SUPPLEMENTARY INFORMATION (one figure and five tables)

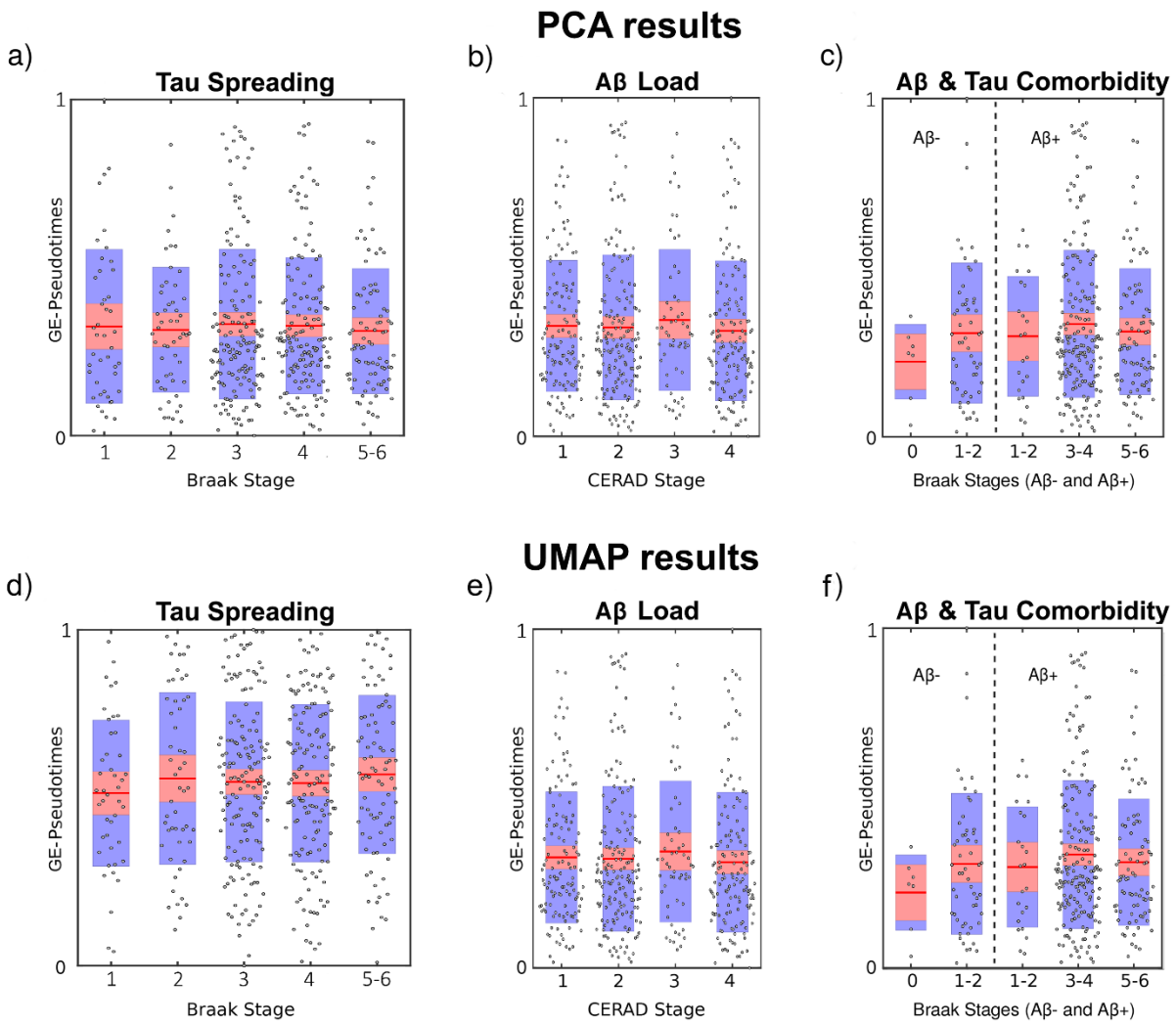

Figure S1. PCA- and UMAP-based GE predictions of neurodegenerative severity for ROSMAP brains. PCA (a-c) and UMAP (d-f) GE-pseudotime predictive associations with Braak (a,d), Cerad (b,e), and Braak for Aβ-/Aβ+ (c,f). Points are layed over a 1.96 standard error of the mean (95% confidence interval) in red and a 1 standard deviation in blue. Notice that, contrary that with results obtained using cPCA (see *Results* section, Fig. 1), non-significant associations were observed (all $P>0.3$, FEW corrected).

Supplementary Table 1. Main demographic characteristics for the three populations.

Variable	**ROSMAP** (N=489)	**HBTRC** (N=736)	**ADNI** (N=744)
Women	299 (61.1%)	354 (47.9%)	336 (45.1%)
Age (years)	86.1 (4.81)	70.8 (15.10)	73.1 (7.03)
Education (years)	16.7 (3.59)	-	16.1 (2.77)

Data are number (%) or mean (std).

Supplementary Table 2. Highly predictive genes of LOAD progression in the three studied populations.

