**Supplementary Tables**

**Supplementary Table 1.** Demographic data of all **18FDG-PET** data

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Samples | Sample size (n) | Mean age SD (age range) | Male sample | Mean age SD (age range) | Females sample | Mean age SD (age range) |
| healthy older: | | | | | | |
|  | n = 266 | 74.36.1  (56 - 89) | n = 137 | 755.86  (60 - 89) | n = 129 | 73.56.22  (56 - 88) |
| early MCI: | | | | | | |
|  | n = 285 | 71.27.4  (55 - 89) | n = 157 | 71.86.99  (55 - 89) | n = 128 | 70.47.83  (55 - 89) |
| late MCI: | | | | | | |
|  | n = 156 | 72.47.49  (55 - 92) | n = 83 | 73.57.16  (56 - 92) | n = 73 | 71.077.66  (55 - 87) |
| AD: | | | | | | |
|  | n = 139 | 74.58.17  (55 - 91) | n = 80 | 75.78.08  (55 - 91) | n = 59 | 738.09  (55 - 91) |

MCI = Mild cognitive impairment; AD = Alzheimer’s Disease; SD = standard deviation; n = number of subjects.

**Supplementary Table 2. ADNI samples characteristics**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | healthy older (n = 266) | | Early MCI (n = 285) | | Late MCI (n = 156) | | AD (n = 139) | |
|  |  |  |  |  |  |  |  |  |
| **n**  **(female)** | 80  (39) | 23  (10) | 105  (54) | 52  (23) | 26  (16) | 72  (35) | 5  (1) | 86  (43) |
| **Age**  **(SD)** | 72.19  (5.61) | 77.3  (4.89) | 68.98  (7.15) | 74.06  (6.67) | 70.35  (8.15) | 73.32  (6.66) | 76.9  (12.51) | 74.41  (8.31) |
| **Education**  **(SD)** | 15.93  (2.96) | 16.83  (2.39) | 16.18  (2.64) | 15.38  (2.90) | 16.38  (2.70) | 16.74  (2.53) | 16.4  (2.7) | 15.23  (2.64) |
| **MMSE**  **(SD)** | 29.04  (1.16) | 29.09  (1.38) | 28.59  (1.56) | 27.63  (1.83) | 28.27  (1.51) | 27.03  (1.77) | 24.8  (10.84) | 22.99  (2.02) |
| ***APOE ϵ4* allele (%)** | 18.75% | 47.83% | 21.9% | 46.15% | 19.23% | 58.33% | 0% | 48.84% |
| **CSF\* Aβ1-42 (pg/mL)**  **(SD)** | 1522.6  (329.04) | 691.68  (146.24) | 1436.5  247.73) | 687.67  (159.62) | 1457  (263.61) | 703.88  (163.54) | 1424.2  (162.46) | 617.25  (159.94) |
| **CSF\*** tTau **(pg/mL)**  **(SD)** | 188.31  (35.54) | 344.53  (61.03) | 189.14  (42.83) | 408.95  (135.47) | 185.70  (41.35) | 398.48  (108.39) | 204.06  (45.72) | 427.19  (143.56) |
| **CSF\*** pTau **(pg/mL)**  **(SD)** | 16.45  (3.10) | 35.25  (7.92) | 16.33  (3.8) | 42.74  (15.31) | 16.16  (3.66) | 40.02  (12.08) | 16.76  (3.89) | 42.72  (15.15) |

\*: Aβ1-42, total (T)-tau and phosphorylated (P)-tau were analyzed using the fully automated Roche Elecsys and cobas e 601 immunoassay analyzer system. For this study, we combined data from the ADNI datasets “UPENNBIOMK9\_04\_19\_17.csv, UPENNBIOMK10\_07\_29\_19.csv

, and UPENNBIOMK12\_01\_04\_21.csv”.

