

Integrated genomic approaches identify major pathways and upstream regulators in late onset Alzheimer's disease

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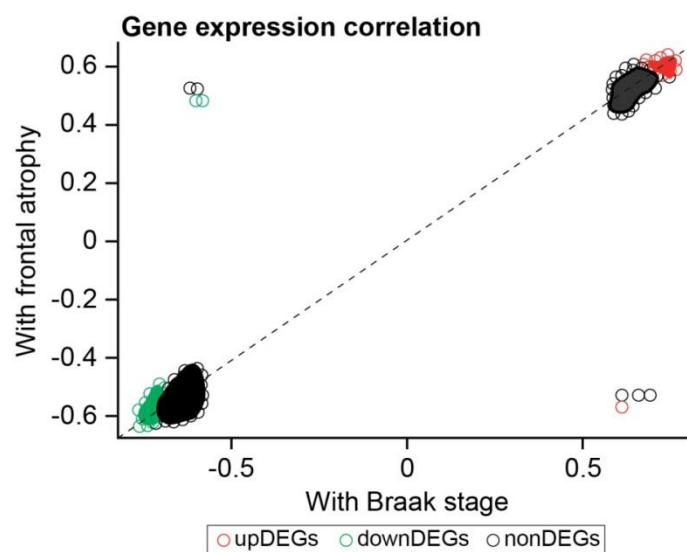
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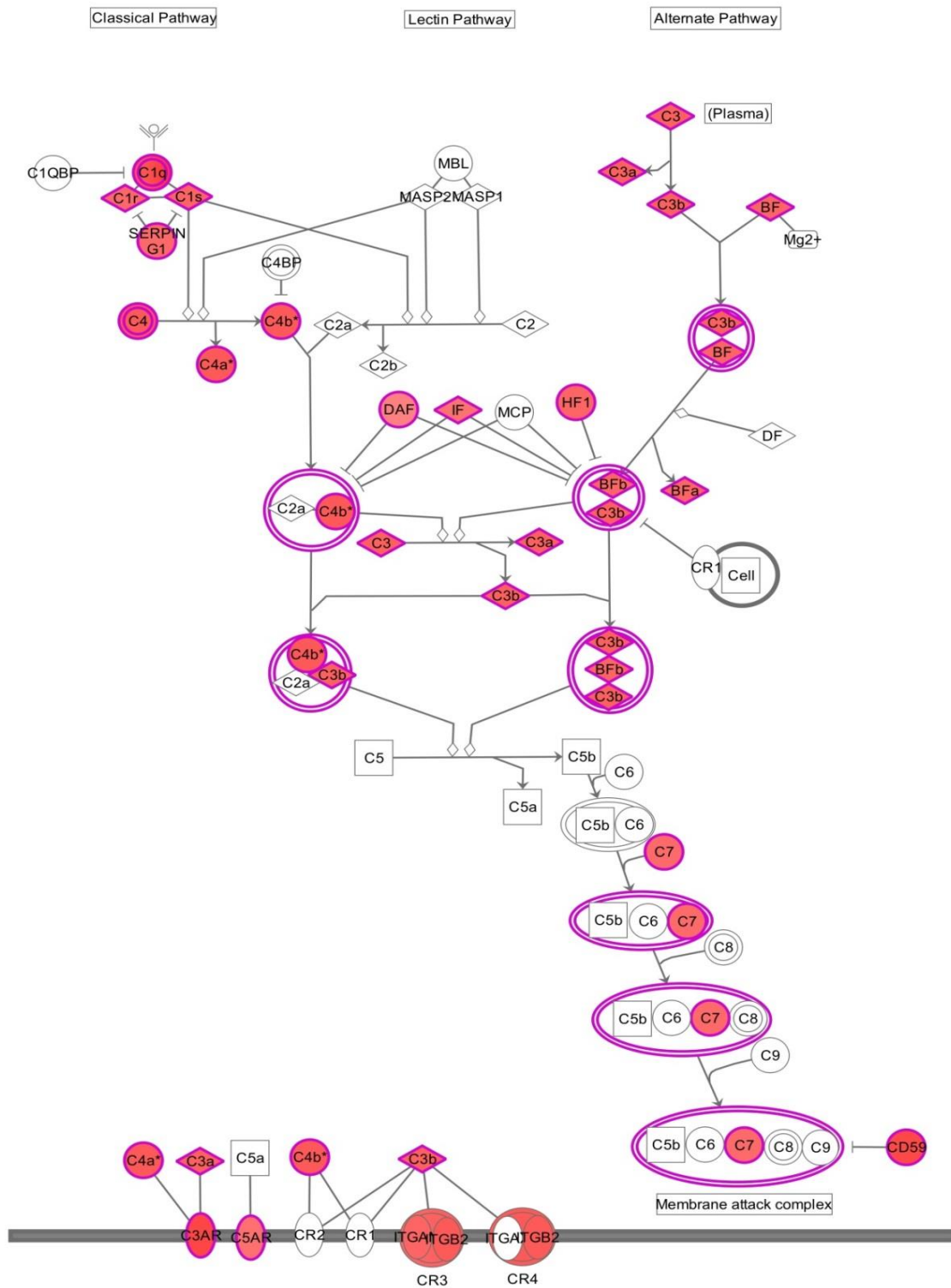
Material and methods: Detail of data collection and pre-processing.