Data	Genes
ROSMAP (N_{genes}=845)	A4GALT, ABCC3, ABHD12B, ACAA1, ACACA, ACADL, ACOT9, ACTA2, ACTG2, ACVR1, ACVR1B, ADAMTSL1, ADCY1, ADCY4, ADORA1, AES, AFMID, AGBL5, AGTR1, AGTRAP, AGXT2L2, AKAP13, AKR1C4, ALDOC, ALG9, ALLC, AMICA1, ANG, ANGPTL5, ANKRD40, ANO4, ANXA2P3, AOX1, AP3M2, APEX2, APOBEC3F, APOC2, APP, ARF5, ARG99, ARHGAP24, ARHGAP28, ARHGEF5, ARNT2, ARPC4, ARRDC4, ASB9, ASIP, ASS1, ATF6, ATP1B3, ATP6V0A1, ATP6V0E2, ATP9A, ATPAF1, B3GAT1, B3GNT8, B4GALT4, BAALC, BAI2, BAIAP2, BBS7, BCAN, BCAP29, BCL2L12, BHMT2, BMP4, BMP6, BMP8B, BMX, BNIP3, BOLA2, BRI3, BSN, BTG2, BTN3A2, BZRAP1, C10ORF132, C10ORF26, C10ORF47, C13ORF33, C14ORF94, C15ORF48, C17ORF28, C18ORF26, C1ORF21, C1ORF54, C1ORF85, C1R, C1S, C2, C20ORF100, C21ORF7, C22ORF32, C3ORF32, C5ORF29, C6ORF134, C6ORF52, C8ORF4, C9ORF21, C9ORF45, C9ORF46, CACNA1E, CACNA2D2, CACNB2, CACNG2, CACNG3, CADM2, CALCRL, CALU, CAMSAP1L1, CAPRIN1, CARD10, CASP4, CAV1, CAV2, CCBL1, CCDC28A, CCDC5, CCDC85A, CCL23, CCL26, CCL5, CCL8, CCT3, CD151, CD248, CD276, CD36, CD37, CD40, CD63, CD69, CD99L2, CDC34, CDC42EP5, CDCP1, CDH1, CDH11, CDH23, CDK2, CDKN1A, CDKN2B, CFH, CH25H, CHGA, CHI3L2, CHODL, CHST1, CHST4, CKLF, CLCNKA, CLEC3B, CLEC4A, CLEC4G, CLEC5A, CLEC7A, CLEC9A, CLECL1, CMAH, CMTM4, CMTM7, CNN2, CNPY3, COBRA1, COCH, COL11A1, COL13A1, COL15A1, COL18A1, COL3A1, COL4A1, COL6A2, COL8A1, COMMD6, COMP, COP1, COPB2, CPAMD8, CPEB3, CPLX2, CPXM1, CPXM2, CPZ, CREG1, CRELD2, CRTAC1, CSF2RA, CSNK1D, CSPG5, CST6, CSTB, CTNNA2, CTSK, CTSL1, CTSS, CXCL12, CXCL6, CXCR4, CXCR7, CYB5R3, CYBASC3, CYP19A1, CYP26A1, CYP39A1, CYP3A5, CYYR1, DACT1, DACT2, DARS2, DBC1, DCDC2, DCLK2, DEFB1, DENND1B, DERL2, DES, DHRS4, DHRS9, DKK2, DKK3, DNAJC3, DNAL1, DOCK11, DRD1IP, DSC2, DSG2, DSP, DTX3L, DUS2L, EBI2, ECEL1, ECGF1, ECM2, EDF1, EDN3, EGFLAM, EIF3D, EIF3H, EIF4A1, EIF4A2, ELF1, ELF4, ELL2, ELMO1, ELN, ELOVL6, EML4, ENPP6, EPB49, EPM2AIP1, ERAP2, ERCC1, ERN1, ESM1, ETFB, EXT1, EXTL1, F10, F13A1, F2R, FAM105B, FAM114A1, FAM119B, FAM124B, FAM132A, FAM133A, FAM171A1, FAM46B, FBLN2, FBLN5, FBP1, FBXO4, FCGR2B, FERMT3, FGD5, FHL5, FIS, FKBP2, FLJ22184, FLJ22222, FLJ40142, FLJ40504, FLJ45717, FMO3, FMOD, FNDC1, FOXI2, FOXP1, FPR3, FRMD6, FRS3, FTL, FUCA2, FZD1, GABBR1, GABRB1, GADL1, GALNT9, GAMT, GARNL4, GAS1, GAS2, GBP1, GCGR, GDAP2, GDF15, GFRA2, GJA3, GLYCTK, GMDS, GMFB, GNB1, GOSR2, GPC3, GPD1L, GPR1, GPR124, GPR126, GPR64, GPRC5A, GPRC5C, GPSN2, GPX7, GRIA2, GRSF1, GSDMA, GSN, GUK1, GZMA, GZMK, HAPLN4, HCG4, HCP5, HEG1, HES1, HGF, HIST1H4K, HIST2H2AA3, HLA-DRB3, HLA-DRB4, HLA-DRB6, HLX, HNRPUL2, HNT, HP, HPS3, HS.13438, HS.134728, HS.145414, HS.167721, HS.193406, HS.197143, HS.201854, HS.202419, HS.255156, HS.286666, HS.288735, HS.435027, HS.445581, HS.46762, HS.48372, HS.4986, HS.512487, HS.537002, HS.543887, HS.545278, HS.551847, HS.554410, HS.560764, HS.562122, HS.565868, HS.566469, HS.568928, HS.569175, HS.570759, HS.575038, HS.576106, HS.8038, HS.93739, HSD17B2, HSPB7, HSPD1, HYAL1, ICOSLG, IFI30, IGF2, IGFBP2, IGFBP3, IL10RA, IL13RA2, IL15, IL1RN, IL8, IMPDH2, INA, IPO4, IRAK4, IRF2BP2, ISG15, ISLR, ITGA1, ITGA10, ITGAL, ITIH2, ITM2C, JAG1, KANK2, KAZALD1, KCNH3, KCNJ13, KCNJ4, KCNMA1, KCNQ2, KDR, KEAP1, KEL, KHDRBS3, KIAA0020, KIAA0406, KIAA1210, KIAA1618, KIAA1644, KIAA1754, KIF1A, KIF1B, KIF20B, KIF5C, KLF6, KLHL36, KLRB1, KRT18, KRT19, KSR1, KYNU, LAMA4, LATS2, LBH, LDLRAD3, LEPR, LGI1, LHFPL2, LIMA1,

