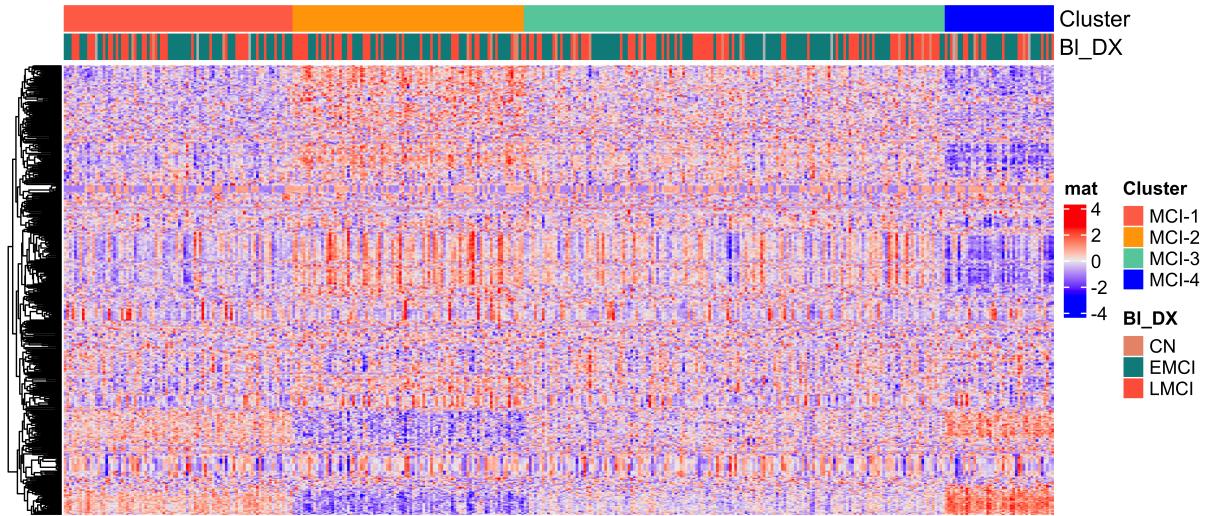
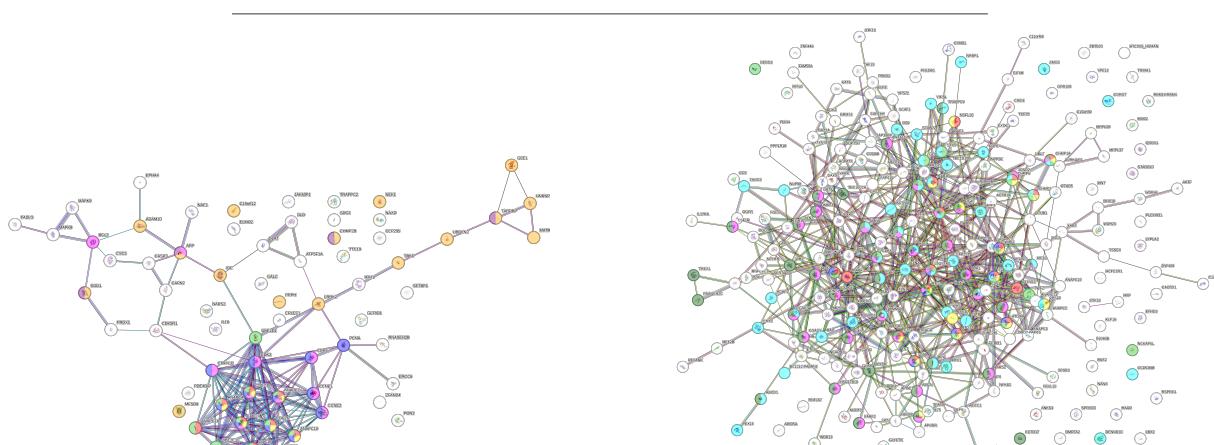


# Additional Information and Supporting Materials

## Clustering-based stratification of mild cognitive impairment patients



**Heatmap of MCI patient clusters transcriptomic profile.** The heatmap displays the expression levels of the 445 selected genes across four identified clusters by QUANTILE NORMALIZATION and *StdDevFilter* of 381 MCI patients. Each column represents a patient, with cluster membership indicated by the color-coded bar at the top. The number of patients in each cluster is also reported. The annotation bar immediately below denotes the baseline diagnosis (Bl\_Dx) for each individual. Genes are represented by rows and are ordered according to hierarchical clustering. The number of genes grouped within each gene cluster is indicated in parentheses.



