Science Advances

Supplementary Materials for

Unified epigenomic, transcriptomic, proteomic, and metabolomic taxonomy of Alzheimer's disease progression and heterogeneity

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Supplementary Text S1
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Text S1 | Neuropathological measurements considered from ROSMAP dataset: Hippocampal sclerosis, arteriolosclerosis, amyloid angiopathy, atherosclerosis, vascular infarcts, chronic microinfarcts, diffuse plaques angular gyrus, diffuse plaques entorhinal, diffuse plaques hippocampus, diffuse plaques midfrontal, diffuse plaques mesial temporal, amyloid angular gyrus, amyloid calcarine, amyloid cingulate, amyloid entorhinal, amyloid hippocampus, amyloid inferior temporal, amyloid mesial temporal, amyloid midfrontal, amyloid superior frontal, PHF tangles angular gyrus, PHF tangles entorhinal, PHF tangles hippocampus, PHF tangles midfrontal, PHF tangles mesial temporal, tangles angular gyrus, tangles calcarine, tangles cingulate, tangles entorhinal, tangles hippocampus, tangles inferior temporal, tangles mesial temporal.
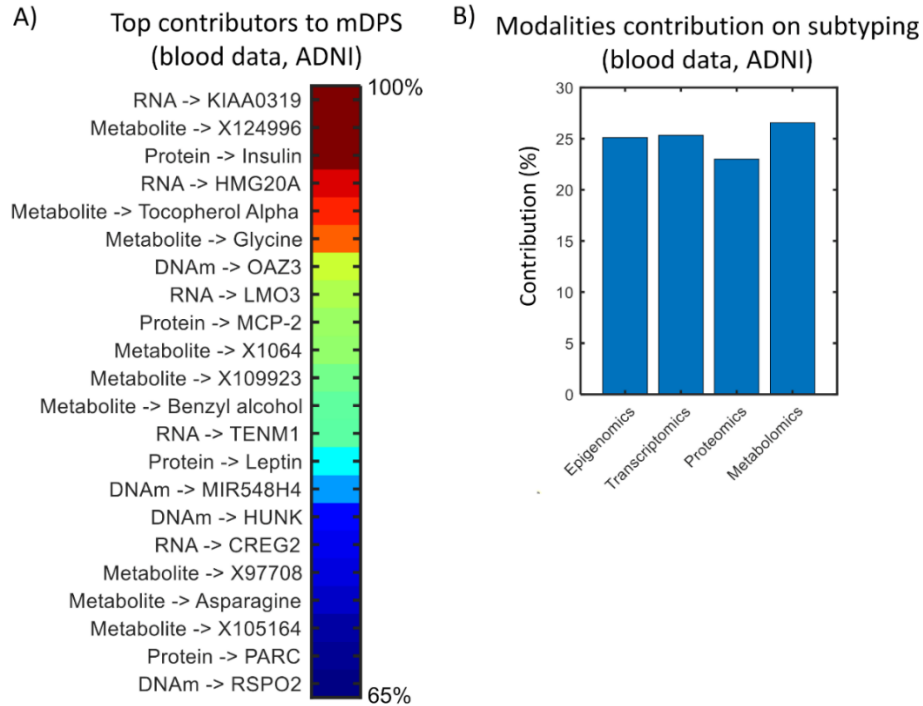
A) Top contributors to mDPS
(blood data, ADNI)

RNA -> KIAA0319
Metabolite -> X124996
Protein -> Insulin
RNA -> HMG20A
Metabolite -> Tocopherol Alpha
Metabolite -> Glycine
DNAm -> OAZ3
RNA -> LMO3
Protein -> MCP-2
Metabolite -> X1064
Metabolite -> X109923
Metabolite -> Benzyl alcohol
RNA -> TENM1
Protein -> Leptin
DNAm -> MIR548H4
DNAm -> HUNK
RNA -> CREG2
Metabolite -> X97708
Metabolite -> Asparagine
Metabolite -> X105164
Protein -> PARC
DNAm -> RSPO2

100%

65%

B) Modalities contribution on subtyping
(blood data, ADNI)

Contribution (%)

Epigenomics — Transcriptomics — Proteomics — Metabolomics

Figure S1 | Molecular omics contributions to AD stratification in *in-vivo* blood tissue. A) Top influential epigenetic, transcriptomic, proteomic, and metabolomic markers during the process of AD trajectories inference. Values are percentages, normalized with regards the maximum (only markers over the 99 percentile are shown; for an extended list, see Table S4). B) Modalities-specific contributions (in percentages) to the identified AD subtypes. For technical details, see *Methods*, subsections *Assessing markers contributions on mDPS* and *Assessing omics contributions on subtyping*, respectively.
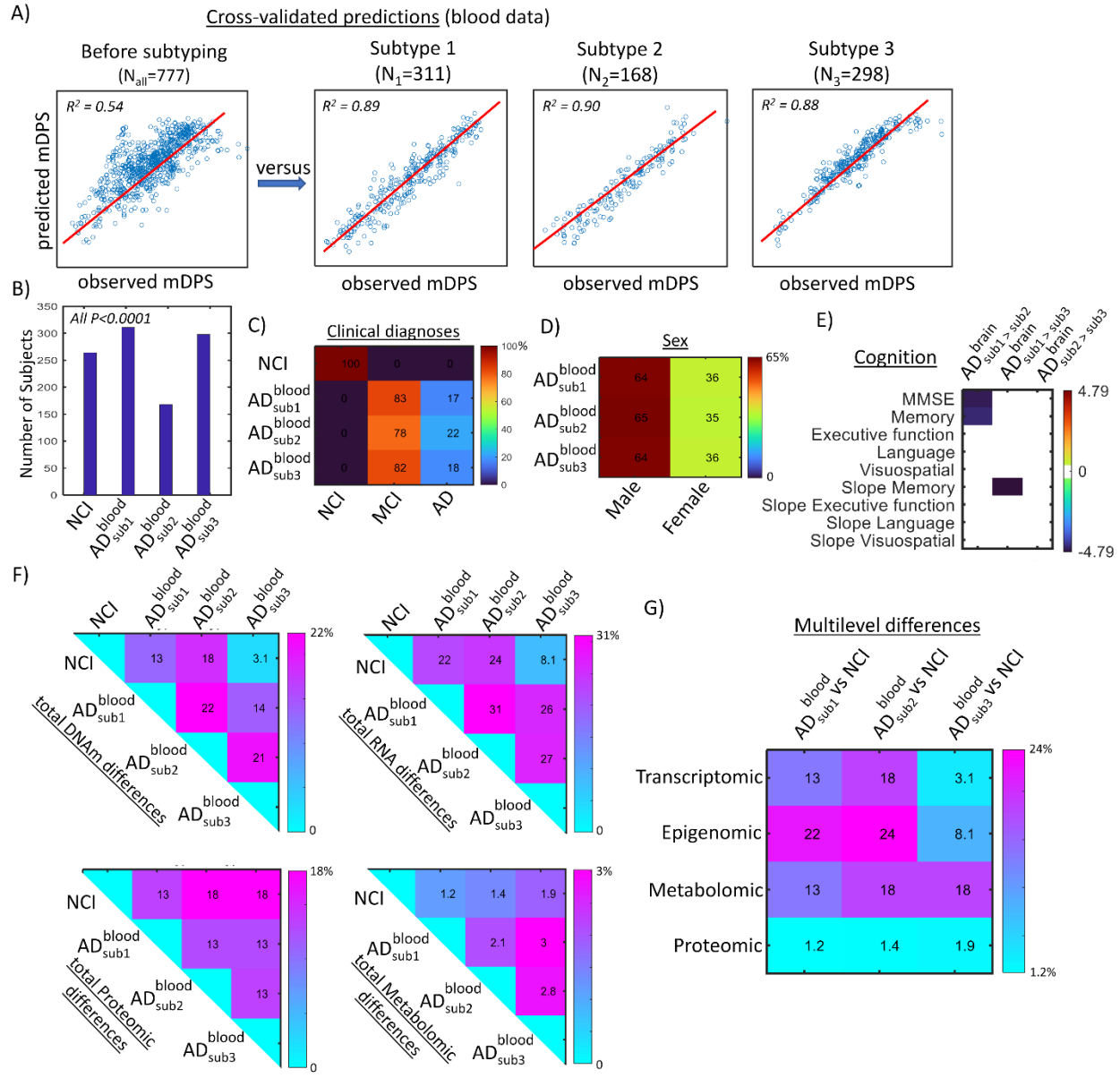
Figure S2 | Three distinctive AD subtypes identified with multi-omics molecular data from the blood (ADNI). A) Cross-validation analysis for identifying the most-likely stratification in terms of predictability of pathological advance. Notice that the decomposition of the whole population in smaller/stable subgroups implies a significant improvement in internal data homogeneity and multi-omics mDPS predictability. B) Number of samples per subtype and corresponding significance obtained with randomization testing (all P<0.001, FEW-corrected). C-D) Subtypes specific clinical diagnoses and sex proportions, respectively. **E) Inter-subtypes differences in cognitive variables and their rates of change over time (all P<0.05, FEW-corrected, based on ANOVA tests with permutations).** Only significant differences are shown, with values corresponding to explained variance and signs reflecting direction (for slopes, a positive value would indicate stronger cognitive decline for the first specified subtype, while a negative value would indicate the contrary). F-G) Total inter-subgroups molecular and neuropathological differences. For each data type and comparison with control population, each matrix element