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	C6orf165, CABC1, CACNG2, CALN1, CAMK2D, CAMKV, CAP1, CASC5, CBL, CBLN1, CBLN2, CCDC13///HIGD1A, CCDC42, CCDC93, CCL15, CCL23, CCL7, CCNJL, CCT8L2, CDCA3, CDCP1, CDH10, CDH9, CENPA, CILP, CLCN6, CLRN1, CMTM4, CNOT2, CNTF, COL13A1, COL19A1, CPLX2, CRADD, CRIM2, CRYGA, CRYGB, CSMD3, CTSF, CXCR3, CXorf36, CXorf48, DACH2, DAOA, DCBLD2, DCX, DDR2, DGAT2L6, DGKD, DKFZP564J0863, DLG7, DOK6, DTL, EBF1, EFCBP1, ELFN2, ELK3, ELK4, EN2, EPB41L1, EPB41L4B, ESCO2, ETV1, EXPH5, FAAH2, FAM124B, FAM12A, FAM19A2, FAM54A, FAM5B, FAM62A, FAM79B, FANCB, FARP1, FBXO42, FGFBP1, FLJ16641, FLJ33360, FLJ36031, FLJ43860, FLRT2, FOXG1, FUT4, FUT5, GAN, GCET2, GCM2, GCNT1, GDAP2, GDPD4, GEMIN7, GIPC2, GLRA4, GNB4, GPRIN2, GRIA4, GRIK2, GRM4, GRM5, GSN, GYPA, HERC1, HESRG, HIST1H1E, HIST1H2BH, HMMR, HRH1, HRH3, HS3ST1, HS3ST3A1, HSPG2, ICAM5, IFNA2, IFNA7, IKZF2, IL16, IL5, IL5RA, INADL, INS, IPO11, ITGB1BP2, JPH3, JPH4, KCNC2, KCND2, KCNIP2, KCNIP4, KCNMA1, KCNMB2, KCNN1, KCNQ2, KCNS1, KIAA0101, KIAA0247, KIAA0574, KIAA0652, KIAA0922, KIF13A, KIF14, KRIT1, KRT24, KRTAP13-3, KRTAP2-4, KRTAP3-1, LAMC2, LAMP3, LCN8, LIMA1, LOC123855, LOC124220, LOC131149, LOC146325, LOC157860, LOC196913, LOC280665, LOC283475, LOC285045, LOC285577, LOC285679, LOC285954, LOC286238, LOC344657, LOC345630, LOC348808, LOC374443, LOC387895, LOC389370, LOC389457, LOC400548, LOC440366, LOC442603, LOC643648, LOC645687///C14orf34, LOC729362///RPL36A, LOC729681, LOC729994, LOC90520, LRCH1, LRRC36, LRRC44, M6PR, MAB21L1, MAGIX, MAPK14, MCF2L, MCM10, MDGA2, MEG3, MGC87631, MIA3, MIAT, MOCOS, MORN1, MPP3, MPPED1, MPZL3, MTMR10, MTSS1, MUM1L1, MYT1, NAALADL2, NDST2, NDST3, NDUFA12, NEIL3, NFASC, NGB, NHLRC2, NIN, NLRP9, NOS1AP, NR0B1, NRK, NRP2, NSL1, NSMCE1, NT5DC4, NTF3, NUDT16P, NUPL1, NUT, OAS3, OBSCN, ODZ4, OPCML, OR10AD1, OR10C1, OR1B1, OR2A1, OR2A2, OR2A42, OR2F2, OR2M4, OR4A16, OR52A1, OR5AK2, OR5B12, OR5B3, OR5D13, OR6C65, OR8H2, OR8I2, PACSIN1, PAG1, PAGE1, PAK6, PAPPA, PAXIP1, PBRM1, PCBD2, PCDH1, PCDH15, PCDHA10, PCDHA7, PCSK2, PDHA2, PIK3R1, PKD2L2, PKIB, PLCH2, PLEK2, PLEKHA6, PLUNC, PPA2, PPFIBP1, PRB2, PTGIR, PTPN22, PTPRT, PURG, PYHIN1, RAPGEFL1, RASSF3, RGAG1, RHAG, RHBG, RHOBTB2, RIMS1, RIPK3, RNF103, RNF144A, ROD1, RP11-49G10.8, RPL3, RPL7L1, RRM2, RS1, RUNDC3A, SCN4B, SELP, SERPINB2, SGPL1, SH2B3, SHANK2, SHANK3, SHC3, SLC10A6, SLC17A7, SLC22A7, SLC26A4, SLC35F4, SLITRK3, SMC4L1, SMR3B, SNIP, SNRPN, SOHLH1, SORCS1, SORT1, SPRED3, SPTB, SRGAP2, SSX4, ST8SIA4, STK10, SUCNR1, SULT4A1, SYNE1, SYT4, TCP10, TESSP2, TFPI, TGFBR1, TM4SF19, TMEM151B, TMEM49, TNFRSF10A, TNFSF15, TRAK1, TRIM43, TRIM67, TSHZ3, TSPAN10, TSPAN9, TUSC4, TXNDC11, UBE4A, UGT2B15, UGT2B17, UNKL, VN1R5, WDR33, WFDC8, WNK2, WT1, XYLB, ZAR1, ZC3H12B, ZDHHC22, ZFX, ZFYVE9, ZIC4, ZNF142, ZNF207, ZNF333, ZNF409, ZNF521, ZNF556, ZNF578, ZNF625, ZNF671, hCG_2007354, hCG_2019139, tAKR, tcag7.967
ADNI (N_{genes}=736)	AAAS, ABCA6, ABCA9, ABCE1, ACBD3, ACD, ACN9, ACTN3, ACTN4, ACTR1A, ACTR2, ADD1, ADH5, ADNP, ADPGK, AGGF1, AGPAT5, AGPAT6, AHCTF1, AIMP1, AKAP1, AKAP13, AKIRIN1, AKT1S1, AKTIP, ALG10B, ALG13, ANKRD28, ANKRD46, ANP32A, ANXA11, AP2M1, AP2S1, AP3B2, AP5M1, APH1B, API5, APPBP2, APPL1, ARAP2, ARFGAP2, ARFIP1, ARHGAP20, ARHGDIA, ARHGEF37, ARID2, ARID4A, ARL4A, ARL6IP6, ARL8B, ARNTL, ARPC5, ARPP19, ARRDC3, ATAD2B, ATF1, ATF6B, ATG9A, ATP5L, ATP6AP2, ATP6V0D1, AZI2, BAZ1B, BBS10, BCAP29, BCL6, BCLAF1, BLZF1, BRD2, BRE, BTAF1, BTBD1, BTN2A1, C10ORF99, C11ORF54, C14ORF142, C16ORF87, C18ORF8, C1ORF63, C21ORF91, C2CD5, C3ORF17, C3ORF38,