We used pre-established cut-offes for CSF AD biomarkers.[1, 2] The cut-off for Aβ(1–42) CSF AD biomarkers which measured by using novel Elecsys CSF immunoassays optimised for concordance of CSF biomarkers with amyloid-PET visual read were defined as 977 pg/mL (Aβ(1–42),)[2]and the cut-offs for pTau and tTau CSF AD biomarkers were optimised for identification of AD patients versus normal controls in the ADNI populations by a sensitivity analysis.[1]The cut-offs identified were 24 pg/mL (pTau) and 266 pg/mL (tTau) in ADNI.[1]

Data are given in mean values and standard deviation, SD. MCI = Mild cognitive impairment; AD = Alzheimer’s Disease; n = number of subjects.

**Supplementary Table 3. Different PET scanner technical procedures manual for FDG imaging in ADNI cohort.**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Phase of study** | **PET scanner** | **Reconstruction Parameters: FDG** | | | | | | | |
| **Grid** | **Field of view (FOV)** | **Slice Thickness** | **Zoom** | **TRIM** | **Voxel size** | **Smoothing**  **Filter** | **All corrections** |
| **ADNI 2 & ADNI GO** | GE Discovery STE and VCT - 47 slice PET/CT scanners |  | 256 mm | 3.27 mm | - | - | 2.0 mm | NONE | ‘On’ |
| GE Discovery ST - 47 slice PET/CT scanners |  | 256 mm | 3.27 mm | - | - | 2.0 mm | NONE | ‘On’ |
| GE Discovery RX - 47 slice (LYSO) PET/CT scanners |  | 256 mm | 3.27 mm | - | - | 2.0 mm | NONE | ‘On’ |
| GE Discovery LS - 35 slice (PET/CT) scanners |  | 256 mm | 4.25 mm | - | - | 2.0 mm | NONE | ‘On’ |
| GE Advance - 35 slice PET scanners |  | 256 mm | 4.25 mm | - | - | 2.0 mm | NONE | ‘On’ |
| Philips Gemini TF - 90 slice PET/CT scanners |  | 256 mm | 2.0 mm | - | - | 2.0 mm | ‘SHARP’ | ‘On’ |
| Philips Gemini and Gemini GXL - 90 slice PET/CT scanners |  | 256 mm | 2.0 mm | - | - | 2.0 mm | ‘SHARP’ | ‘On’ |
| Philips Allegro - 90 slice PET scanners |  | 256 mm | 2.0 mm | - | - | 2.0 mm | ‘SHARP’ | ‘On’ |
| Philips Allegro |  | - | - | - | - | 2.0 mm | - | - |
| Siemens ECAT Exact HR+ (BGO) 63-slice scanners |  | - | - | 2.0 | - | - | NONE | ‘On’ |
| Siemens HRRT 207-slice scanners |  | - | 1.219 mm | - | - | 1.219 mm | 2mm Gaussian | ‘On’ |
| Siemens BioGraph mCT - 81 or 109 (TrueV) slice PET/CT scanners |  | - | ~2.027 mm | 2.0 | - | ~1.018 mm | NONE | ‘On’ |
| Siemens BioGraph TruePoint - 81 or 109 (TrueV) slice PET/CT scanners (Model 1093) (TRIM:Off) |  | - | ~2.027 mm | 2.0 | Off | ~1.015 mm | NONE | ‘On’ |
| Siemens BioGraph TruePoint - 81 or 109 (TrueV) slice PET/CT scanners (Model 1093) (TRIM:ON) |  | - | ~2.027 mm | 2.0 | ON | ~2.03 mm | NONE | ‘On’ |