corresponds to the percent of significantly different features (all q<0.05, FDR corrected, based on ANOVA tests with subtype as grouping variable; *Materials and Methods, Statistical Analyses*). For each subtype-subtype matrix element, the reported value represents the percent of data features that are abnormal for one subtype but not for the other (mismatch level).
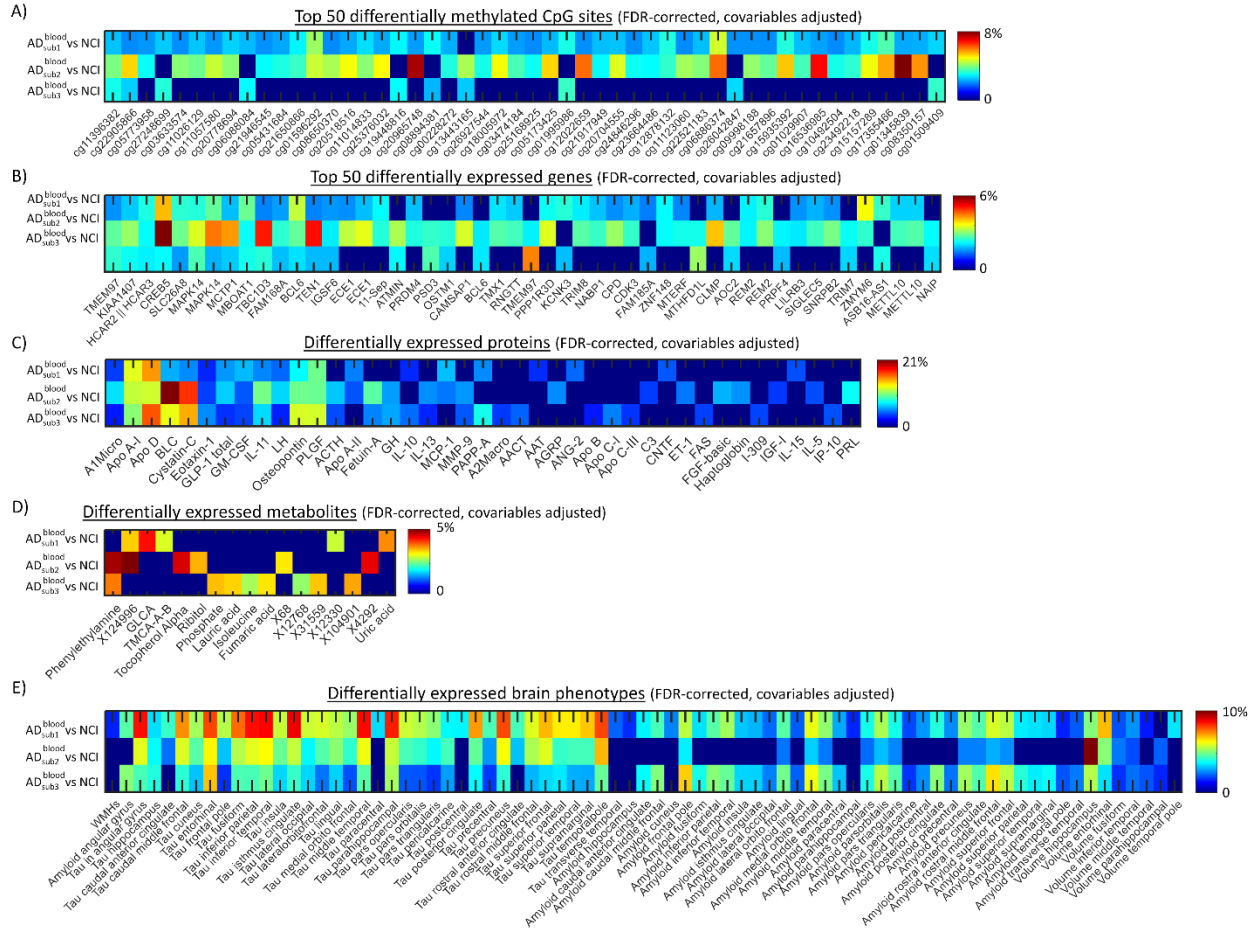

Figure S3 | Differentially expressed genes, CpG sites, proteins, metabolites, and brain phenotypes in blood-based AD subtypes. Only significantly expressed features are presented (q<0.05 FDR-corrected). ANOVA tests with subtype as grouping variable were used (data was previously adjusted by age, sex, educational level and experimental confounders; *Materials and Methods, Multi-omics cTI definition*). Color scale corresponds to explained variance. For RNA and DNAm, only the top 50 most significant genes and CpG sites are presented, respectively.
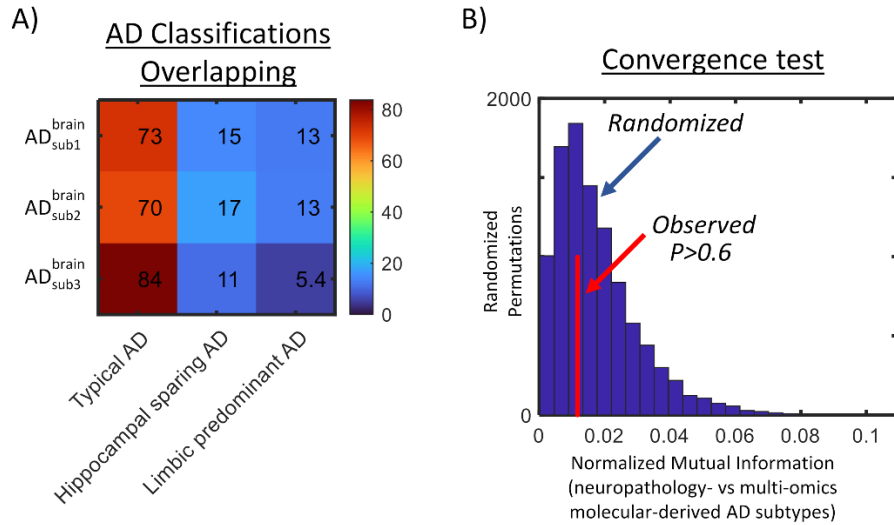
Figure S4 | Multi-omics molecular-derived vs Neuropathology-based AD classifications. A) Subtypes overlapping across the two different classification systems. For each multi-level molecular AD subtype, the reported values correspond to the percentages of participants identified as typical AD (tAD), hippocampal sparing (HpSp), and limbic predominant (LP) AD *(15, 40)*, respectively. B) Convergence test comparing normalized mutual information between the two independently obtained AD stratifications. For technical details, see *Methods*, subsection *Comparative analysis with neuropathological subtypes*.

Table S1 | Main demographic and data characteristics for the two populations. Of note, all subjects have at least two different molecular data types.

Variable	ROSMAP (N=822)	ADNI (N=1041)
Women	532 (64.7%)	440 (42%)
Age (years)	86.6 (4.59)	73.9 (7.18)
Education (years)	16.3 (3.51)	15.8 (2.85)
NCI	274 (33.3%)	264 (25%)
RNA	Brain: 489 (59.4%), Monocytes: 168 (20 %)	658 (63 %)
DNAm	708 (86.1%)	595 (57 %)
Metabolomics	111 (14%)	635 (61 %)

| Proteomics | 822 (100%) | 551 (53 %) |
| Neuropathological (based on *post-mortem* evaluations or *in-vivo* PET/MRI) | 822 (100%) | 610 (58 %) |

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

Table S2 | Top markers contributing to the multi-omics molecular AD progression scores.

Tissue	Markers
Brain (ROSMAP data)	RNA -> HOXC9, Metabolite -> 6-ketoLCA, Protein -> tau_77G7, DNAm -> PRDM6, RNA -> TCEB3B, DNAm -> NRN1L, Metabolite -> C0, Metabolite -> PC aa C38:3, DNAm -> C3orf55, DNAm -> JAK1, Metabolite -> LCA, RNA -> PFKP, DNAm -> C2orf42, DNAm -> KPNA2, Metabolite -> LCA-3S, DNAm -> DISC1, DNAm -> SLC2A4RG, Metabolite -> Putrescine, RNA -> HS.564153, Metabolite -> NorDCA, DNAm -> TTLL13, Metabolite -> Spermidine, Metabolite -> PC aa C34:2, DNAm -> APOLD1, Metabolite -> C4:1, Metabolite -> GHCA, RNA -> LRP8, DNAm -> PLAG1, DNAm -> WDR67, DNAm -> AKAP12, DNAm -> MIR379, DNAm -> CYP27C1, DNAm -> KCTD8, Metabolite -> CDCA, DNAm -> CFD, DNAm -> PFN1, Metabolite -> lysoPC a C18:2, DNAm -> ERGIC1, DNAm -> RABIF, DNAm -> EML1, DNAm -> TMEM150A, Metabolite -> Spermine, DNAm -> KIF22, Metabolite -> t4-OH-Pro, DNAm -> HIF1AN, DNAm -> SDK1, Metabolite -> PC aa C24:0, DNAm -> PAPOLB, Protein -> tau_AT100_t217, RNA -> KRT13, RNA -> HIST1H2BO, Metabolite -> C16-OH, Metabolite -> 12-ketoLCA, RNA -> LOC642521, DNAm -> TDG, DNAm -> OR51S1, RNA -> RXRG, DNAm -> TRIP10, RNA -> HS.145476, DNAm -> SLC1A3, DNAm -> G3BP1, RNA -> ZNF334, DNAm -> GOLPH3L, DNAm -> PBLD, DNAm -> HRK, RNA -> ADAD2, DNAm -> ZNF266, RNA -> HS.550430, Metabolite -> TUDCA, DNAm -> RPLP0, RNA -> LOC153328, DNAm -> FLOT1, DNAm -> ABCA2, RNA -> ARHGAP9, RNA -> POMT1, DNAm -> UCRC, DNAm -> MGC23284, DNAm -> RPS24, DNAm -> MYOM2, DNAm -> LMNB2, DNAm -> GRHL2, DNAm -> TP53INP2, DNAm -> GLG1, DNAm -> CSMD1, DNAm -> RNU5E, Metabolite -> GHDCA, Metabolite -> TCA, DNAm -> PAPOLB, DNAm -> RNH1, DNAm -> OPCML, RNA -> LOC440934, DNAm -> PAPOLB, RNA -> HS.407028, RNA -> SEC22C, Metabolite -> lysoPC a C16:1, DNAm -> COMP, Metabolite -> bUCA, Metabolite -> Cit, DNAm -> FAM41C, Metabolite -> PC aa C40:2, DNAm -> CNNM4, DNAm -> PCDHGA4, Metabolite -> Creatinine, Metabolite -> SDMA, DNAm -> SNORD53, DNAm -> SIGLEC6, DNAm -> FAM155A, DNAm -> TRIP10
Blood (ADNI data)	RNA -> KIAA0319, Metabolite -> X124996, Protein -> Insulin, RNA -> HMG20A, Metabolite -> TOCOPHEROL.ALPHA, Metabolite -> Glycine, DNAm -> OAZ3, RNA -> LMO3, Protein -> Monocyte Chemotactic Protein 2 (MCP-2), Metabolite -> X1064, Metabolite -> X109923, Metabolite -> BENZYLALCOHOL, RNA -> TENM1, Protein -> Leptin (ng/mL), DNAm -> MIR548H4, DNAm -> HUNK, RNA -> CREG2, Metabolite -> X97708, Metabolite -> ASPARAGINE, Metabolite -> X105164, Protein -> Pulmonary and Activation-Regulated Chemo, DNAm -> RSPO2, DNAm -> TBX5, Protein -> C-peptide (ng/ml), DNAm -> ATOH1, Metabolite -> X43729, Metabolite ->