	C4ORF3, C5ORF28, C6ORF106, C6ORF120, CAAP1, CALML4, CAND1, CANX, CARS, CCDC47, CCDC88A, CCNB1IP1, CCND2, CCNL1, CCNY, CCPG1, CD2BP2, CDC23, CDC37L1, CDC40, CDK8, CDKN2AIP, CELF2, CENPC, CEP57, CEP85L, CHD4, CHD6, CHDH, CHID1, CHMP2B, CHORDC1, CHST6, CHTOP, CLDN15, CLIC2, CLK4, CLN3, CMAHP, CMAS, CNOT2, CNOT6L, CNTNAP2, COA5, COG4, COL1A2, COL3A1, COL4A1, COL4A2, COL4A3BP, COMMD10, COMMD8, COPS8, COX11, COX18, COX8C, CPNE8, CPOX, CPSF6, CPT1C, CREBL2, CREBZF, CSDE1, CSNK1A1, CSNK1A1 || ENSG00000230551, CSPP1, CTDNEP1, CTGF, CTNNBL1, CUL3, CXCL12, CYB5R3, CYR61, DARS, DCAF11, DCP2, DCTN4, DDB1, DDX17, DDX3Y, DDX5, DENND1B, DENND6A, DHX36, DHX9, DIMT1, DKK1, DLG1, DLG2, DMTF1, DNAJB14, DNAJB9, DNAJC16, DNAJC21, DNAJC24, DNM1L, DNMT1, DOK1, DPYS, DTWD1, DUSP12, DUSP6, DYRK3, EDARADD || ENO1, EDC4, EDEM3, EDIL3, EFTUD2, EGR1, EIF2AK3, EIF3B, EIF3E, EIF4G1, EIF4H, EIF5, ELF2, EMC6, EML4, ENO1, EP400, EPGN, EPM2AIP1, EPN1, EPT1, ERP29, EXOC1, EYA2, FA2H, FAM102B, FAM107B, FAM217B, FAM65B, FAM83A, FAM91A1, FAM96A, FAM98B, FANCF, FBXL3, FBXO11, FBXO3, FBXO33, FBXW11, FCHO2, FCRL2, FCRL5, FLNA, FMNL1, FN1, FOS, FRMD6, FSTL4, FTSJ3, FYB, G0S2, GABARAPL2, GABRB2, GAL, GALNT1, GANAB, GFM1, GFM2, GLCCI1, GLG1, GMPPA, GNA13, GNAI2, GNB4, GOLGB1, GOLT1B, GON4L || YY1AP1, GOPC, GPI, GPS1, GPT2, GPX4, GSK3A, GSK3B, GSPT1, GTPBP1, GYPA, H3F3B, HADHA, HAS3, HAUS6, HDLBP, HECTD1, HEPACAM2, HHEX, HIBADH, HIPK1, HK1, HLA-E, HMGCS1, HNRNPA1, HNRNPA1 || HNRNPA1P10, HNRNPA3, HNRNPUL1, HNRNPUL2, HP1BP3, ICK, IDH3B, IGFBP4, IGFBP5, IGSF3, IK, IMPACT, ING1, ING3, INSIG1, INSIG2, IRF2BP2, ISOC1, ITGB1, ITSN1, JAK2, JAZF1, JMJD1C, KANSL2, KDM3A, KDM5A, KIAA0101, KIAA0907, KIAA1033, KIAA1430, KIAA1468, KIAA1551, KIDINS220, KIF21B, KIF2A, KIF3A, KLF9, KLHDC2, KLHDC3, KLHL15, KLHL20, KPNB1, KRR1, LAMP2, LANCL1, LAPTM4A, LARP4, LASP1, LDLRAD4, LIG4, LMBR1, LOC100996626 || PNRC2, LONRF1, LRRC2, LY75, LYPLAL1, MAF, MAK16, MAOA, MAP2K7, MAP3K7, MAP3K8, MAP4K1, MAP4K3, MAP4K5, MARCKS, MCFD2, MEAF6, MECP2, MED14, MED15, MED28, MEF2A, METTL10, MGAT2, MGAT4A, MICU3, MIER1, MIS18BP1, MMADHC, MOB1B, MOCOS, MON2, MOSPD1, MPC2, MRPS14, MRPS25, MRPS35, MRS2, MSH2, MTL5, MTM1, MTMR2, MTPN || LUZP6, MTRR, MTX3, MVP, MYCBP2, MZT1, N4BP2L1, N4BP2L2, NAA25, NAA50, NAP1L1, NCOR1, NDC1, NDFIP1, NDFIP2, NECAP1, NEDD1, NEMF, NFKBIZ, NHS, NME9, NOM1, NOP2, NR3C1, NRBP1, NUCB1, NUDT19, NUP54, NUS1, NXPH4, OCIAD1, OGT, OPA1, ORC4, OSBPL8, OTUD5, PA2G4, PAN3, PAPD4, PAPOLG, PARP1, PARPBP, PAXBP1, PCGF5, PCNX, PCNXL4, PEX1, PGGT1B, PGM2, PGM2L1, PGRMC2, PHF20, PHF6, PIK3AP1, PKM, PKN1, PLAA, PLAGL1, PLEKHG1, PLSCR4, PM20D2, PNN, PNP, PNPLA2, PNPLA8, POC1B, POLD2, POLI, POLR1D, POLR2B, POSTN, POU2F1, PPM1A, PPP1CC, PPP2CA, PPP2CB, PPP2R3A, PPP2R5E, PPTC7, PQBP1, PRIMPOL, PRKCB, PRKD2, PRKRIR, PRMT7, PRNP, PRPF39, PRPF6, PRSS50, PRTN3, PSMB10, PSMC4, PSMD10, PSMD13, PSMD2, PSMD7, PSME4, PTGS2, PTPN12, PTPN23, PURB, PWP1, PXDN, PXK, PYROXD1, QTRTD1, RAB11A, RAB1A, RAB1B, RAB22A, RAB28, RAB2A, RABEP1, RALGAPA1, RALY, RANBP2, RANBP6, RANBP9, RANGAP1, RASGRF1, RASSF5, RBM12, RBM18, RBM25, RBM7, RBMXL1, RCBTB2, RCN2, RCSD1, RDX, RECK, RECQL, RERE, RFXANK, RFXAP, RGS4, RHAG, RIF1, RNASEH2A, RNF121, RNF125, RNF145, RNF19A, RNF40, RNFT1, RNGTT, ROR1, RPA3-AS1, RPE, RPL15, RPS6KB1, RSBN1L, RSRC2, RTF1, RUNX2, RWDD4, RYK, S100A2, SAFB2, SAMD12, SAP30BP, SAR1B, SART3, SASS6, SATB1, SCAI, SCML1, SCYL2, SDHD, SEC22C, SEC23IP, SEC62, SEC63, SEPSECS, SERP1, SERPINE1, SF3B2, SFRP2, SFSWAP, SGK1, SH3BP2,