**PPI network and functional enrichment of *g1* and *g2* genes.**

### Clinical and Laboratory Variables Used in This Study

Variable	Description	Information Type
VISCODE2	Visit	Patient info
SubjectID	SubjectID	Patient info
DX	Diagnosis at the visit	Patient info
B1_DX	Baseline Diagnosis	Patient info
AGE	Age	Patient info
PTGENDER	Gender	Patient info
PTEDUCAT	Education	Patient info
PTETHCAT	Ethnicity	Patient info
PTRACCAT	Race	Patient info
PTMARRY	Marital	Patient info
APOE4	Number of APOEe4 alleles	Genetic
FDG	FDG-PET metaROI	Imaging
PIB	Average PIB SUVR of frontal cortex, anterior cingulate, pre-cuneus cortex, and parietal cortex	Imaging
AV45	PET AV45 ratio (cortical grey matter/whole cerebellum)	Imaging
FBB	FBB ratio (cortical grey matter/whole cerebellum)	Imaging
ABETA	CSF ABETA	CSF Biomarker
TAU	CSF TAU	CSF Biomarker
PTAU	CSF PTAU	CSF Biomarker
CDRSB	Clinical Dementia Rating Scale - Sum of Boxes	Cognitive
ADAS11	Alzheimer's Disease Assessment Scale (ADAS11)	Cognitive
ADAS13	Alzheimer's Disease Assessment Scale (ADAS13)	Cognitive
ADASQ4	Alzheimer's Disease Assessment Scale (ADASQ4)	Cognitive
MMSE	Mini Mental State Examination	Cognitive
RAVLT.immediate	Rey Auditory Verbal Learning Test	Cognitive
RAVLT.learning	Rey Auditory Verbal Learning Test	Cognitive
RAVLT.forgetting	Rey Auditory Verbal Learning Test	Cognitive
RAVLT.perc.forgetting	Rey Auditory Verbal Learning Test	Cognitive
LDELTOTAL	Logical Memory - Delayed Recall	Cognitive
DIGITSCOR	Digit Symbol Substitution	Cognitive
TRABSCOR	Trail Making Test	Cognitive
FAQ	Functional Activity Questionnaire	Cognitive
MOCA	Montreal Cognitive Assessment	Cognitive
EcogPtMem	Everyday Cognition – Patient Memory	Cognitive
EcogPtLang	Everyday Cognition – Patient Language	Cognitive
EcogPtVisspat	Everyday Cognition – Patient Visuospatial	Cognitive
EcogPtPlan	Everyday Cognition – Patient Planning	Cognitive
EcogPtOrgan	Everyday Cognition – Patient Organization	Cognitive
EcogPtDivatt	Everyday Cognition – Patient Divided Attention	Cognitive
EcogPtTotal	Everyday Cognition – Patient Total Score	Cognitive
EcogSPMem	Everyday Cognition – Study Partner Memory	Cognitive
EcogSPLang	Everyday Cognition – Study Partner Language	Cognitive
EcogSPVisspat	Everyday Cognition – Study Partner Visuospatial	Cognitive
EcogSPPlan	Everyday Cognition – Study Partner Planning	Cognitive
EcogSPOrgan	Everyday Cognition – Study Partner Organization	Cognitive
EcogSPDivatt	Everyday Cognition – Study Partner Divided Attention	Cognitive
EcogSPTotal	Everyday Cognition – Study Partner Total Score	Cognitive
FLDSTRENG	MRI Field Strength	MRI info
FSVERSION	FreeSurfer Software Version	MRI info
IMAGEUID	LONI Image ID	MRI info
Ventricles	UCSF Ventricles	Imaging
Hippocampus	UCSF Hippocampus	Imaging
WholeBrain	UCSF WholeBrain	Imaging
Entorhinal	UCSF Entorhinal	Imaging
Fusiform	UCSF Fusiform	Imaging
MidTemp	UCSF Middle temporal gyrus	Imaging
ICV	Intracerebral volume	Imaging
mPACCdigit	Preclinical Alzheimer's Cognitive Composite	Cognitive