X124283, DNAm -> IMPAD1, DNAm -> GJC1, RNA -> BNIP1, Metabolite -> X4292, Metabolite -> X130463, Metabolite -> DODECANOL, Metabolite -> X91, Metabolite -> X1873, Protein -> Apolipoprotein A-I (Apo A-I), RNA -> NAT8, Metabolite -> X44509, DNAm -> SEC14L2, Protein -> Apolipoprotein E (Apo E), Metabolite -> X1909, DNAm -> MPL, RNA -> EPB41L5, Protein -> Calbindin (ng/ml), Metabolite -> X47358, RNA -> ANKUB1, DNAm -> SDK1, DNAm -> STEAP2, Protein -> Platelet-Derived Growth Factor BB (PDGF), DNAm -> PRDM16, RNA -> GLIS2, DNAm -> MANEAL, DNAm ->CCDC54, Metabolite -> X103390, Metabolite -> X1872, DNAm -> BEND2, Metabolite -> GLUCONIC.ACID, RNA -> DEFB106A || DEFB106B, Metabolite -> X130465, Metabolite -> X130461, Metabolite -> X16788, RNA -> COL10A1, RNA -> ABI1, DNAm -> TNFRSF8, DNAm -> GRAMD1B, Metabolite -> X1912, RNA -> ZNF512B, Metabolite -> LAURIC.ACID, Protein -> Ferritin (FRTN), Metabolite -> TOCOPHEROL.GAMMA., DNAm -> KIAA1026, Metabolite -> X25321, RNA -> ANKRD44, Metabolite -> GLYCERIC.ACID, Protein -> Matrix Metalloproteinase-1 (MMP-1), Protein -> E-Selectin (ng/mL), Metabolite -> X1996, RNA -> CCP110, RNA -> GABRB3, Metabolite -> X130479, Metabolite -> X2430, Protein -> Chemokine CC-4 (HCC-4), Metabolite -> X3258, Metabolite -> X494, Metabolite -> SUCCINIC.ACID, Metabolite -> X490, Metabolite -> BETA.SITOSTEROL, Metabolite -> METHIONINE.SULFOXIDE, DNAm -> RTBDN, RNA -> SLC6A11, Metabolite -> X1.5.ANHYDROGLUCITOL, Metabolite -> X4746, Metabolite -> X130713, Metabolite -> X3286, RNA -> TOM1L2, RNA -> KRT6C, Metabolite -> X11523, Metabolite -> SUCROSE, Metabolite -> X130466, DNAm -> C10orf88, Metabolite -> XYLULOSE.NIST, RNA -> LSAMP, Protein -> Interleukin-8 (IL-8), Protein -> Interleukin-6 (IL-6), Metabolite -> EPSILON.CAPROLACTAM, Protein -> Alpha-1-Antitrypsin (AAT), DNAm -> LSR, Metabolite -> TARTARIC.ACID, DNAm -> WFIKKN2

* Only markers with contribution over the 95 percentile are reported (in order of contribution).

Table S3 | Differentially methylated and expressed genes in AD subtypes.

Differentially expressed	DNA-Methylation	RNA
AD1-Brain (ROSMAP)	*GREM2, LHX8, DUSP5P, GREM2, PCNXL2, LOC731275, FNBP1L, RGS4, C1orf106, SLAMF8, GREM2, GOLPH3L, CDC42SE1, MLLT11, NEGR1, ISG20L2, PIGK, S100A13, PUM1, S100A10, RPE65, C1orf14, ATP1A1, GOLPH3L, NADK, SNORA14B, TOMM20, PPM1J, FAM189B, TOMM40L, SYDE2, MXRA8, PADI3, C1orf194, KIAA1324, MOBKL2C, SYPL2, PODN, SFRS4, BCL2L15, SNHG12, SNORA44, SNORA16A, SNORA61, HDAC1, CNST, CASZ1, DISC1, TSNAX-DISC1, EPHA10, GREM2, IARS2, ERMAP, CCDC23, ERMAP, FMO5, DSTYK, RABIF, PLEKHA6, GREM2, FDPS, CTTNBP2NL, CNNM4, SPHKAP, DARS, CACNB4, RHBDD1, KLHL29, ABCB6, SNRNP27, SPATS2L, USP37, RQCD1, TUBA3D, BOLL, ZFP36L2, LASS6, LBH,*	*RERE, PPIL5, LOC440248, ITGA10, RBM17, HS.407028, CDIPT, ALG14, DCN, NFATC3, CTH, OTUD5, REC8, WDR6, HS.583475, SPAG9, MRTO4, ZNF706, DOCK6, HS.321580, ZNF627, AP4E1, FRAS1, LOC649783, GPER, TRIM5, QSOX2, HS.314177, GRTP1, HSPC111, RAB5C, MTMR3, CA2, CCRN4L, SEC22C, TAZ, TFDP1, TRIML2, KLHL35, GPER, NCALD, TMEM50A, PHF20L1, LRDD, POLR3F, FAM62C, NDUFA7, CALD1, LOC651621, H1F0, PSMD8, TLK2, ABCC10, ZC3HAV1L, ALKBH6, BCL2L1, LOC653717, PCID2, PRKDC,*

BOLL, BOLL, CNNM4, IMMT, TMEM131, DIS3L2, BOLL, KCTD18, RPS7, CYP27A1, SNORD53, WDR43, TMEM150A, BRE, MAP2, ATG16L1, ALS2CR8, WDR12, ALS2CR8, NCRNA00164, LRRFIP1, NMI, CNNM4, C2orf74, SLC9A2, KIF5C, MYT1L, C3orf55, WNT7A, MME, LIPH, NCEH1, C3orf55, COPG, WWTR1, GRM7, FNDC3B, SUMF1, C3orf72, GPX1, TEX264, GAP43, OSBPL11, NIT2, DOCK3, GLT8D1, RBP1, CCDC71, LRRC33, HTR3D, GPR160, EHHADH, SLCO2A1, ACTR8, SYN2, NCK1, DNASE1L3, PAQR9, ACTL6A, HDAC11, G3BP2, UGT2A2, SEC24D, UBE2D3, RCHY1, DGKQ, TRIML1, MTNR1A, FAM190A, SHROOM3, SPOCK3, SH3TC1, PACRGL, INTU, ZNF718, AMTN, PPARGC1A, STK32B, PCDHGA4, KCTD16, C5orf42, RNU5E, SLC6A18, C5orf32, CTNND2, NDFIP1, PAPD4, RASGEF1C, SGCD, SLC1A3, P4HA2, CEP72, FER, MBLAC2, KCTD16, 3/3/2019, UTP15, EBF1, AMACR, FBXW11, PPAP2A, PCDHB12, PCDHGA2, C5orf39, CETN3, PCDHGA2, FAM134B, CEP72, HGC6.3, NRSN1, ZNRD1, DOPEY1, ZDHHC14, RIMS1, OOEP, RIPK1, BMP6, KIAA1919, HLA-J, CD2AP, CMAH, GCNT2, TAPBP, RPP40, MTO1, COL11A2, ARID1B, C6orf10, DDAH2, SFRS18, USP49, TPBG, CDSN, GNL1, AKAP12, LY6G6F, PAPOLB, RADIL, LSM5, SLC26A5, 9/13/2019, PTPRN2, YWHAG, EXOC4, EPHA1, CDK6, ELMO1, STEAP4, ZNF498, FOXK1, BCAP29, MAGI2, OSBPL3, RBM33, STEAP4, PMS2L2, FAM20C, RADIL, ZNF680, STEAP4, SPATC1, ST18, MAL2, MSRA, SFRP1, GRHL2, BAI1, TSNARE1, CSMD1, MFHAS1, MTERFD1, XPO7, POP1, SFRP1, ADAM9, ADAM32, SFRP1, MCPH1, GRHL2, KIAA0196, ASAP1, YTHDF3, PLAG1, CSMD1, MTUS1, MTMR9, GRHL2, MYOM2, TRIM14, C5, SVEP1, DENND1A, INPP5E, ABCA2, TMC1, STX17, C10orf88, CPEB3, FRAT2, LOC100133308, ECD, COMTD1, VENTX, SLC16A9, TNKS2, ZMIZ1, DIP2C, DNA2, DPF2, ACTN3, LOC729799, KBTBD4, KCNQ1, BDNF, SLN, MACROD1, CHEK1, OR51S1, OPCML, METT5D1, CCDC34, PLEKHB1, TSG101, ARHGEF17, POLR2G, GLYATL1, ANO9, CAPN1, LEMD3, SCNN1A, PEBP1, HOXC4, KRAS, KCNA1, FRS2, APOLD1, ST8SIA1, ACSS3, RPLP0, CCNT1, POLR3B, ACAD10, TDG, ANO6, RAB5B, MYO1H, MPHOSPH9, MAPKAPK5, F7, C13orf27, KATNAL1, FARP1, C13orf16, CDK8, KL, COX8C, EML1, PRPF39, PSMC6,	*ZNF235, CAB39L, PDIA3P, MXI1, USP24, SERINC3, C11ORF88, ZMYND12, HS.458154, HS.581405, BBS2, STAG1, TRIM8, COL17A1, DHX40, MLL3, C19ORF10, PPAP2A, KIAA1147, ZNF518B, NPIP, IL17RB, AXIN2, METT11D1, ALDH1A1, HS.539639, RANBP3L, BMI1, TMEM203, ZMYND8, VPS25, PEX16, WDR77, GEM, FSCB, ACOX1, PRMT8, TRIM13, CYB5R1, SERPINB9, RERE, LOC645447, TBC1D8B, LYRM4, ACADVL, HS.255242, DNMT1, SETD2, LOC653764, ANXA11, POMT1, ZZZ3, TXNL2, LOC653210, ANKRD23, MAPKBP1, SNUPN, RCC2, HS.389988, CD59, BBS2, FAM71E1, RAB3IP, DEFB119, NIN, GEM, CEP110, TRAPPC2L, ERBB2IP, LOC730534, ZNF197, RCN1, MCF2L2, MED25, TFPT, LRCH4, DUS2L, ADH1C, MANBAL, APTX, SLTM, NAT5, FLJ44815, FAM169B, PPT2, SMYD2, NIN, SLC38A2, HS.543015, LOC399888, SEC14L1, LOC23117, PEMT, PDE4DIP, SLC43A2, HS.434957, CCDC56, PHACTR4, CD151, LOC728734, HS.10862, HS.527103, HS.576530, ABL2, TUBB4Q, METTL1, LOC728888, LOC652875, ELL3, NCAPH2, ZNF598, ATG4B, EIF3A, EMX2, TIMM17B, ALDH8A1, C6ORF111, HS.547738, PASK, MT1E, DNAJC18, KRT13, LOC650494, GSTO2, GOLPH3, PNLIPRP2, LOC153328, MGC27345, C15ORF38, TENC1, C17ORF61, PNOC, PHEX, CAB39L, LOC440356, KPNA5, PFKP, LOC441086, MEIS3, EGR3, ZCCHC17, SLC39A12, BBS4, ACP2, HSP90B1, HS.581313, PTPRE, GRK4, NUDT2, ITIH5, ABCA7, LOC158376, SLC43A3, PRNPIP, FAM139A, MYADM, HBA2, HS.555533, LOC440934, PRDM2, SCPEP1, KIF5B, LOC442597, ZCCHC14, NUDT2, ZNF26, ZCCHC8, PPP1CC, WDR64, PBX4, LOC728308, RFP,*