	SHPRH, SLAIN2, SLBP, SLC25A46, SLC2A13, SLC2A4, SLC30A1, SLC30A5, SLC35A3, SLC35B3, SLC35F5, SLC36A4, SLC39A10, SLC44A1, SLC4A1AP, SLC6A13, SLC9A1, SMARCA2, SMARCAD1, SMARCC2, SMARCE1, SMG1, SMG7, SMIM15, SOX6, SP3, SPAG9, SPCS2, SPIB, SPIDR, SPPL3, SPTLC1, SPTSSA, SPTY2D1, SREK1, SRRM1, SRRM1 || SRRM1P1, SRRM2, SRRT, SRSF11, SRSF8, SSFA2, SSRP1, STAM, STIL, STK3, STRADA, STRN3, STX5, SUCLA2, SUPT6H, SUZ12, SYNCRIP, SYNJ1, SYNJ2BP, TAB3, TAC3, TAF1, TAF4, TAF9B, TAL2, TBC1D15, TBC1D17, TBC1D4, TBC1D8B, TBK1, TBPL1, TCERG1, TCF12, TEAD2, TERF2IP, TFRC, TGFBR2, TIMM44, TIMM50, TLN1, TM2D3, TM6SF1, TM9SF3, TMA16, TMCO1, TMCO3, TMED4, TMEM126B, TMEM165, TMEM170A, TMEM170B, TMEM181, TMEM19, TMEM230, TMEM30A, TMEM56, TMEM57, TMEM63B, TMEM66, TMEM87A, TMF1, TNPO1, TOX4, TRAF5, TRAPPC10, TRAPPC13, TRAPPC8, TRIM23, TRIM33, TRNT1, TSEN15, TSN, TSSC4, TUBB4B, TUBE1, TVP23C || TVP23B, U2SURP, UBA2, UBA6, UBE2B, UBE2D1, UBE2D2, UBE2F-SCLY || SCLY, UBE2N, UBE2V2, UBL3, UBQLN2, UBR1, UBR5, UBXN1, UROD, USP12, USP15, UTP23, VCP, VEZT, VMA21, VPS26A, VTA1, WASL, WBP2, WDFY3, WDR33, WDR43, WDR44, WDTC1, WIPI2, WNK1, WTAP, XPO7, YAF2, YIPF6, YME1L1, YTHDC2, YY1AP1, ZADH2, ZBTB1, ZBTB21, ZBTB38, ZBTB6, ZC3H14, ZC3H7A, ZCCHC7, ZDHHC2, ZEB2, ZFC3H1, ZFP36L2, ZHX1, ZMYND11, ZMYND8, ZNF146, ZNF148, ZNF24, ZNF254, ZNF268, ZNF280C, ZNF281, ZNF302, ZNF316, ZNF493, ZNF507, ZNF639, ZNF654, ZNF664, ZNF700, ZNF770, ZNF807 || ZNF181 || ZNF302, ZRANB1