| Siemens BioGraph HiRes - 81 slice PET/CT scanners (Model 1080) |  | - | 2mm | 2.0 | ON | ~2.031 mm | NONE | ‘On’ |
| Siemens BioGraph (LSO) 47-slice PET/CT scanners |  | - | - | 2.0 | ON | - | NONE | ‘On’ |
| Siemens ECAT Exact (BGO) and Accel (LSO) 47-slice scanners |  | - | - | 2.0 | - | - | NONE | ‘On’ |
| **ADNI 3** | GE Discovery 600, 610, 690, and 710 - PET/CT scanners |  | 256 mm | 3.27 mm | - | - | 1.333 mm | NONE | ‘On’ |
| GE Discovery STE - PET/CT scanners |  | 256 mm | 3.27 mm | - | - | 2.0 mm | NONE | ‘On’ |
| GE Discovery ST - PET/CT scanners |  | 256 mm | 3.27 mm | - | - | 2.0 mm | NONE | ‘On’ |
| GE Discovery LS - 35 slice (PET/CT) scanners |  | 256 mm | 4.25 mm | - | - | 2.0 mm | NONE | ‘On’ |
| GE Advance - 35 slice PET scanners |  | 256 mm | 4.25 mm | - | - | 2.0 mm | NONE | ‘On’ |
| Philips Ingenuity TF - PET/CT scanners |  | 256 mm | 2.0 mm | - | - | 2.0 mm | ‘SHARP’ | ‘On’ |
| Philips Gemini TF - PET/CT scanners |  | 256 mm | 2.0 mm | - | - | 2.0 mm | ‘SHARP’ | ‘On’ |
| Philips Gemini and Gemini GXL - 90 slice PET/CT scanners |  | 256 mm | 2.0 mm | - | - | 2.0 mm | ‘SHARP’ | ‘On’ |
| Philips Allegro - 90 slice PET scanners |  | 256 mm | 2.0 mm | - | - | 2.0 mm | ‘SHARP’ | ‘On’ |
| Siemens BioGraph mCT - mCT TrueV PET/CT scanners |  | - | ~2.027 mm | 2.0 | - | ~1.018 mm | NONE | ‘On’ |
| Siemens BioGraph TruePoint – and TruePoint TrueV PET/CT  scanners (Models 1093, 1094) |  | - | ~2.027 mm | 2.0 | - | ~1.015 mm | NONE | ‘On’ |
| Siemens BioGraph HiRes - 81 slice PET/CT scanners (Model  1080) |  | - | ~2.00 mm | 2.0 | - | ~2.03 mm | NONE | ‘On’ |
| Siemens ECAT Exact HR+ (BGO) 63-slice scanners |  | - | - | 2.0 | - | - | NONE | ‘On’ |
| Siemens HRRT 207-slice PET-only scanners |  | - | 1.219 mm | - | - | 1.219 mm | 2mm Gaussian | ‘On’ |
| Siemens BioGraph (LSO; Models 1023,1024) 47-slice PET/CT  scanners |  | - | - | 2.0 | ON | - | NONE | ‘On’ |
| Siemens ECAT Exact (BGO) and Accel (LSO) 47-slice PET-only  scanners |  | - | - | 2.0 | - | - | NONE | ‘On’ |
| Siemens PET Systems (HR+, ECAT EXACT, and ACCEL using V7.2.2 software) |  | 155 mm | - | 2.5 | - | - | NONE | ‘On’ |
| Siemens PET Systems-Biograph |  | - | - | 2.5 | ON | 2.12 mm | All pass | ‘On’ |
| Siemens PET Systems - Biograph HiRez |  | - | - | 2.0 | ON | - | All pass | ‘On’ |
| GE Advance/ GE Discovery LS |  | 256 mm | - | - | - | - | NONE | ‘On’ |
| GE Discovery LST |  | 256 mm | - | - | - | - | NONE | ‘On’ |
| Philips Allegro/Gemini | - | 256 mm | - | - | - | - | - | ‘On’ |