RDH11, ESRRB, YLPM1, GMPR2, MIR379, NGB, SRP54, FAM181A, SPATA7, BATF, KIAA1409, TC2N, TRPM1, FRMD5, TRPM7, MIR548H4, IGF1R, C15orf29, ATP10A, PLA2G4D, IQCH, SNORD115-13, LOC390594, FAM103A1, CHRNA7, SNORD116-14, PEX11A, ZNF609, PRRT2, CHP2, NRN1L, HS3ST2, CRAMP1L, AFG3L1, UNKL, TXNDC11, RABEP2, DECR2, MGC23284, BAIAP3, RGS11, COX4NB, MT1F, LMF1, LOC283856, CDH1, KIAA0430, KIAA0182, PFN1, TBCD, GALK1, TBCD, MYO18A, KPNA2, ABR, C17orf89, TNS4, CENPV, PHB, CCDC144C, NXN, C1QTNF1, STXBP4, OSBPL7, GPRC5C, SPNS3, FAM27L, FOXK2, STARD3, TCF4, TNFRSF11A, TMX3, CPLX4, CTAGE1, ZNF397OS, MIR526B, NFIC, SBK2, CFD, CACNG7, TRIP10, PAFAH1B3, NAPSA, NAPSA, LMNB2, C19orf22, MIR519C, PDE4C, ZNF585B, SMARCA4, SIN3B, FZR1, PRKD2, ZNF266, PRR12, ATCAY, EPHX3, KLK9, REXO1, AKT1S1, SERTAD3, NAPSA, CCDC155, DUS3L, SHISA7, COMP, CCDC155, SIGLEC9, SIGLEC6, ZNF560, NAPSA, GIPC3, CD70, TOX2, ROMO1, CHRNA4, GNASAS, NAPB, C20orf20, BFSP1, KRTAP24-1, C21orf67, TTC3, SLC37A1, IFNGR2, SLC19A1, RABL4, UCRC, TNRC6B, CYTH4, KREMEN1, A4GALT, C22orf27, CDC42EP1	*SAFB2, LOC23117, C19ORF48, PLAG1, HIST1H2BO, CYP11A1, NSMCE1, ZNF622, PHYHD1, NSUN5C, DDX3X, ESPL1, CBR1, PTPRF, PSMD5, HS.205112, KANK2, AKR1C4, GPER, SIL1, HS.536451, HS.561174, EMD, LOC644143, S100PBP, HPS4, GPR120, HS.490981, SPRYD3, CHN2, C21ORF114, DNHD1, LOC148915, PAN3, NCOA6, TMEM2, TIMM8A, HS.279208, PSD2, HS.194225, RP5-1022P6.2, PLAC8L1, LOC727927, LOC642450, KCNJ16, SPAG9, MBTPS1, SDSL, CCDC52, FLYWCH1, FNDC5, MUC20, CASC4, KCNK2, ADAD2, CHKB, HS.531457, MTG1, LOC441046, ARS2, NRIP2, HS.527535, TMEM97, TRAPPC1, ADD3, HS.391327, HS.418134, TDRD6, CLK1, CHCHD9, PPP2R3B, OR7A5, HBB, HS.576914, ANGPT2, NAP1L1, COL11A1, AXIN1, YARS, MRPS18A, COMMD9, FLJ20674, ATP6V0C, MMACHC, TAKR, EIF1, RASGRP2, EIF3C, LOC647941, C7ORF26, C16ORF90, SF3B1, SPHK2, HS.570308, PAXIP1, FRMPD2, C1ORF102, ZNF143, HS.298873, HS.554346, LOC646806, SLC26A6, TMCC2, TMEM14C, TYSND1, MANEAL, SNRP70, EIF2S1, LOC650887, FUT8, FOXD1, ARRDC2, CSPP1, YPEL4, PRR13, C9ORF78, UCKL1, OTUD4, TNFRSF25, S100A4, ELF1, MPI, LOC645681, PPFIBP1, PDCD2, LOC644334, LAMA5, MESP1, INSM1, POLR1E, FBXL22, OR2A14, HMGN2, HS.559929, BRE, PHB2, ODC1, CHCHD8, HS.564803, PASK, LRRFIP2, DOM3Z, HSF4, LOC613037, SHPRH, KLC4, STARD7, HSD17B4, HS.550430, ST8SIA4, ILK, LST-3TM12, NAV2, CALD1, LRRC51, ATM, LOC650155, LOC388237, SCAPER, COIL, ZCCHC11, FLJ41481, NSDHL, ERCC2, MAX, NFKBIA, IVNS1ABP, FLJ45300, LOC283755, HS.538763, SLC44A1, ERBB2IP, PROCA1, SLC30A3,*

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*SRD5A2, BOLL, LOC100133985,
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BOLL, KCTD18, NCK2, CYP27A1,
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MME, TRH, LIPH, NCEH1, C3orf55,
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ST3GAL6, FNDC3B, CHST2, USP13,
SUMF1, C3orf72, GPX1, C3orf10, TEX264,
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SLCO2A1, C3orf26, ACTR8, NCK1, DOCK3,
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AFAP1, PDLIM5, SHROOM3, SPOCK3,
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PDE6B, HSPA4L, FRAS1, PACRGL,
TBC1D1, NFXL1, TBCK, ZNF718, AMTN,
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C5orf42, RNU5E, SLC6A18, C5orf32,
TRIM23, SPRY4, PDZD2, FBXW11, MAML1,
MCTP1, NDFIP1, RASGEF1C, SGCD, EBF1,
P4HA2, UNC5A, CEP72, NDUFS4, NHP2,
HMMR, MBLAC2, KCTD16, 3/3/2019, PPIC,
AMACR, PPAP2A, FAM172A, C5orf39,
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KIAA1919, RPP21, LOC285740, SLC35A1,
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DCDC2, MIR548H3, AKAP12, PPP1R10,
PAPOLB, PAPOLB, SLC26A5, RADIL,
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YWHAG, EXOC4, EPHA1, CDK6, ELMO1,
PAPOLB, IQCE, BCAP29, MAGI2, OSBPL3,
RADIL, CNOT4, STEAP4, SPATC1, WDR67,
ST18, SFRP1, LYPLA1, GRHL2, TSNARE1,
CSMD1, ZFP41, MFHAS1, MTERFD1,
XPO7, POP1, SFRP1, ADAM9, ADAM32,
SFRP1, PDGFRL, KLF10, PPP2R2A, ASAP1,
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RNF139, TRIM14, C5, SVEP1, OR1Q1,
NFIL3, ABCA2, TMC1, STX17, TOMM5,
WDR37, ARMC4, CISD1, GOT1, CPEB3,
RPS24, C10orf12, HIF1AN, LOC100133308,
ECD, C10orf26, C10orf11, VENTX, SLC16A9,
TNKS2, LOC283050, DNA2, KCNMA1,
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FOLR1, KCNQ1, BDNF, OR8U8, CHEK1,
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*MTMR3, GOLT1A, INO80B, CA2,
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FAM62C, MED12, NDUFA7,
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BCL2L1, LOC653717, PCID2,
PRKDC, ZNF235, LOC338799,
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SERINC3, C11ORF88, ZMYND12,
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ACOX1, PRMT8, SERPINB9,
RERE, LOC645447, TBC1D8B,
LYRM4, HS.255242, DNMT1,
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HIST1H2AH, ANKRD23, CLDN15,
MAPKBP1, SNUPN, RCC2,
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BBS2, SH3RF1, FAM71E1,
C11ORF76, PARN, GEM,
LOC200810, CEP110,
LOC648364, TRAPPC2L,
ERBB2IP, LOC730534, ZNF197,
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HS.434957, CCDC56, PHACTR4,
CD151, HS.10862, ZNF215,
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UBXD6, PHEX, CAB39L, KPNA5,
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ZCCHC17, SLC39A12, TNPO1,
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		LYRM1, WSB2, IMP4, HS.184721, SLC15A2, HS.543232, HSPB3, THAP11, UBAC2, ARD1A, FIBP, ATP5J2, SCRIB, C10ORF61, HS.545454, HBA2, PRELP, KIF5A, PRKCG, KIAA0090, GCDH, MRPL17, WDR51A, OR51G1, CHP, RNF10, UBAP1, ASMTL, IPO11, ETFB, MANBAL, CREBBP, DUSP1, BTBD6, QDPR, MRAS, C16ORF58, NF1, PITPNM1, FLJ46230, CIAO1, DNAJC5B, LOC388681, ANKFY1, OR5D18, HS.529514, LOC391692, PRELP, HS.120938, TRAF5, HIGD1B, PFKFB2, ST3GAL3, BRUNOL6, SDCCAG3, CGREF1, PRPF19, SAFB2, ABCF2, SOCS4, C11ORF48, PRPF4B, C11ORF61, PHF17, SLC4A11, TPD52L1, AGRP, FRAS1, SFRS4, APLN, ASCL2, BCL2L13, GPKOW, HS.580702, NPIP, CXCR4, HNRPA1L-2, DSCR3, DKFZP586H2123, EXOC6, PPM1B, OSBPL9, USP42, ATP6V0B, LOC651029, ADORA2A, RFWD2, ZNF442, SSR4, SRRM2, PPFIA1, ZNF706, C1ORF66, HS.542571, ELA2
AD1-Blood (ADNI)	*SPOCK3, COL4A6, CLN5, KCTD5, PTGFRN, AGAP1, SLA, TG, CLIP4, CEP57L1, DNAJA3, IL20RA, BMS1P1, BMS1P5, PPP1R12B, SNX19, APCDD1L, TMEM86B, SAPS1, C20orf166, MIR133A2, RNF19A, PNMA5, FNTB, CHURC1-FNTB, MAX, BTLA, HCCA2, SLC25A22, PLCL2, GMDS, USP7, KIAA0930, ZNF204P, ST6GALNAC5, FBLN1, 3/3/2021, HAVCR1, PCGF3, VWA5B1, DUT, C5orf66, FAM19A5, HCCA2DUSP8, EHHADH, EHHADH, STXBP5-AS1, EPSTI1, LOC101927907, LRRTM4, OR4D1, IGF2, HIRA, C1orf57, SFRS16, JAZF1, PHGDH, VPS13B, ANTXR2, NAV2, UTRN, IGFALS, VBP1, GRIA3, IQGAP2, TBCD, FAM3C, DHRS7B, DUSP8, ATP11B, MIR221, MIR222, HPN-AS1, LINC01065, ITLN2, MRPL3, ZNF384, SPRY1, ATF6, EFEMP2, FRMD1, CCS, GJD2, PGK2, SQRDL, MNT, SLC39A8, DLGAP1-AS5, DLGAP1, B4GALT1, FAM53B, C9orf139, FUT7, PPP2R2C, FGGY, AP2A2, GRAMD1B, KYNU*	*CACNG8, MTOR, B4GALT1, SETD2, ECE1, ECE1, ATP9A, 11-Sep, EPT1, PRDM4, UHRF2, WLS, CYB5B, MMP9, LDLR, APH1B, CAMSAP1, TMX1, RNGTT, MAPK13, TMEM97, PRKCB, KIAA1407, CYYR1, HCAR2, CREB5, TMUB2, PI16, LPGAT1, KREMEN1, ZNF251, ZNF512B, PPP1R14C, CD300A, PPP1R3D, GRIA3, RWDD3, KCNK3, TRIM8, NABP1, SUGP2, CPD, TEN1-CDK3, ACMSD, FAM185A, HPD, ZNF148, MTERF, PLCL1, LYSMD1, GINS1, OR51E1, MAX, CLMP, NMNAT1, CASK, SLC26A9, REM2, REM2, SLC26A8, LOC101929809, SIGLEC5, EIF1AD, NRTN, UNC5A, PTRF, CD177, CA4, MYL1, SNRPB2, TRIP13, STAG3, ADRB3, C8ORF74, FERD3L, DCHS2, CNGB1, WLS, MAP2, ZMYM6, LSM11, ABRA, CREG2, LCE1C, ASB16-AS1, MXD3, ALX3,*