Supplementary Figure S1. Scatter plot between two correlation coefficients: gene expression and Braak stage vs. gene expression and frontal atrophy



Supplementary Figure S1. Scatter plot between two correlation coefficients: gene expression and Braak stage vs. gene expression and frontal atrophy. Data came from Zhang B. et al's study ¹ (data set GSE4470). Genes without correlation to Braak and frontal atrophy were discarded in this figure. Up regulated DEGs are highlighted by red points and down regulated DEGs by green points. DEGs tend to have higher correlation with Braak or frontal atrophy compared to non-DEGs ($p_{\text{val}} < 2.2E-16$, t-test). Eight outliers have been removed for enrichment analysis in the main text.

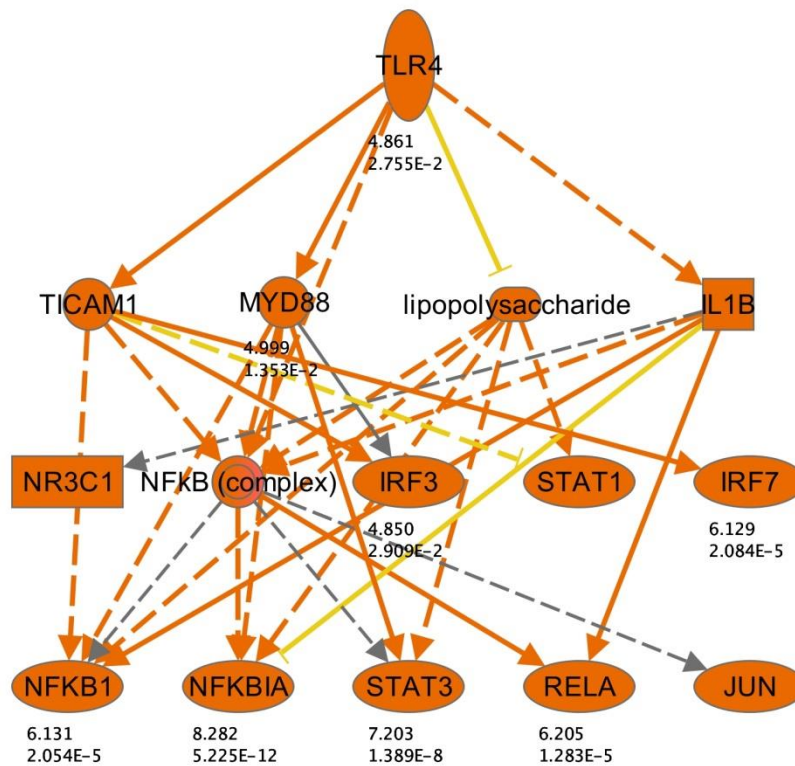
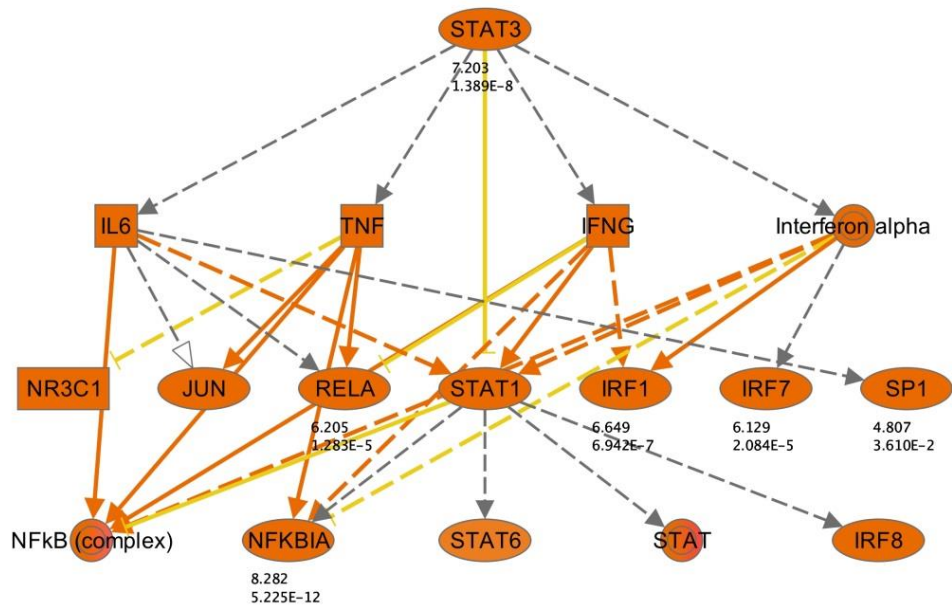
Supplementary Figure S2. Complement System pathway in late onset Alzheimer's disease