Supplementary Table 3. Molecular pathways underlying GE trajectories associated to LOAD progression in brain tissues (ROSMAP).

Pathway name	**Presence (%)**
p38 MAPK	5.5
Pentose phosphate	5.5
Huntington disease	5.2
Parkinson disease	4.6
Insulin/IGF pathway-mitogen activated protein kinase kinase/MAP kinase cascade	4
Blood coagulation	3
Adrenaline and noradrenaline biosynthesis	2.7
CCKR signaling map	2.7
Plasminogen activating cascade	2.7
De novo purine biosynthesis	2.7
Notch signaling	2.4
Oxytocin receptor mediated signaling	2.4
Wnt signaling	2.1
p53 pathway feedback loops 2	2.1
Opioid proopiomelanocortin	2.1
Cortocotropin releasing factor receptor signaling	2.1
Inflammation mediated by chemokine and cytokine signaling	1.8
B cell activation	1.8
GABA-B receptor II signaling	1.5
Enkephalin release	1.5
5HT2 type receptor mediated signaling	1.5
Alzheimer disease-amyloid secretase	1.2
Muscarinic acetylcholine receptor 1 and 3 signaling	1.2
Metabotropic glutamate receptor group III	1.2
Allantoin degradation	1.2
EGF receptor signaling	1.2
Circadian clock system	1.2
Cell cycle	1.2
Axon guidance mediated by Slit/Robo	0.90
Angiogenesis	0.90
p53	0.90
Transcription regulation by bZIP transcription factor	0.90
Toll receptor signaling	0.90
Heterotrimeric G-protein signaling pathway-Gi alpha and Gs alpha mediated pathway	0.90
Opioid prodynorphin	0.90
General transcription regulation	0.90
Histamine H2 receptor mediated signaling	0.90
Beta3 adrenergic receptor signaling	0.90
Beta2 adrenergic receptor signaling	0.90
5HT4 type receptor mediated signaling	0.90
5HT1 type receptor mediated signaling	0.90