## Supervised Gene Sets from Multiple Sources Related to Alzheimer's and Neurodegenerative Diseases

DisGeNET	Emon et al. 2020	DisGeNET + Emon et al. 2020	Human Phenotype Ontology (HPO)	DisGeNET + Emon et al. 2020+HPO	Reactome R-HSA-9675126
A2M, ACE, APOC1, ATP5A1, BACE1, BAX, BDNF, BIN1, CD2AP, CLU, CR1, EPHA1, GRN, HFE, IDE, IGF1R, IGF2, IL1B, INSR, LEP, MPO, NOS3, NPY, PLAU, SORL1	AKT1, CD33, CDK5, CRH, CYCS, DNMT1, DYRK1A, GDNF, IL18, IL6, MAPK8, MAPK9, MTHFR, NLRP3, PRKACA, SDC2, TP53, H3F3A, UCN	BCL2, CASP3, GSK3B, PICALM, TOMM40	AARS2, ABCD1, ANG, ATXN2, ATXN3, C19ORF12, CCNF, CHCHD10, COASY, COQ2, CSF1R, DAO, DCTN1, EPHA4, ERBB4, FOLR1, FUS, GUSB, HNRNPA1, HSD17B10, HTT, IDUA, MATR3, MFSD8, NAE1, NARS2, NEFH, OPTN, PANK2, PCNA, PDE8B, PFN1, PLA2G6, PON1, PON2, PON3, PPARGC1A, SLC2A3, SOD1, SPTBN1, SQSTM1, TAF15, TBK1, TREX1, TXN2, UBQLN2, UBTF, UCHL1, UNC13A, VCP, WDR45, ADAR, ANXA11, C21ORF2, CARKD, DLAT, ERCC6, FA2H, FIG4, FTL, GALC, GLE1, GLT8D1, GM2A, IDS, IFIH1, LSM11, LYST, NBN, NEK1, PRPH, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, TANGO2, TTC19, VAPB, ZBTB20	CHMP2B, MAPT, TARDBP, TREM2	CCND1, CCNE2, CDK4, CDK6, CDKN1A, CDKN1B, DAXX, E2F1, RB1, TFDP1, ANAPC1, ANAPC10, ANAPC11, ANAPC15, ANAPC16, ANAPC2, ANAPC4, ANAPC5, ANAPC7, ATRX, CCND2, CCND3, CCNE1, CDC16, CDC23, CDC26, CDC27, CDK2, CDKN1C, E2F2, E2F3, FZR1, SKP2, TFDP2, UBE2C, UBE2D1, UBE2E1, UBE2S
Reactome R-HSA-9565265	Reactome R-HSA-8862803	KEGG Disease DB "Alzheimer"	DisGeNET + KEGG Disease DB "Alzheimer"	Disgenet + Reactome R-HSA-8862803 + KEGG Disease DB "Alzheimer"	Hubs from HENA network
OGG1	BCL2L11, CAPN1, CAPN2, CAST, CDC25B, CDC25C, CDK5R1, FASLG, FOXO3, GOLGA2, JUN, LMNA, LMNB1, PRDX1, PRDX2, SOD2, CAPNS1, CAPNS2, CDC25A, YWHAE	DLD, GBA, LRRK2, OGDH, SNCB	ABC7, ADAM10, PSEN1, PSEN2, SNCA	APP	AGAP2, GRIA1, KALRN, MLKL, PLXNA4, UBN1, ALDH1L2, C3ORF55, C9ORF172, CACNA1D, DEDD, DMBT1, DMRTA2, DNAH14, DPF1, ELMO2, ERLEC1, FAM168A, FARP2, ILDR2, JAK-M1P1, KIAA1045, KIAA1456, KIAA1731, LINC00473, LINC00598, CT45A3, LRRC14B, MBD1, MBOAT1, MUC20, NEK10, PAK6, PDE4DIP, PEAR1, SETBP1, SH3RF3, ST6GALNAC3, SYNE3, SYNGAP1, THRIB, TRAPPC2, ZBTB4, ZFAND4, ZNF391, ZNF771
DisGeNET + Emon et al. 2020 + KEGG Disease DB "Alzheimer"					APOE