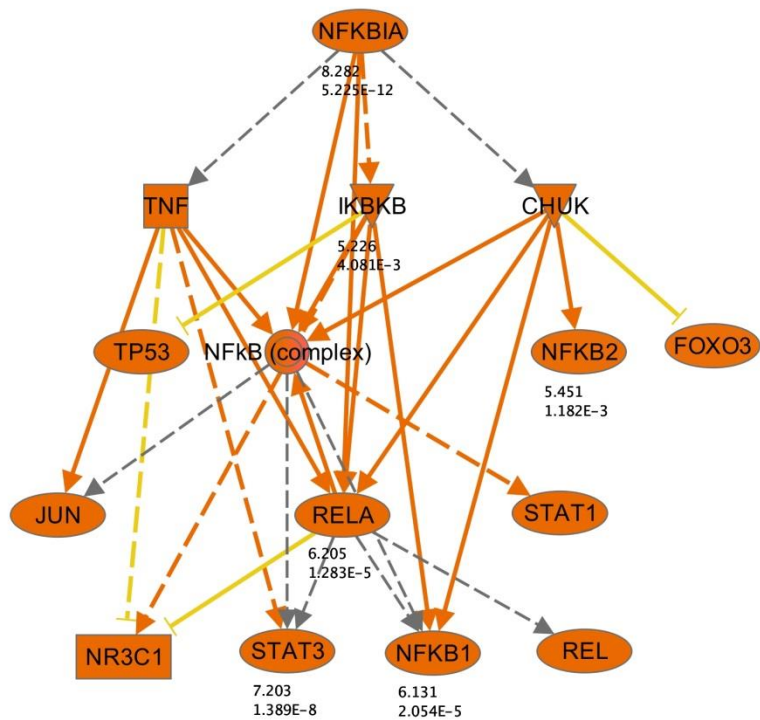


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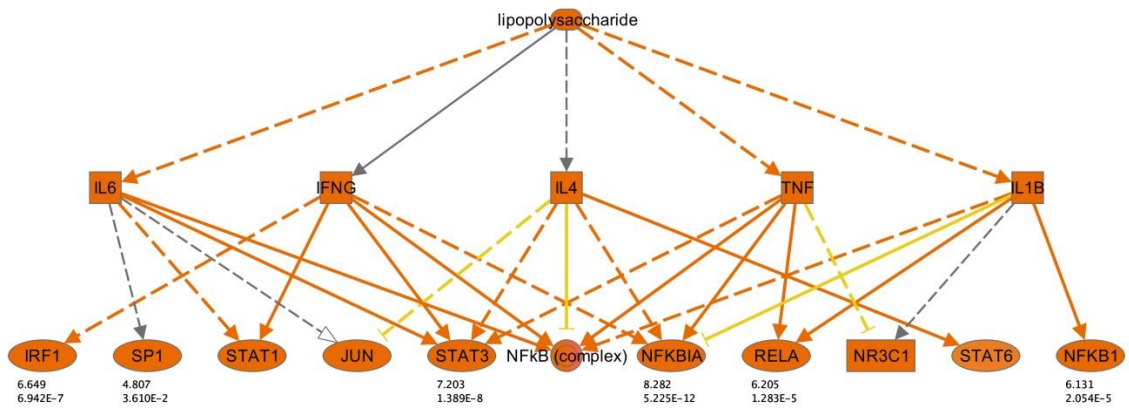
Supplementary Figure S2. Complement System pathway in late onset Alzheimer's disease. It is among the top 10 pathways identified by IP for the up regulated DEGs. However no down regulated DEGs founded. 16 (red highlighted) out of in total 33 molecules are up regulated DEGs. See Figure 3 and Supplementary Table S2 online.

Supplementary Figure S3. Mechanistic network for upstream regulators LPS, STAT3, TLR4 and NFKBIA predicted by IPA for upregulated DEGs.