		PRDM7, DHX16, CPLX2, METTL10, METTL10, GABRA3, MMP16, FBXL13, MAGIX, ECE1, NIM1*, TENM1, ABHD12B, OR8G5, RIPPLY3, TNFSF14, TTL, CREB5, GINS3, CENPP, ARL11, KIAA0319, LHX4, MAGIX, NSMAF, NSMAF, FBXL13, HIST1H2AA, KCNA2, HIST1H3D, CASC1, TNFSF14, KCNJ1, METTL20, LAMA3, MAPK14, SUPT20HL2, MAPK14, OR6C76, PABPN1L, LRRC6, USP47, OLAH, PRPSAP1, CCL4L2, CCDC90B, CCDC90B, RPAIN, WLS, ATF6, RPTOR, TTTY14, PAPOLA, AHSG, PRKAR2A, MXD3, INSC, TP53TG5, METTL20, SPOCK3, WBP11, WBP11, JADE1, SOX15, CCR5, SLC2A11, FMO1, PXN, USP42, ATF7, CEP72, TTTY9B, TXNRD1, ZNF45, CREB5, SQLE, SNX10, SNX11, KLHL14, GUSBP11, STOML1, MCTP1, KCTD8, ADAMTS7, MBOAT1, MDM2, IQCK, LGALSL, TMEM168, ASAP1, PHLDB1, MTMR10, SFXN5, SNX10, TBC1D3, GOLGA6L1, NCOA3, BLCAP, RAB28, GNAQ, FAM168A, BCL6, MAX, ENSG00000239521, STAT5B, STAT5B, LOC254896, ZNF511, EIF3H, PRKACA, C9ORF84, SETD6, SUGP1, SMARCD1, PHLDB1, HERC2P9, TDRD1, IGSF6, ITGAX, CR1, DAPP1, BRD4, ZNF215, MSRA, ENSG00000215265, LRP10, ATP6V0D1, TMC5
AD2-Blood (ADNI)	*SPOCK3, XYLT1, CNKSR3, AGAP1, C17orf75, CEP57L1, UNC80, CRH, TMCC1, NDUFAF6, SNX19, LOC399959, MIR125B1, NAT15, TULP4, CTBP2, IKZF5, TBC1D22B, RNF19A, OR8D1, FNTB, CHURC1-FNTB, MAX, BTLA, HCCA2, REV1, TTC21B, USP7, DDX4, ST6GALNAC5, B4GALT1, PLCB1, PDE11A, INTS8, HAVCR1, CHN2, TRABD2A, NXT2, PCGF3, FMNL2, VWA5B1, RCOR2, OSBPL5, GLG1, PRICKLE2-AS1, SHANK2, SOGA1, HCCA2, DUSP8, LOC100130357, PHACTR1, FBXL22, BRD9, INS-IGF2, IGF2, OSBPL9, C7orf50, TACC1, C10orf40, LINC00944, SACS, FZD1, RSPO2, AIFM2, JAZF1, EBF3, CHORDC1, FGFR4,*	*FAF2, NDUFA8, ECE1, ECE1, SLC39A9, MKLN1, 11-Sep, ATMIN, SNRPE, IPO5, PRDM4, ACAP2, C14ORF166, GLIS2, LARS2, PSD3, PAICS, TMEM41A, PEX5, UBL4A, OSTM1, HEATR6, USP4, NFU1, CAMSAP1, PDE5A, ELP3, BCL6, TMX1, LYRM4, RNGTT, TMEM97, TMEM97, ZW10, PTPRD, KIAA1407, PARS2, NT5C2, HCAR2, RAB5A, CREB5, GPN1, CEP41, ZBTB9, ABHD5, PHF10, PHF10, ZSCAN26, ZNF853, GPR68, HCN4, DOK5, PPP1R3D, ANP32E, HNRNPL,*

	TACC1, PHGDH, VPS13B, TMCO3, MYOM2, SETBP1, ANTXR2, UTRN, BTG4, MIR34C, MIR34B, EMC7, TSC1, IGFALS, DGKE, STEAP2, STEAP2-AS1, IQGAP2, HAPLN1, RAB3IL1, TBCD, UST, PDE4C, COA4, PAAF1, SGSM1, RPA3, UMAD1, CMIP, HERC2, DUSP8, CHRM2, RIC8B, MIR221, MIR222, HPN-AS1, ITLN2, ANKRD62, MRPL3, TRIM55, LOC100996324, PTPN4, TXLNG, GNG12, B3GALT5, LOC283761, ELMO1, FAM126A, LMCD1-AS1, MYCNUT, NCALD, KCNB1, FAM53B, IMPAD1, PTPRN2, FAM149A;FAM149A, GALNT18, NSMCE2, FAM5C, C7orf50	*TRIM8, NABP1, MAP6D1, CPD, TEN1-CDK3, ADAMTSL3, ZNF148, MTERF, MTHFD1L, MAX, NFU1, CLMP, AOC2, REM2, REM2, PRPF4, SLC26A8, LOC101929809, SIGLEC5, HECW2, PPP1R8, AKIRIN1, LRRN1, ATXN7, ZNF789, SNRPB2, SLC22A1, ACKR2, KCNA3, TRIM7, TP53TG3, GON4L, MANBAL, SLC35B4, ZMYM6, UMPS, LRRK2, SMCO2, TNP2, METTL10, METTL10, PODXL, NAIP, FBXL13, SLC22A10, MEFV, ECE1, S100A7A, ABHD12B, SLCO2B1, NFE2L2, CACUL1, MAP3K2, CREB5, GINS3, PTPRE, BCL6, ZFYVE16, TNIK, STAG2, ATP10A, ARL11, KIAA0319, FBXL13, P2RY10, TNFSF14, KCNJ1, METTL20, SIM2, MAPK14, CD46, MAPK14, OR4B1, MTERFD2, PPAPDC2, STAG2, USP47, MOSPD2, RPL32, PRPSAP1, STGC3*, TDP1, RPAIN, ZWILCH, ATF6, HN1L, ABI1, ELF2, ELF2, TSC22D4, SPIDR, INTS6, USP15, RASSF2, SETD6, MXD3, NPY6R, 1-Mar, METTL20, JADE1, TCAIM, SLC2A14, SERINC2, SOX15, PLEKHH1, ZDHHC17, PXN, ABI1, SMEK1, SNW1, VPS13B, BCL6, CREB5, SNX10, TSC22D4, CD46, LBR, RTCB, MCTP2, MEFV, MCTP1, GABRG1, RTCB, PGM2, MBOAT1, NIF3L1, GPC3, TSC22D4, TMEM168, SPAG9, ASAP1, C16ORF80, VTCN1, LOC441155, NUPL1, KCNU1, SNRPB2, MLH1, MTMR10, PISD, RASSF2, SNX10, TBC1D3, FAM157B, SNHG1, EDEM3, MUC20, BAZ1A, NCOA3, RAB3IP, TRIM25, RFWD2, HEATR1, ZNF281, GNAQ, CHRNA3, FAM168A, ZNF284, BCL6, USP15, STAT5B, STAT5B, ZNF511, EIF3H, VNN3, C9ORF84, GIT2, TALDO1, SGSH, HERC2P9, RANBP10, IGSF6, PSMB9, ITGAX, TSPAN32, ESR2, CR1, DAPP1, LRP10, TMC5, RBPJ*
AD3-Blood (ADNI)	*NLGN1, DIDO1, BMS1P1, PTPN20B, PTPN20A, PLCL2, CDHR2, DGKH, B4GALT1, HAVCR1, SERINC5, STXBP5-AS1,*	*NEU1, UNC119B, ATMIN, PSD3, OSTM1, MINOS1, BCL6, MTSS1L, TMEM97, TMEM97, ANKRD12,*

TBX5, PRKAR1B, VBP1, TLR8, LOC349408, JUB, GRIK4, CCDC74B, HLA-DQB1, ATF6, CCS, SLC39A8, CCNJL	*KIAA1407, ACTA2, HCAR2, CREB5, HLA-DQA1, HOXA9, KCNK3, GPC4, FAM185A, ORC6, MTHFD1L, MTHFD1L, HYKK, AOC2, PRPF4, SLC26A8, LSMEM1, TRIM7, ASB16-AS1, METTL6, LMOD2, NAIP, TRPC3, PRG3, TRPV1, HYKK, COX15, LDLRAD1, NPC1L1, MAPK14, MAPK14, LRRC6, CCP110, SPATA18, BZW2, SLC2A14, ZDHHC17, TRPM8, CTPS1, FAM221B, RNF17, ANO3, MCTP1, MBOAT1, TAC3, IQCK, VTCN1, GDPD3, KLK8, SEC14L2, NUS1P3, TBC1D3, SNHG1, GOLGA6L1, ZNF689, FAM168A, BCL6, ENSG00000239521, LOC254896, ENSG00000224113, ARL2, DNM1, IGSF6, TSPAN32, MT1DP, VASH2, STMN4*

Table S4 | Molecular pathways presence levels across AD subtypes and omics modalities.