### Differences in gene expression levels among patient groups

Groups	Gene	logFC	AveExpr	t	P.Value	adj.P.Val
MCI-1 Vs CN	CASP8AP2	1.06	4.17	11.64	6.84E-29	1.75E-25
	ZNF92	1.01	4.14	11.58	1.22E-28	2.73E-25
	CCNT2	1.01	4.32	11.07	1.82E-26	1.13E-23
	KIAA1033	1.07	6.89	11.07	1.85E-26	1.13E-23
	LRRC40	1.05	5.83	10.85	1.49E-25	5.76E-23
	SGTB	1.01	5.33	10.71	5.53E-25	1.52E-22
	SLC35F5	1.13	4.87	10.65	9.47E-25	2.32E-22
	FNDC3A	1.07	5.53	10.31	2.20E-23	2.86E-21
	SACS	1.14	5.34	10.31	2.23E-23	2.88E-21
	EEA1	1.11	4.63	10.12	1.27E-22	1.21E-20
MCI-1 Vs AD	NEK7	1.17	6.33	10.10	1.46E-22	1.35E-20
	TMEM55A	1.08	5.72	10.01	3.13E-22	2.51E-20
	NUDT21	1.09	6.20	10.52	3.26E-24	2.85E-21
	ZNF92	1.01	4.14	10.34	1.62E-23	8.79E-21
	CASP8AP2	1.03	4.17	9.97	4.59E-22	1.26E-19
	LRRC40	1.07	5.83	9.76	2.93E-21	5.07E-19
	ABCB10	1.06	5.79	9.74	3.48E-21	5.74E-19
	SACS	1.21	5.34	9.67	6.37E-21	9.48E-19
	TRPC1	1.01	3.21	9.55	1.83E-20	2.23E-18
MCI-1 Vs MCI-2	SLC35F5	1.00	4.88	12.60	1.18E-30	3.01E-28
MCI-2 Vs MCI-3	SACS	1.07	5.36	16.29	1.21E-45	8.12E-43
	FNDC3A	1.04	5.55	16.19	3.03E-45	1.90E-42
	PTBP2	1.05	5.26	15.08	1.22E-40	3.37E-38
	EEA1	1.03	4.67	14.15	7.79E-37	1.10E-34
	NEK7	1.10	6.37	13.45	5.33E-34	4.87E-32

### Differences in gene expression levels among patient MCI-1 and MCI-2 groups

Gene	logFC	AveExpr	t	P.Value	adj.P.Val
BZW1	1.25	7.68	28.20	2.81E-95	9.43E-92
CBFB	1.72	6.67	27.81	1.00E-93	2.87E-90
CCDC88B	-1.13	6.89	-26.24	2.00E-87	2.51E-84
FAM13B	1.02	7.61	26.21	2.72E-87	3.22E-84
N4BP2L1	1.39	7.46	26.11	6.96E-87	7.76E-84
CLINT1	1.04	7.17	26.10	7.74E-87	8.19E-84
SGPP1	1.50	5.15	26.09	8.54E-87	8.58E-84
TCEA1	1.26	7.16	25.87	6.60E-86	5.53E-83
SACS	2.05	5.36	25.83	9.73E-86	7.82E-83
FAM208B	1.26	6.70	25.33	1.02E-83	7.08E-81
SRSF11	1.10	7.29	25.28	1.77E-83	1.18E-80
BRWD1	1.10	5.07	24.98	2.98E-82	1.71E-79
FNDC3A	1.91	5.55	24.69	4.83E-81	2.42E-78
NUDT21	1.71	6.22	24.56	1.53E-80	7.30E-78
CAAP1	1.57	5.21	24.40	7.44E-80	3.18E-77
HIAT1	1.31	6.87	24.13	9.97E-79	4.01E-76
FBXL3	1.48	6.42	24.12	1.06E-78	4.16E-76
PRNP	1.39	4.64	24.10	1.30E-78	5.01E-76
PURA	1.02	7.93	24.02	2.84E-78	1.07E-75
TMEM209	1.07	4.45	23.87	1.21E-77	4.28E-75
SLC38A1	1.12	8.07	23.40	1.07E-75	3.07E-73
SLC30A7	1.65	6.15	23.39	1.14E-75	3.22E-73
CASP8AP2	1.69	4.20	23.38	1.30E-75	3.63E-73
RNF111	1.26	6.84	23.36	1.51E-75	4.10E-73
ATP11C	1.23	6.79	23.26	3.96E-75	1.05E-72
NUP54	1.17	5.19	23.25	4.62E-75	1.17E-72
ADNP	1.01	8.25	23.21	6.34E-75	1.56E-72
PPIL4	1.23	7.27	23.17	9.98E-75	2.36E-72
SLC35F5	1.96	4.88	23.13	1.42E-74	3.27E-72
CREBZF	1.04	5.57	23.00	5.20E-74	1.17E-71
VPS36	1.29	6.62	22.87	1.70E-73	3.53E-71
BNIP2	1.42	7.38	22.84	2.40E-73	4.93E-71
PCNXL4	1.28	6.94	22.83	2.50E-73	5.07E-71
LRRC40	1.77	5.87	22.82	2.72E-73	5.47E-71
PTBP2	1.91	5.26	22.79	3.90E-73	7.69E-71
C2CD5	1.28	6.28	22.74	6.23E-73	1.20E-70
ARL6IP6	1.18	7.90	22.72	7.79E-73	1.46E-70
PGRMC2	1.06	5.93	22.66	1.37E-72	2.49E-70

