junction organization	8	11

Supplementary Table S7: HumanBase FTD-MAPT up modules.

Module	Top terms (max 5)	Genes	Terms
M1	pantothenate metabolic process, Fc receptor signaling	139	59

	pathway, vitamin metabolic process, cilium organization, cilium assembly		
M2	positive regulation of cell migration, positive regulation of cellular component movement, positive regulation of cell motility, transmembrane receptor protein tyrosine kinase signaling pathway, positive regulation of protein kinase B signaling	52	124
M3	epithelial cell differentiation, endothelial cell differentiation, endothelium development, epithelium development, regulation of T cell receptor signaling pathway	48	77
M4	positive regulation of ERK1 and ERK2 cascade, collagen metabolic process, regulation of ERK1 and ERK2 cascade, ERK1 and ERK2 cascade, formation of primary germ layer	24	68
M5	hormone metabolic process, regulation of hormone levels	9	2
M6	transmembrane receptor protein tyrosine kinase signaling pathway, regulation of cell morphogenesis, vascular endothelial growth factor receptor signaling pathway, regulation of blood pressure, cellular response to vascular endothelial growth factor stimulus	52	50
M7	response to insulin, odontogenesis of dentin-containing tooth, smoothened signaling pathway, response to glucocorticoid, response to corticosteroid	61	43
M8	endocytosis, import into cell, response to organonitrogen compound, response to lipid	7	4

Supplementary Table S8: Statistics of miRNA mimic and inhibitor experiments.

miRNA	**Cell type**	**Experiment type**	**# Samples**
hsa-miR-150-5p	neurons	mimic	3
hsa-miR-150-5p	neurons	inhibitor	3
hsa-miR-150-5p	microglia	mimic	3
hsa-miR-150-5p	microglia	inhibitor	3
hsa-miR-19b-3p	neurons	mimic	3
hsa-miR-19b-3p	neurons	inhibitor	3

hsa-miR-19b-3p	microglia	mimic	3
hsa-miR-19b-3p	microglia	inhibitor	3
hsa-miR-193a-3p	microglia	mimic	3
hsa-miR-193a-3p	microglia	inhibitor	3