Molecular pathway	Abbreviation	RNA AD 1-Brain	RNA AD 2-Brain	RNA AD 3-Brain	DN Am AD 1-Brain	DN Am AD 2-Brain	DN Am AD 3-Brain	RNA AD 1-Blood	RNA AD 2-Blood	RNA AD 3-Blood	DN Am AD 1-Blood	DN Am AD 2-Blood	DN Am AD 3-Blood
Thyrotropin-releasing hormone receptor signaling pathway	TRH	4.3	0.5	5.5	2.7	0.6	0.5	2.8	1.4	0	4.3	5.1	4.5
Wnt signaling pathway	Wnt	2.2	1	2.5	0.7	0.6	1.1	1.1	1.4	4.3	0	3.4	9.1
Inflammation mediated by chemokine and cytokine signaling pathway	Chemokine/ cytokine	4.3	0.5	0.6	0.7	2.3	1.1	3.4	1.4	2.1	4.3	1.7	4.5
$5HT_2$ type receptor mediated signaling pathway	$5HT_2$	5	0.5	0.6	1.3	0.6	1.1	0.6	1.4	4.3	4.3	1.7	4.5

Pathway	Abbrev											
Metabotropic glutamate receptor group II pathway	mGluR II	0	3	1.2	11.4	1.7	1.6	0.6	0	0	0	1.7	4.5
Integrin signalling pathway	Integrin	2.9	0.5	1.2	1.3	0.6	7.4	0.6	2.7	2.1	4.3	1.7	0
Heterotrimeric G-protein signaling pathway-Gi alpha and Gs alpha mediated pathway	Gi α/Gs α	0.7	0.5	1.2	0.7	1.7	1.6	2.2	6.8	2.1	0	1.7	4.5
Interleukin signaling pathway	Interleukin	0	4	3.1	0	1.1	2.1	0.6	4.1	0	8.7	0	0
Alzheimer disease-amyloid secretase pathway	AD-Amyloid secretase	4.3	4.5	0.6	0.7	0.6	3.2	3.4	1.4	2.1	0	1.7	0
Oxytocin receptor mediated signaling pathway	OXTR	0.7	0.5	0.6	0.7	2.3	0.5	1.7	1.4	0	4.3	3.4	4.5
Histamine H1 receptor mediated signaling pathway	H_1	1.4	1	0.6	0	2.8	1.6	1.1	1.4	0	4.3	1.7	4.5
Interferon-gamma signaling pathway	INF-γ	0.7	2.5	3.1	5.4	0	1.6	1.1	2.7	2.1	0	0	0
CCKR signaling map	CCKR	1.4	0.5	1.2	0.7	3.4	1.1	0.6	1.4	2.1	0	6.8	0
Cadherin signaling pathway	Cadherin	1.4	4	1.8	1.3	1.7	0.5	0	0	2.1	0	1.7	4.5
Apoptosis signaling pathway	Apoptosis	0.7	0.5	2.5	0.7	1.1	0.5	2.2	1.4	0	4.3	0	4.5

Pathway	Abbr.												
p53 pathway	p53	3.6	1	2.5	1.3	2.3	2.1	3.9	0	0	0	1.7	0
Transcription regulation by bZIP transcription factor	bZIP	3.6	0.5	5.5	0	0	0	0.6	1.4	2.1	0	0	4.5
Cortocotropin releasing factor receptor signaling pathway	CRFR	0	0	0	0.7	1.1	10.5	1.1	1.4	0	0	3.4	0
Gonadotropin-releasing hormone receptor pathway	GRHR	0.7	2.5	1.2	0.7	1.1	0.5	1.7	1.4	2.1	0	1.7	4.5
FGF signaling pathway	FGF	2.2	0.5	1.2	0.7	1.1	0.5	1.1	2.7	2.1	4.3	1.7	0
β_1 adrenergic receptor signaling pathway	β_1 receptor	0	0	0	0.7	10.2	0.5	2.8	0	0	0	3.4	0
Huntington disease	Hunt.	0.7	0.5	0.6	2.7	0.6	1.1	0	0	2.1	4.3	0	4.5
Muscarinic acetylcholine receptor 1 and 3 signaling pathway	M_1/M_3	4.3	1.5	3.7	0	0.6	1.6	0.6	1.4	0	0	3.4	0
Metabotropic glutamate receptor group III pathway	mGluR III	0	4	0.6	0.7	1.1	1.1	0.6	0	0	4.3	0	4.5
Angiogenesis	Angiogenesis	2.2	1	3.1	2	0.6	0.5	2.2	1.4	2.1	0	1.7	0
T cell activation	T cell	6.5	3.5	0.6	2	0.6	0.5	0	0	2.1	0	0	0
EGF receptor signaling pathway	EGFR	0.7	0.5	2.5	0.7	1.7	1.1	0.6	1.4	2.1	4.3	0	0

Oxidative stress response	Oxi.	0.7	0.5	0.6	0	0	0	0.6	2.7	4.3	4.3	1.7	0
Hedgehog signaling pathway	Hedgehog	3.6	0.5	1.8	0.7	0.6	2.6	0.6	0	0	0	0	4.5
Heterotrimeric G-protein signaling pathway-Gq alpha and Go alpha mediated pathway	Gq α/Go α	0.7	0.5	0.6	2.7	0.6	4.2	2.2	1.4	0	0	1.7	0
Ionotropic glutamate receptor pathway	iGluR	0	0	0	0.7	0	1.1	2.2	0	0	4.3	1.7	4.5
Endothelin signaling pathway	Endothelin	0.7	2	0.6	0.7	0	0	1.1	1.4	0	0	3.4	4.5
VEGF signaling pathway	VEGF	1.4	0.5	0.6	2.7	0.6	1.1	3.9	1.4	2.1	0	0	0
Alzheimer disease-presenilin pathway	AD-Presenilin	0.7	0.5	1.2	2	0.6	1.6	1.1	2.7	2.1	0	1.7	0
Notch signaling pathway	Notch	0.7	0.5	2.5	0	6.8	0.5	1.1	1.4	0	0	0	0
Ubiquitin proteasome pathway	Ubiquitin	1.4	3	4.3	0.7	0.6	1.1	2.2	0	0	0	0	0
Parkinson disease	PD	0.7	0.5	3.7	0.7	1.1	1.1	0.6	2.7	2.1	0	0	0
Muscarinic acetylcholine receptor 2 and 4 signaling pathway	M_2/M_4	0	0.5	0.6	1.3	0.6	0.5	0.6	0	0	0	3.4	4.5
Insulin/IGF pathway-protein kinase	IGF pathway	0	0	0	0.7	1.1	1.1	2.8	0	0	4.3	1.7	0

B signaling cascade												
Nicotine pharmacodynamics pathway	Nicotine	0.7	1.5	0.6	0.7	1.1	1.1	1.1	2.7	2.1	0	0	0
Toll receptor signaling pathway	Toll	1.4	0.5	0.6	0	0	0	1.1	1.4	2.1	0	0	4.5
Vitamin D metabolism and pathway	Vit. D	0.7	0.5	3.1	2.7	1.1	1.1	0	0	2.1	0	0	0
General transcription regulation	GTR	0.7	1	3.1	0	0	0	1.1	5.4	0	0	0	0
Angiotensin II-stimulated signaling through G proteins and beta-arrestin	Angiotensin II	0	0.5	0	0	1.1	1.1	2.8	4.1	0	0	1.7	0
General transcription by RNA polymerase I	RNA poly. I	5	4.5	0.6	0	0	0	1.1	0	0	0	0	0
TGF-beta signaling pathway	TGF-β	1.4	1.5	0.6	0.7	1.1	0.5	1.7	1.4	2.1	0	0	0
Cytoskeletal regulation by Rho GTPase	ρ-GTPase	4.3	1	1.8	0.7	0.6	0	0	0	2.1	0	0	0
p53 pathway by glucose deprivation	p53-glucose	0	0	0	0	3.4	3.7	1.7	0	0	0	1.7	0
Opioid proenkephalin pathway	Opioid PENK	0.7	2	0.6	0	1.1	1.1	1.1	0	2.1	0	1.7	0
B cell activation	B cell	0.7	1	0.6	1.3	1.1	0	2.2	1.4	2.1	0	0	0
Cholesterol biosynthesis	Cholesterol	2.9	0.5	2.5	1.3	2.3	0	0.6	0	0	0	0	0
Enkephalin release	ENK	1.4	1	1.2	1.3	0.6	0.5	2.2	0	0	0	1.7	0
Nicotinic acetylcholine receptor	nAChR	0	4	0.6	0.7	0	1.1	0	1.4	2.1	0	0	0

signaling pathway													
P53 pathway feedback loops 1	p53 fb 1	0	0	0	2.7	2.8	2.6	1.7	0	0	0	0	0
Dopamine receptor mediated signaling pathway	Dopamine	1.4	0.5	1.2	0	0.6	2.1	1.7	0	2.1	0	0	0
$5HT_1$ type receptor mediated signaling pathway	$5HT_1$	0	0	0	1.3	1.1	0.5	0.6	0	4.3	0	1.7	0
p53 pathway feedback loops 2	p53 fb 2	0.7	1	0.6	0.7	0.6	0.5	0.6	2.7	2.1	0	0	0
$GABA_B$ receptor II signaling	$GABA_B$ II	0	0.5	0	0.7	1.1	1.6	0.6	0	0	0	0	4.5
Mannose metabolism	Mannose	0.7	4	0	0	0	0	0	0	0	4.3	0	0
Opioid proopiomelanocortin pathway	POMC	0	0	0	0.7	0.6	1.6	2.2	0	2.1	0	1.7	0
Metabotropic glutamate receptor group I pathway	mGluR I	0	0	0	0	0	1.1	0.6	2.7	0	0	0	4.5
Ras Pathway	Ras	0.7	2	0.6	0.7	0.6	0	0.6	1.4	2.1	0	0	0
mRNA splicing	mRNA splicing	0	1	3.7	0	0	0	1.1	2.7	0	0	0	0
Opioid prodynorphin pathway	PDYN	0	0	0	1.3	0.6	1.1	0	0	2.1	0	3.4	0
Pentose phosphate pathway	PPP	0	0	0	0	0	0	0	4.1	0	4.3	0	0
$5HT_4$ type receptor mediated signaling pathway	$5HT_4$	0	0	0	0.7	1.1	1.6	1.1	0	2.1	0	1.7	0