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Gene	logFC	AveExpr	t	P.Value	adj.P.Val
SRSF1	1.03	5.19	22.60	2.34E-72	4.13E-70
KIAA1033	1.79	6.91	22.58	2.87E-72	4.97E-70
RNF138	1.73	6.48	22.56	3.64E-72	6.25E-70
CHD9	1.06	4.09	22.46	9.55E-72	1.57E-69
ABCE1	1.02	5.97	22.44	1.10E-71	1.76E-69
UBA2	1.00	6.05	22.43	1.25E-71	1.98E-69
LRIF1	1.25	7.20	22.36	2.34E-71	3.59E-69
CNIH1	1.08	6.95	22.33	3.38E-71	5.06E-69
ZNRF2	1.77	5.88	22.31	3.75E-71	5.58E-69
PPP3CB	1.13	5.82	22.30	4.25E-71	6.28E-69
MICU2	1.01	7.72	22.27	6.02E-71	8.77E-69
DNAJB14	1.06	6.49	22.23	8.44E-71	1.22E-68
CSGALNACT2	1.49	7.24	22.21	9.90E-71	1.42E-68
AEBP2	1.38	4.39	22.20	1.11E-70	1.59E-68
CCNT2	1.65	4.35	22.15	1.93E-70	2.64E-68
THUMPD1	1.13	7.84	22.08	3.75E-70	5.02E-68
KLHL20	1.14	4.27	22.04	5.29E-70	6.99E-68
FAM3C	1.38	4.58	22.04	5.37E-70	7.03E-68
SLC30A5	1.08	5.85	21.94	1.45E-69	1.80E-67
B3GNT2	1.18	4.83	21.93	1.55E-69	1.90E-67
JMJD1C	1.50	6.92	21.92	1.69E-69	2.04E-67
UBR5	1.05	7.17	21.92	1.70E-69	2.04E-67
LOC100996626/PNRC2	1.15	7.05	21.90	2.07E-69	2.44E-67
EEA1	1.92	4.67	21.82	4.76E-69	5.50E-67
NUS1	1.40	5.64	21.79	6.08E-69	6.98E-67
C1ORF52	1.16	6.64	21.75	8.91E-69	1.02E-66
ZBTB33	1.02	6.67	21.72	1.22E-68	1.38E-66
AP1AR	1.49	4.97	21.70	1.46E-68	1.63E-66
OTUD1	1.03	9.19	21.63	2.82E-68	3.08E-66
USP32P1/USP32P2/USP32	1.26	8.45	21.54	6.78E-68	7.09E-66
TRAPPCL3	1.60	4.39	21.51	9.13E-68	9.31E-66
ZBTB1	1.39	5.43	21.48	1.29E-67	1.30E-65
ZNF292	1.45	6.22	21.46	1.51E-67	1.51E-65
ABCB10	1.66	5.82	21.43	2.09E-67	2.08E-65
USP32P1/USP32P2/USP32/USP6	1.27	8.81	21.40	2.67E-67	2.61E-65
TSNAX	1.11	7.38	21.35	4.28E-67	4.11E-65
TRMT1L	1.00	5.83	21.33	5.31E-67	5.01E-65
SLC5A3	1.43	6.21	21.25	1.22E-66	1.12E-64
PLEKHA3	1.08	7.20	21.22	1.64E-66	1.50E-64
ZNF644	1.32	5.97	21.21	1.76E-66	1.60E-64
PCNP	1.06	8.13	21.12	4.20E-66	3.72E-64
CMTR2	1.54	6.44	21.05	8.62E-66	7.40E-64
ANKRA2	1.29	3.28	21.03	1.01E-65	8.58E-64
MZT1	1.49	4.05	20.99	1.42E-65	1.18E-63
PPP2CA	1.25	5.15	20.99	1.46E-65	1.21E-63
DNAJC21	1.01	5.14	20.94	2.50E-65	2.04E-63
STXBP3	1.03	8.06	20.92	2.90E-65	2.35E-63
SCAI	1.40	3.97	20.91	3.25E-65	2.61E-63