Axon guidance mediated by netrin	0.60
Gonadotropin-releasing hormone receptor	0.60
Mannose metabolism	0.60
Formyltetrahydroformate biosynthesis	0.60
T cell activation	0.60
Nicotinic acetylcholine receptor signaling	0.60
Endogenous cannabinoid signaling	0.60
Arginine biosynthesis	0.60
Insulin/IGF pathway-protein kinase B signaling cascade	0.60
Heterotrimeric G-protein signaling pathway-rod outer segment phototransduction	0.60
Heterotrimeric G-protein signaling pathway-Gq alpha and Go alpha mediated pathway	0.60
Opioid proenkephalin	0.60
Nicotine degradation	0.60
FGF signaling	0.60
FAS signaling	0.60
Histamine H1 receptor mediated signaling	0.60
5HT3 type receptor mediated signaling	0.60
Apoptosis signaling	0.30
Alzheimer disease-presenilin	0.30
VEGF signaling	0.30
Fructose galactose metabolism	0.30
TGF-beta signaling	0.30
PI3 kinase	0.30
PDGF signaling	0.30
Oxidative stress response	0.30
Muscarinic acetylcholine receptor 2 and 4 signaling	0.30
Metabotropic glutamate receptor group II	0.30
Androgen/estrogene/progesterone biosynthesis	0.30
Ionotropic glutamate receptor	0.30
Interleukin signaling	0.30
Interferon-gamma signaling	0.30
Integrin signalling	0.30
Thyrotropin-releasing hormone receptor signaling	0.30
Ras	0.30
P53 pathway feedback loops 1	0.30
Glycolysis	0.30
General transcription by RNA polymerase I	0.30
Nicotine pharmacodynamics	0.30
Salvage pyrimidine ribonucleotides	0.30
Dopamine receptor mediated signaling	0.30
Angiotensin II-stimulated signaling through G proteins and beta-arrestin	0.30
Gamma-aminobutyric acid synthesis	0.30
Endothelin signaling	0.30
Cytoskeletal regulation by Rho GTPase	0.30
Proline biosynthesis	0.30
Cadherin signaling	0.30
Beta1 adrenergic receptor signaling	0.30

Supplementary Table 4. Molecular pathways underlying GE trajectories associated to LOAD progression in brain tissues (HBTRC).

Pathway name	**Presence (%)**
Beta1 adrenergic receptor signaling	6.3
JAK/STAT signaling pathway	5
Heterotrimeric G-protein signaling pathway-rod outer segment phototransduction	4.4
Opioid proopiomelanocortin pathway	4.4
Histamine H2 receptor mediated signaling	4.4
Parkinson disease	3.8
De novo pyrimidine deoxyribonucleotide biosynthesis	3.1
Ionotropic glutamate receptor pathway	3.1
Inflammation mediated by chemokine and cytokine signaling pathway	2.5
Huntington disease	2.5
Alzheimer disease-amyloid secretase	1.9
p53	1.9
Metabotropic glutamate receptor group I pathway	1.9
Interleukin signaling	1.9
Insulin/IGF pathway-mitogen activated protein kinase kinase/MAP kinase cascade	1.9
Thyrotropin-releasing hormone receptor signaling pathway	1.9
Ras	1.9
Beta3 adrenergic receptor signaling	1.9
5HT2 type receptor mediated signaling pathway	1.9
Angiogenesis	1.3
Plasminogen activating cascade	1.3
Muscarinic acetylcholine receptor 1 and 3 signaling	1.3
Metabotropic glutamate receptor group II	1.3
Synaptic vesicle trafficking	1.3
Ascorbate degradation	1.3
Metabotropic glutamate receptor group III	1.3
Integrin signalling pathway	1.3
Hypoxia response via HIF activation	1.3
p38 MAPK pathway	1.3
Opioid prodynorphin pathway	1.3
Pyruvate metabolism	1.3
B cell activation	1.3
5HT1 type receptor mediated signaling pathway	1.3
Axon guidance mediated by netrin	0.60
Apoptosis signaling pathway	0.60
Gonadotropin-releasing hormone receptor pathway	0.60
Alzheimer disease-presenilin pathway	0.60
CCKR signaling map	0.60
Wnt signaling	0.60
VEGF signaling	0.60
Toll receptor signaling	0.60
T cell activation	0.60
TGF-beta signaling pathway	0.60