PI3 kinase pathway	PI3 kinase	0	0	0	0.7	0.6	1.1	1.7	4.1	0	0	0	0
FAS signaling pathway	FAS	0.7	3	0.6	1.3	1.1	1.1	0	0	0	0	0	0
Alpha adrenergic receptor signaling pathway	α	0.7	1	2.5	0	0	0	1.7	0	0	0	1.7	0
p38 MAPK pathway	p38 MAPK	2.2	0.5	0.6	0	0	0	0.6	1.4	2.1	0	0	0
PDGF signaling pathway	PDGF	0.7	0.5	1.2	0.7	1.7	0.5	0.6	1.4	0	0	0	0
De novo purine biosynthesis	DNPS	0	3.5	0.6	0	0	3.2	0	0	0	0	0	0
Adrenaline and noradrenaline biosynthesis	NA/A	0	0.5	1.2	2.7	0.6	0.5	0	1.4	0	0	0	0
β3 adrenergic receptor signaling pathway	β3	0	0	0	0.7	1.1	0.5	2.8	0	0	0	1.7	0
Histamine H2 receptor mediated signaling pathway	H2	0	0	0	0.7	1.1	1.1	1.7	0	0	0	1.7	0
Heterotrimeric G-protein signaling pathway-rod outer segment phototransduction	G-protein/photo	0	0	0	0	3.4	0.5	0.6	0	0	0	1.7	0
DNA replication	DNA rep.	0	1	0	2.7	0.6	0	0	1.4	0	0	0	0
Phenylethylamine degradation	PEA	0	0	0	0	0	0	0	1.4	4.3	0	0	0
Ornithine degradation	Ornithine	0.7	4	0.6	0	0	0	0	0	0	0	0	0

Pathway	Abbrev.											
Axon guidance mediated by netrin	Netrin	1.4	1	0.6	0	0.6	0	1.7	0	0	0	0	0
β_2 adrenergic receptor signaling pathway	β_2	0	0	0	0.7	0.6	1.6	0.6	0	0	0	1.7	0
JAK/STAT signaling pathway	JAK/STAT	0	0	0	0	0	1.1	0.6	1.4	2.1	0	0	0
Formyltetrahydrofolate biosynthesis	FOL	0	0	0	0	0	0	0	2.7	2.1	0	0	0
$5HT_3$ type receptor mediated signaling pathway	$5HT_3$	0	0	0	0	0	0	1.7	0	2.1	0	0	0
5-Hydroxytryptamine degredation	5-HT	0.7	1	1.2	0.7	0	0	0	0	0	0	0	0
De novo pyrimidine ribonucleotides biosythesis	De novo pyr.	0	0	0	0	0	0	0	1.4	2.1	0	0	0
Synaptic vesicle trafficking	Vesicle	0	1.5	0.6	0.7	0.6	0	0	0	0	0	0	0
Hypoxia response via HIF activation	HIF	0.7	0	0.6	0	0	0	1.1	0	0	0	0	0
Axon guidance mediated by Slit/Robo	Slit/Robo	0.7	1	0.6	0	0	0	0	0	0	0	0	0
Vasopressin synthesis	Vasopressin	0	0	0	0	0	0	0	0	2.1	0	0	0
Blood coagulation	Coagulation	0.7	0.5	0	0.7	0	0	0	0	0	0	0	0
Salvage pyrimidine ribonucleotides	Savlage pyr.	0.7	0.5	0.6	0	0	0	0	0	0	0	0	0

Methionine biosynthesis	Methionine	0.7	0.5	0.6	0	0	0	0	0	0	0	0	0
Pyruvate metabolism	Pyruvate	0	1.5	0	0	0	0	0	0	0	0	0	0
TCA cycle	TCA	0	0.5	0.6	0	0	0	0	0	0	0	0	0
Axon guidance mediated by semaphorins	Semaphorins	0	0.5	0.6	0	0	0	0	0	0	0	0	0
Plasminogen activating cascade	Plasminogen	0	0	0	0	0	0	1.1	0	0	0	0	0

Table S5 | Differentially expressed monocyte genes for brain-derived AD subtypes.

Tissue	Genes
AD1-Brain (ROSMAP)	*ARID3C, ASTN1, CD9, CDC42P2, CEP295NL, CLPTM1LP1, H2BP3, HMGN1P9, HNRNPA1P23, KIF3C, LIN54, LINC02218, MSH5-SAPCD1, MTRF1, RNA5SP423, RNF126, RPL13P12, RPL23AP40, RPL23AP7, RPL26P20, RPL6P9, RPS10P16, SNRPGP12, TCEAL6, TRAT1, UCP3, UPF3B, VDAC1P2, VN1R107P, ZNF37CP, ADGRG7, ADORA2B, AOX1, ARL2BPP1, ARSJ, BANF1P4, BAZ2B, CAPZA1P5, CCDC122, CCDC17, CENPUP1, CEP164, CEP57, CERS4, COL9A1, CRISP1, CSF1R, CTAGE13P, CUX1, CYCSP39, DENND5A, DIPK1A, DUX4L13, EFCAB2, ELL2P2, FAHD2P1, FCN2, FGF7P6, FNTAP1, GAPDHP54, GBAP1, GEN1, GOLGA6L3, GP6, GPR42, GSG1, GSTK1, H2AC18, H2AC20, HDAC3, HMGB1P47, HOXB7, HSD17B10, HTT, IFI35, IGHM, IGKV1-8, KLF4P1, KRTAP10-1, LHX6, LPAR1, LRRFIP2P1, LTBP4, MAGEA3, MEST, METTL22, MRGBP, MTCO1P31, MTCO2P34, MTFR1L, MTHFSD, MTND1P19, MTND1P2, MYLIP, NDRG4, NPY, NUDT11, NXF5, OFD1P6Y, OR11Q1P, OR2F2, OR5F1, PAQR5, PCBP2P1, PCDH19, PCP2, PICK1, PKD1P3, PORCN, PPIAP28, PSD4, PTH2R, PTP4A1P2, RAB11AP1, RHEBP1, RHOB, RHPN2, RNA5SP197, RNA5SP223, RNA5SP27, RNA5SP346, RNA5SP508, RNLS, RPL22L1, RPL30P10, RPL34P17, RPL36AP36, RPL7AP71, RPN2, RPS23P5, RPS24P17, RPS3AP9, SEMA4G, SERBP1P6, SERPINB11, SETD5, SFXN5, SNRPEP3, SOWAHB, SPATA24, SPICE1, SS18L1, SUMO2P2, SYCP2L, TAF1, TBX2, TCP10L2, TFPI2, THEM7P, TMEM178A, TP53TG3GP, TRAPPC13P1, UBE2C, UBE2W, VN1R3, VWDE, WNT2, ZBTB47, ZDHHC13, ZFYVE9P1, ZNF209P, ZNF23, ZNF354C, ZNF519P4*
AD2-Brain (ROSMAP)	*ASTN1, CEP295NL, CLPTM1LP1, CYP2AB1P, DLSTP1, FUZ, HNRNPA3P13, IGKV3OR22-2, KIF3C, LIN54, LINC02218, MSH5-SAPCD1, MTRF1, OR3A1, OR4H12P, RNA5SP423, RNA5SP492, RNF126, RPL13P12, RPL23AP40, RPL23AP7, RPL26P20, RPL35AP12, RPL6P9, RPS10P16, SMIM42, SNRPGP12, TAAR8, TRAT1, U2AF1, UCP3, UPF3B, VDAC1P2, VN1R107P, ABL1, ACAT2, ACBD5, ACOT9, ACTBP2, ACTG1P25, ACTN4P1, ACTR1A, ADAD1, ADAMTS17, ADAMTS4, ADAMTSL2, ADAP1, ADGRE2, AICDA, AIPL1, AKAP13, AKR1C6P, ANKRD26P4, ANKRD36BP2, ANKRD45, ANKRD66, ANKRD9, AP1M1, AP5B1, APCS, APIP, ARAF, ARAFP1, ARAP2, ARF6, ARFGEF1, ARGFX, ARHGAP42P4, ARHGDIB, ARID5A, ARL10, ARL11, ARL8A, ARPIN, ARRB1, ARRB2, ATG12P2, ATG3P1, ATN1, ATP5MC2P1,*