**Cognitive test performance** Differences of cognitive performance metrics detected among the three MCI clusters through the pairwise Wilcoxon Rank Sum and Signed Rank Tests (\*\*\*\*  $p$ -value  $\leq 0.0001$ ; \*\*\*  $p$ -value  $\leq 0.001$ ; \*\*  $p$ -value  $\leq 0.01$ ; \*  $p$ -value  $\leq 0.05$ ; ns= not significant).

Metric	Description	Type	MCI-1 vs MCI-2	MCI-1 vs MCI-3	MCI-2 vs MCI-3
ADAS11	Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) 11	Cognitive	*	**	ns
ADAS11.bl	Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) 11	Cognitive at baseline	ns	*	ns
ADAS13	Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) 13	Cognitive	*	**	ns
ADAS13.bl	Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) 13	Cognitive at baseline	ns	*	ns
ADASQ4	Alzheimer's Disease Assessment Scale (ADAS4)	Cognitive	ns	*	ns
EcogSPLang	Everyday Cognition filled out by study partners	Cognitive	ns	*	ns
EcogSPLang.bl	Everyday Cognition filled out by study partners	Cognitive at baseline	ns	**	ns
EcogSPTotal	Everyday Cognition filled out by study partners	Cognitive	ns	*	ns
EcogSPTotal.bl	Everyday Cognition filled out by study partners	Cognitive at baseline	ns	*	ns
FAQ	Functional Activity Questionnaire	Cognitive	ns	*	**
FAQ.bl	Functional Activity Questionnaire	Cognitive at baseline	ns	*	ns
FDG	FDG-PET Meta Region of Interest	Imaging	ns	*	*
FDG.bl	FDG-PET Meta Region of Interest	Imaging at baseline	ns	**	**
MOCA	Montreal Cognitive Assessment	Cognitive	ns	**	ns
MOCA.bl	Montreal Cognitive Assessment	Cognitive at baseline	ns	**	ns
mPACCtrailsB	Preclinical Alzheimer's Cognitive Composite	Cognitive	ns	*	ns
RAVLT.immediate	RAVLT immediate assessment	Cognitive	*	****	*
RAVLT.immediate.bl	RAVLT immediate assessment	Cognitive at baseline	ns	***	*
RAVLT.learning	Rey Auditory Verbal Learning Test	Cognitive	ns	*	ns
RAVLT.learning.bl	Rey Auditory Verbal Learning Test	Cognitive at baseline	ns	**	ns
TAU	Cerebrospinal Fluid TAU	CSF Biomarker	*	ns	ns
TRABSCOR	Trail Making Test	Cognitive	ns	**	ns
TRABSCOR.bl	Trail Making Test	Cognitive at baseline	ns	**	ns
Ventricles	Ventricular volume	Imaging	ns	ns	*