TCA cycle	0.60
De novo purine biosynthesis	0.60
PI3 kinase	0.60
PDGF signaling	0.60
Oxidative stress response	0.60
Muscarinic acetylcholine receptor 2 and 4 signaling	0.60
GABA-B receptor II signaling	0.60
Endogenous cannabinoid signaling	0.60
Interferon-gamma signaling pathway	0.60
Insulin/IGF pathway-protein kinase B signaling cascade	0.60
p53 pathway feedback loops 2	0.60
Oxytocin receptor mediated signaling pathway	0.60
Heterotrimeric G-protein signaling pathway-Gq alpha and Go alpha mediated pathway	0.60
Heterotrimeric G-protein signaling pathway-Gi alpha and Gs alpha mediated pathway	0.60
Opioid proenkephalin	0.60
Nicotine pharmacodynamics	0.60
Enkephalin release	0.60
FGF signaling	0.60
Dopamine receptor mediated signaling pathway	0.60
FAS signaling	0.60
Angiotensin II-stimulated signaling through G proteins and beta-arrestin	0.60
Histamine H1 receptor mediated signaling	0.60
Cortocotropin releasing factor receptor signaling pathway	0.60
Endothelin signaling	0.60
EGF receptor signaling	0.60
Cytoskeletal regulation by Rho GTPase	0.60
Cell cycle	0.60
Cadherin signaling pathway	0.60
Blood coagulation	0.60
Beta2 adrenergic receptor signaling	0.60
5HT4 type receptor mediated signaling pathway	0.60

Supplementary Table 5. Molecular pathways underlying GE trajectories associated to LOAD progression in blood tissues (ADNI).

Pathway name	**Presence (%)**
Adenine and hypoxanthine salvage	5.7
TGF-beta signaling	5.4
Beta1 adrenergic receptor signaling	5.4
Heterotrimeric G-protein signaling pathway-rod outer segment phototransduction	4.3
Thyrotropin-releasing hormone receptor signaling	3.9
Blood coagulation	3.9
Ubiquitin proteasome	2.9
Ras	2.9
Muscarinic acetylcholine receptor 1 and 3 signaling	2.5
Pyruvate metabolism	2.1
Histamine H1 receptor mediated signaling	2.1
Mannose metabolism	1.8
Muscarinic acetylcholine receptor 2 and 4 signaling	1.8
Ascorbate degradation	1.8
Cadherin signaling	1.8
Xanthine and guanine salvage	1.4
Integrin signalling	1.4
Insulin/IGF pathway-mitogen activated protein kinase kinase/MAP kinase cascade	1.4
p38 MAPK	1.4
Pyrimidine Metabolism	1.4
Alzheimer disease-amyloid secretase	1.1
Adrenaline and noradrenaline biosynthesis	1.1
Parkinson disease	1.1
Notch signaling	1.1
Nicotinic acetylcholine receptor signaling	1.1
Interferon-gamma signaling	1.1
p53 pathway feedback loops 2	1.1
Opioid proenkephalin	1.1
Angiotensin II-stimulated signaling through G proteins and beta-arrestin	1.1
Purine metabolism	1.1
Beta3 adrenergic receptor signaling	1.1
Pentose phosphate	1.1
5HT2 type receptor mediated signaling	1.1
5HT1 type receptor mediated signaling	1.1
Axon guidance mediated by semaphorins	0.70
Apoptosis signaling	0.70
CCKR signaling map	0.70
VEGF signaling	0.70
Plasminogen activating cascade	0.70
Metabotropic glutamate receptor group II	0.70
GABA-B receptor II signaling	0.70
Interleukin signaling	0.70

Insulin/IGF pathway-protein kinase B signaling cascade	0.70
p53 pathway by glucose deprivation	0.70
Oxytocin receptor mediated signaling	0.70
Huntington disease	0.70
Opioid prodynorphin	0.70
Glycolysis	0.70
General transcription regulation	0.70
General transcription by RNA polymerase I	0.70
FGF signaling	0.70
Dopamine receptor mediated signaling	0.70
FAS signaling	0.70
Histamine H2 receptor mediated signaling	0.70
Cortocotropin releasing factor receptor signaling	0.70
Cholesterol biosynthesis	0.70
Cell cycle	0.70
Beta2 adrenergic receptor signaling	0.70
5-Hydroxytryptamine degredation	0.70
Axon guidance mediated by Slit/Robo	0.40
Gonadotropin-releasing hormone receptor	0.40
Angiogenesis	0.40
Alzheimer disease-presenilin	0.40
p53	0.40
Wnt signaling	0.40
Heme biosynthesis	0.40
Transcription regulation by bZIP transcription factor	0.40
Fructose galactose metabolism	0.40
Toll receptor signaling	0.40
T cell activation	0.40
PI3 kinase	0.40
PDGF signaling	0.40
Oxidative stress response	0.40
Metabotropic glutamate receptor group I	0.40
Endogenous cannabinoid signaling	0.40
Metabotropic glutamate receptor group III	0.40
JAK/STAT signaling	0.40
Inflammation mediated by chemokine and cytokine signaling	0.40
Vasopressin synthesis	0.40
Heterotrimeric G-protein signaling pathway-Gq alpha and Go alpha mediated pathway	0.40
Heterotrimeric G-protein signaling pathway-Gi alpha and Gs alpha mediated pathway	0.40
Opioid proopiomelanocortin	0.40
Hedgehog signaling	0.40
Nicotine pharmacodynamics	0.40
Enkephalin release	0.40
Endothelin signaling	0.40
EGF receptor signaling	0.40
DNA replication	0.40

Cytoskeletal regulation by Rho GTPase	0.40
Circadian clock system	0.40
B cell activation	0.40
5HT4 type receptor mediated signaling	0.40