ATP5PBP3, ATP5PD, ATP5PDP1, ATP6V1B2, ATXN1L, B4GALT5, BCAS4, BCRP9, BEND2, BEST4, BMP7, BRI3BP, C19orf47, C19orf48, C2orf83, C7, CALHM2, CAPN2, CARTPT, CBX3P1, CBY1, CC2D2B, CCAR2, CCDC134, CCDC144A, CCDC74A, CCL24, CCNK, CCNYL7, CCR12P, CCR3, CD109, CD300C, CD300E, CD44, CD68, CD74, CD93, CDC37, CDC37L1, CDC73, CDH9, CDK10, CDKL1, CDRT15P9, CENPN, CEP78, CHD1, CHP2, CHRNA5, CLN3, CLPX, CNKSR3, CNOT8, COA7, COG5, COL6A3, COPG1, COPS2, CPHXL, CREG1, CRISP1, CRPPA, CRY1, CSDC2, CSF2, CSF2RA, CSN3, CSTF2T, CT45A5, CUL4B, CYB5AP2, CYBA, CYP1A2, CYP27C1, CYP2B6, CYP2J2, DAXX, DBT, DCAF1, DCN, DDA1, DEFA1, DEFB125, DENND5B, DHFR, DHFRP3, DHTKD1, DHX33, DLX6, DOC2B, DPF1, DPY19L3, DUSP12P1, DUSP5, EAF1, EDC4, EEF1A1, EEF1A1P33, EEF1A1P38, EFHD2, EHHADH, EIF1AD, EIF1B, EIF2AP4, EIF2S2P1, EIF2S2P3, EIF3FP3, EIF4A1P11, EIF4EP1, ELF2, ELF4, ELOCP33, EMC1, EMC3-AS1, EML2, EMP2, ENO3, EP400P1, ERCC4, ERF, ERGIC1, ERVV-2, EXOC5, EXOC7, EXT1, FABP5P14, FABP5P9, FAM151B, FAM172BP, FAM241A, FAM30B, FAM3C2P, FANCE, FARSA, FAUP1, FBRS, FBXL18, FBXO2, FBXW2, FCHO2, FEM1A, FGD5, FGFBP3, FKBP14, FNDC4, FNDC9, FOS, FOXK1, FOXRED2, FRY, FUT1, FZD4, FZD5, G6PD, GART, GATAD1, GCLM, GDPGP1, GET4, GFI1B, GID4, GIMAP1-GIMAP5, GIMAP2, GJC1, GLIPR2, GLMN, GLRXP3, GLULP4, GMFB, GMPS, GPR108, GPR142, GPR153, GRM6, GTDC1, GTF2IP20, GTF2IP23, GTSF1, GYPC, GZF1, H1-2, H1-3, H2AC19, H2AC21, H2BC10, H3-3B, H3C4, H3P31, HACD2, HCAR1, HDHD3, HFE, HIKESHI, HLA-DQA2, HMGA1P1, HMGB1P38, HMGB3P18, HMGN2P20, HMGN2P36, HNRNPA1P5, HNRNPH1, HOXD4, HRK, HSP90AA4P, HSP90AB7P, HSPBAP1, HSPE1, HSPE1P10, HSPE1P20, HTR3B, HYKK, ID1, IER2, IFFO1, IFT22, IGDCC4, IGHV7-27, IGHV7-56, IGKV2D-23, IKZF3, IL10RA, IL17RA, INGX, INO80C, INPP5F, INTS11, IRF9, IRS2, KATNAL1, KCNA4, KCNJ12, KDM5B, KIAA1841, KIF1C, KIN, KLF10, KLF2P4, KLF3, KLHL15, KMT2D, KNDC1, KREMEN1, KRT18P31, KRT8P36, KRT8P44, KRTAP10-11, KRTAP10-6, KRTAP10-9, KXD1, LAMC2, LCP2, LELP1, LEPR, LINC01085, LINC01347, LITAF, LITAFD, LLPHP2, LMF2, LNPEP, LOXHD1, LRRC19, LRRC37A16P, LSM11, LSM6P2, LSP1, MACC1, MACROH2A2, MANBA, MANSC1, MAP3K11, MAP3K15, MAP4K1, MAPK1IP1L, MAPKAPK5, MARCHF2, MARK2P8, MBD6, MCF2L2, MDH1B, MDH2, MDM4, ME2, MED15, MED28, MED9, METAP2P1, MFAP5, MFSD14C, MGRN1, MICOS10-NBL1, MID1IP1, MINK1, MITD1, MLANA, MLF2, MMAB, MMD, MMS22L, MOB3A, MOCS3, MPEG1, MPLKIP, MRPL42, MRPL49, MRPL55, MRPS23, MT-ATP6, MT-ATP8, MT-CO1, MT-CO2, MT-ND1, MT-ND4L, MT-ND5, MT-ND6, MT1P3, MTATP6P1, MTATP6P9, MTCO1P2, MTCO2P12, MTCO2P21, MTCYBP15, MTHFD1, MTHFD2P1, MTHFD2P7, MTND2P23, MTND4LP30, MTND4P30, MTND4P6, MTND4P7, MTND5P11, MTRNR2L1, MTSS1, MXRA5Y, MYH9, MYL10, MYLK3, MYO1F, NACA2, NANOGP10, NANOS1, NBEAL2, NBPF17P, NCMAP, NCSTN, NDUFA9, NDUFS1, NEK5, NEK9, NET1, NETO1, NF1P3, NFAM1, NFASC, NFIL3, NIPAL3, NLRC5, NLRX1, NOC2LP2, NOTCH2, NPHP3, NPHS1, NPIPB13, NPIPB2, NPLOC4, NRBF2, NRGN, NSMCE3, NUDCD2, NUP188, NUP54, NUP62, NWD1, NXT1, OAF, OGFOD3, OR10K1, OR11G2, OR12D1, OR2A25, OR2AP1, OR4A48P, OR4C10P, OR4E2, OR52K3P, OR52Q1P, OR5H14, OR5P4P, OR7A17, OR7E94P, OR7G2, OTUB1, P2RX1, P2RX5-TAX1BP3, P2RY8, PAF1, PARVA, PATL1, PCBD2, PCBP1, PCDH11X, PCDHAC2, PCDHB2, PDE11A, PDIA3, PEX14, PHLDA3, PHYH, PIAS4, PKD1L2, PKIA, PKN3, PLCB2, PLCE1, PLD1, PLEKHA3, PLXNC1, PLXND1, PM20D2, PNMA3, PNMA6B, PNPT1, POLG2, POLR2A, PPIAP21, PPIAP22, PPIAP36, PPM1K, PRKCSH, PRKX, PRL, PRORSD1P, PRSS47, PSMA7, PSMB2, PSMD10P2, PSPN, PTH, PTOV1, PTPN1, PTPN14, PTPN22, PXMP4, PYGM, PYHIN1, RAB1A, RAB3B, RAB5C, RAD1, RAD51D, RASSF8, RASSF9,

	RBM22P2, RBM23, RBM28, RBM39, RBMS2, RBMXL2, RBPJP5, RECQL, RELCH, RETREG3, RFTN2, RGS17P1, RILPL1, RIMS1, RNA5SP279, RNA5SP282, RNA5SP286, RNA5SP338, RNA5SP346, RNA5SP508, RNA5SP90, RNA5SP97, RNASE10, RNF115, RNF133, RNF144A, RNF144B, RNF207, RNF26, RNF8, RPL10AP3, RPL12P5, RPL12P7, RPL17P1, RPL17P45, RPL19P13, RPL21P30, RPL23AP23, RPL29P32, RPL35AP2, RPL39L, RPL39P16, RPL4P2, RPL7AP23, RPL7L1, RPL7P27, RPS16P5, RPS19P7, RPS3AP10, RPS3AP13, RPS4XP2, RPS6P7, RPS7P4, RPSAP36, RRP12, RTL6, RUNX3, RWDD2A, S1PR2, SARS1, SASH3, SAT2, SBDS, SCAI, SCAND2P, SCNM1, SCO1, SDHDP3, SDR42E1, SEC14L5, SEC14L6, SEC61A1, SEMA6B, SERPINA7, SERPING1, SESN1, SETBP1, SF3A1, SF3B4, SFRP2, SGK1, SH3BGRL, SH3BGRL3, SH3GL1, SHISA9, SHMT1, SIGLEC6, SIK2, SIRT1, SLC30A7, SLC31A2, SLC35B4, SLC38A6, SLC5A5, SLC6A17, SLC7A14, SLC7A5P2, SLC8A1, SLC9A8, SMAD9, SMCR8, SMIM11B, SNF8P1, SNX18P10, SOX3, SPI1, SPPL2A, SPRR2A, SRF, SRP9, SRRM4, ST8SIA6, STAR, STARD8, STEAP4, STK10, STKLD1, STOML1, STRIP2, STX1B, SUB1P4, SULT2A1, SUMF1, SUPT6H, SWSAP1, SYNJ2BP, SYNPO2, SYTL4, TAF11L12, TAMALIN, TANGO6, TARS1, TBX2, TCERG1, TCHHL1, TCTN3, TET3, TFE3, THAP12, TICAM1, TIMM23, TIPIN, TIRAP, TLL2, TMEM140, TMEM156, TMEM165, TMEM192, TMEM198B, TMEM209, TMEM236, TMEM252, TMEM47, TMEM70, TNFRSF9, TNFSF12, TNS4, TPH1, TPH2, TPMT, TPSB2, TPT1P12, TPT1P14, TPTEP2, TRAJ46, TRAM1L1, TRAPPC2, TRAV37, TRAV39, TRAV8-7, TRBV8-2, TRIB1, TRIM71, TRIM72, TRUB2, TSG101, TTC24, TTC39B, TTC7B, TTI2, TTYH3, TUBA5P, TXLNB, TYRL, TYRO3P, UBA52P3, UBBP2, UBE2M, UCP2, UFC1, UGT1A10, UHRF1, ULBP3, UMPS, UPF2, UPF3AP3, URAHP, USB1, USP24, USP37, USP6NL, UTP6, VIM, VN1R53P, VN1R8P, VSTM4, VWC2, WARS2P1, WASF2, WASH5P, WASH7P, WDR38, WWC1, YIPF4, YIPF6, YLPM1, YPEL5P1, YTHDC1, YWHAG, ZADH2, ZBED6, ZBTB7A, ZC3H8, ZCWPW1, ZFAND5, ZFP36L2, ZFP82, ZG16, ZIM3, ZMIZ1, ZNF141, ZNF175, ZNF37A, ZNF394, ZNF414, ZNF426, ZNF439, ZNF485, ZNF490, ZNF578, ZNF585B, ZNF593, ZNF609, ZNF654, ZNF669, ZNF699, ZNF70, ZNF710, ZNF723, ZNF813, ZNF90P1, ZNFX1, ZRANB1, ZYG11A, ZYX
AD3-Brain (ROSMAP)	*ARID3C, CD9, CDC42P2, CYP2AB1P, DLSTP1, FUZ, H2BP3, HMGN1P9, HNRNPA1P23, HNRNPA3P13, IGKV3OR22-2, OR3A1, OR4H12P, RNA5SP423, RNA5SP492, RPL26P20, RPL35AP12, SMIM42, TAAR8, TCEAL6, U2AF1, ZNF37CP, ACTRT2, ADGRE1, AGR2, AKAP17BP, ANXA8L1, ARID3B, ATP5F1AP3, ATP5PDP4, BCAS4, BRD7P5, BRPF1, BTBD6, C11orf24, C9orf57, CAPNS1, CFAP100, CIITA, CLDN10, COL9A1, COP1P1, CRB3P1, CRISP1, CROCC2, CRYGGP, CSGALNACT2P2, CT45A8, CYCSP26, CYFIP2, CYP4F10P, DEPDC1, DYNC2I1, EGR2, EXOC3, F12, FAM86B3P, FBXW4P1, FBXW8, GAS2L1, GPM6BP3, GPR6, H3P17, HMGB1P41, HMGN1P30, HMGN2P13, IFNA13, IGHJ2, IL17REL, KCNG4, KCNK1, KIFAP3, KIFBP, KRT19P1, KRTAP20-3, LCE5A, LDC1P, LHX6, LRBA, MACROH2A1, MAPK6P6, MARCHF1, MARS2, MED15P5, MED28P7, MICU1, MMP1, MRPL22P1, MRPL57P7, MTCYBP13, MTND5P10, MYO18A, NADSYN1, NDUFB4P7, NKRF, NSMCE2, NT5C3AP2, OFD1P6Y, OR10G5P, OR4A21P, OR4X7P, OR51C1P, OR5A2, P3R3URF, PHBP20, PHLDA2, PLSCR2, POTEM, PRELID3BP8, PRKAR2A, PRKRIP1, PRXL2A, PTGES3P5, PTMAP12, PTP4A1P5, RARRES2P2, RCL1, RDM1P4, RLN3, RNA5SP223, RNA5SP249, RNA5SP357, RNA5SP379, RNA5SP508, RNA5SP97, RNASE9, RNPS1P1, RPL22P23, RPL36P16, RPL4P7, RPS15AP9, RPS27AP15, RPS29P19, RPS29P32, RPS3AP5, SEC61A2, SEPTIN7P14, SLC10A6, SLC24A5, SLC5A6, SNRPGP7, SPATA21, SRMP3, STMN3, SYNCRIP, SYT12, TAAR9, TACSTD2, TAFA3, TARS2, TBX2, TCTE1, TK1, TM2D3, TMEM262, TP53TG3GP, TRBV6-2, TRMT13, TTLL11, UBE3A, UPF1, UQCRHP3, VDAC1P9, VPS13C, VWA8P1,*

| | WDR48, YY1AP1, ZAN, ZBTB2P1, ZNF114P1, ZNF212, ZNF251, ZNF513, ZNF736P4Y |