**Supplementary Table 4. Hub genes of the transcriptomic network that up-regulated and down-regulated AD-related genes reported in Xu et al. [3].**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Number** | **Gene** | **Upstream regulator9** | **Number** | **Gene** | **Upstream regulator9** | **Number** | **Gene** | **Upstream regulator\*** |
| 1 | *ADD3* | no | 31 | *GLTP* | no | 61 | *STXBP1* | no |
| 2 | *AGT* | yes | 32 | *NDE1* | yes | 62 | *SYT1* | no |
| 3 | *ATP1A2* | yes | 33 | *FA2H* | no | 63 | *TUBA4A* | no |
| 4 | *EPS8* | no | 34 | *TJAP1* | yes | 64 | *UCHL1* | yes |
| 5 | *GJA1* | yes | 35 | *CLIC1* | no | 65 | *YWHAB* | no |
| 6 | *HDAC1* | yes | 36 | *COL1A2* | no | 66 | *YWHAZ* | no |
| 7 | *HSPB1* | yes | 37 | *IL4R* | no | 67 | *RBM10* | no |
| 8 | *MSN* | yes | 38 | *OGN* | no | 68 | *SLC25A12* | no |
| 9 | *NOTCH2* | no | 39 | *STAT3* | no | 69 | *PEX11B* | no |
| 10 | *PON2* | yes | 40 | *TIMP1* | no | 70 | *INA* | no |
| 11 | *SOX9* | no | 41 | *TNFRSF1A* | no | 71 | *SNAP91* | no |
| 12 | *SSPN* | no | 42 | *IFITM3* | no | 72 | *CAP2* | no |
| 13 | *PRDX6* | no | 43 | *IFITM2* | no | 73 | *MLLT11* | no |
| 14 | *YAP1* | yes | 44 | *AMPH* | no | 74 | *STMN2* | yes |
| 15 | *FERMT2* | no | 45 | *ATP6V1B2* | no | 75 | *GHITM* | no |
| 16 | *PBXIP1* | no | 46 | *ATP6V1C1* | no | 76 | *TAGLN3* | no |
| 17 | *SLC31A2* | no | 47 | *ATP6V1E1* | no | 77 | *RAPGEFL1* | no |
| 18 | *LPAR1* | no | 48 | *DDX1* | no | 78 | *REEP1* | yes |
| 19 | *ERBB3* | no | 49 | *ENO2* | no | 79 | *VCAN* | no |
| 20 | *HSPA2* | yes | 50 | *GABRG2* | no | 80 | *CTNNA1* | no |
| 21 | *MAL* | no | 51 | *GLRB* | no | 81 | *SMAD5* | no |
| 22 | *KLK6* | yes | 52 | *GOT1* | no | 82 | *SP1* | no |
| 23 | *SOX10* | no | 53 | *GUCY1B3* | no | 83 | *SYPL1* | no |
| 24 | *TF* | no | 54 | *PCMT1* | no | 84 | *TJP1* | no |
| 25 | *UGT8* | no | 55 | *PFN2* | no | 85 | *TYK2* | no |
| 26 | *VEZF1* | no | 56 | *SERPINI1* | no | 86 | *SNAP23* | no |
| 27 | *ST18* | no | 57 | *MAPK9* | no | 87 | *IQGAP1* | no |
| 28 | *RASSF2* | no | 58 | *PSMD1* | no | 88 | *KAT2B* | no |
| 29 | *SLC44A1* | yes | 59 | *SCG5* | no | 89 | *BBX* | no |
| 30 | *DAAM2* | no | 60 | *SH3GL2* | yes |  |  |  |

\* Upstream regulator[3]: hub genes showed consistent early expression alterations in Mouseac [4] or in other two replicating datasets (GSE29317 [5] and GSE31372). 17 Genes highlighted in green are candidate upstream regulators, as indicated by early alteration.

Reference:

1. Blennow K, Shaw LM, Stomrud E, Mattsson N, Toledo JB, Buck K, et al. Predicting clinical decline and conversion to Alzheimer's disease or dementia using novel Elecsys Abeta(1-42), pTau and tTau CSF immunoassays. Sci Rep. 2019;9(1):19024.

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3. Xu M, Zhang DF, Luo R, Wu Y, Zhou H, Kong LL, et al. A systematic integrated analysis of brain expression profiles reveals YAP1 and other prioritized hub genes as important upstream regulators in Alzheimer's disease. Alzheimers Dement. 2018;14(2):215-29.

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