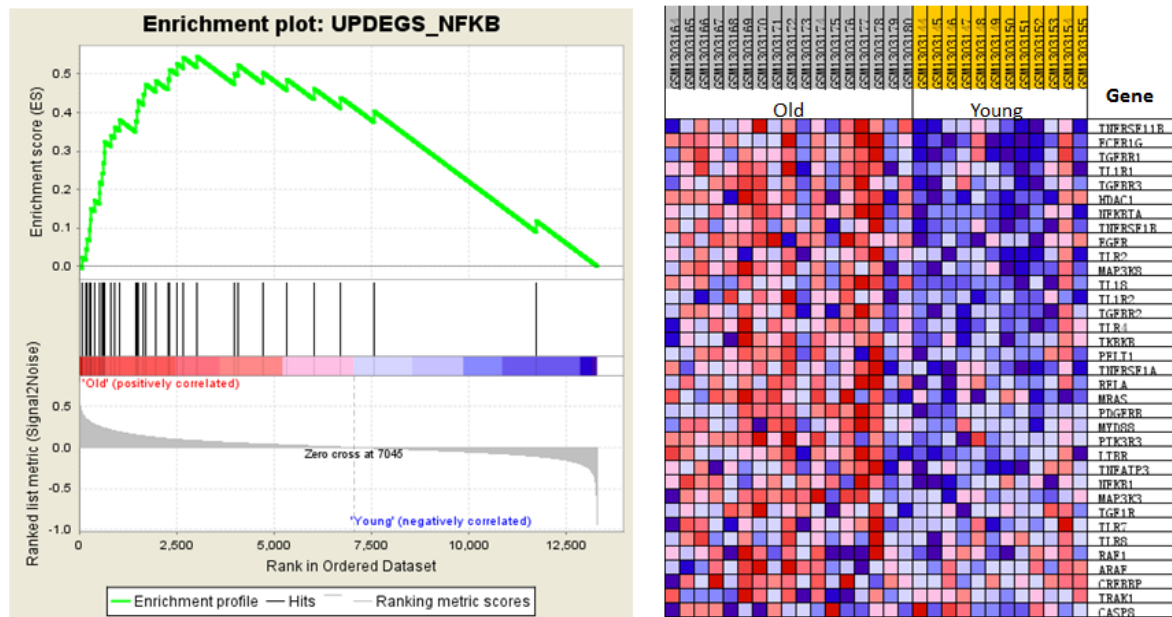
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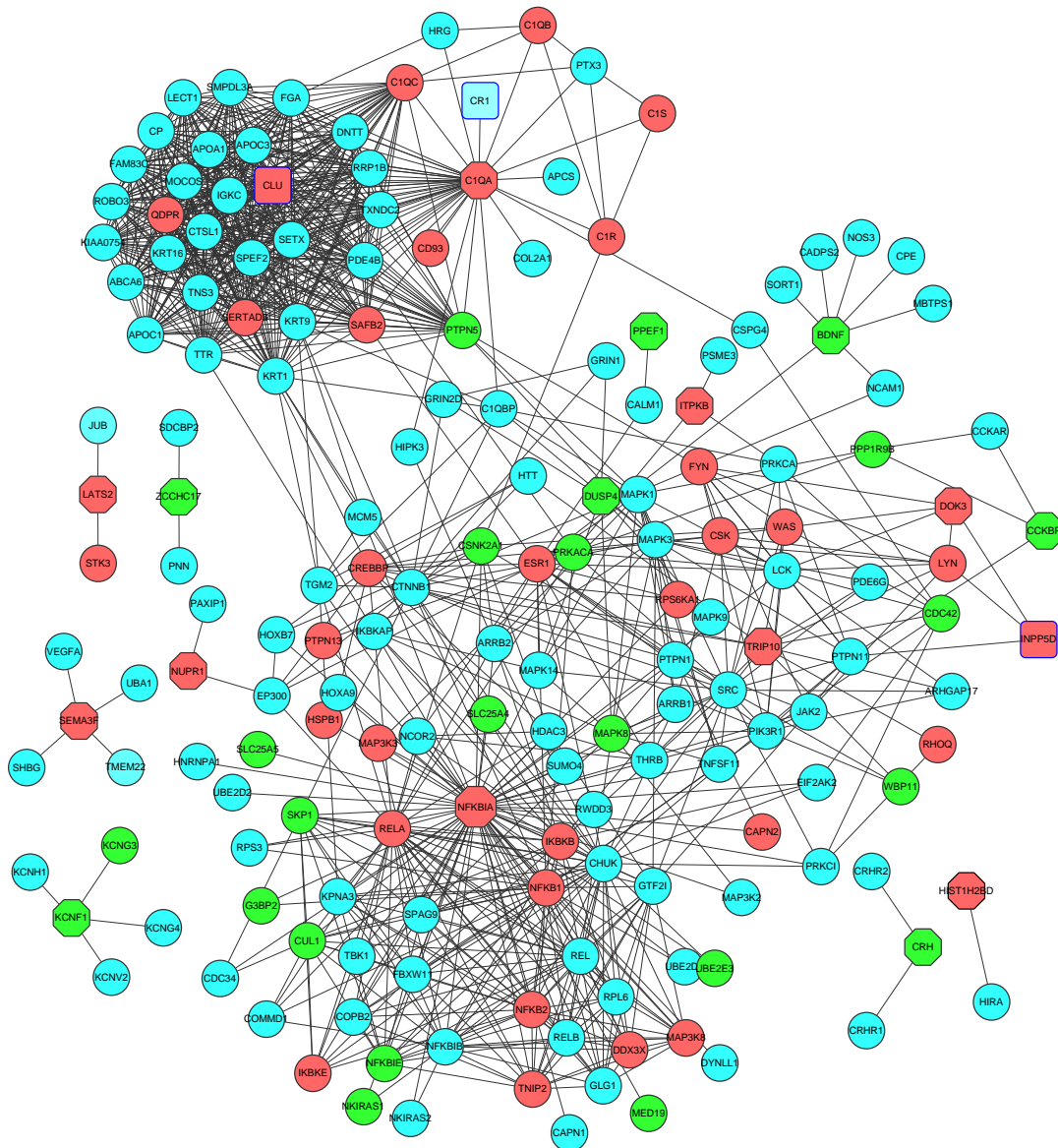
Supplementary Figure S3. Mechanistic network for upstream regulators LPS, STAT3, TLR4, and NFKBIA predicted by IPA for upregulated DEGs. DEGs are indicated by their metaZscores and Bonferroni adjusted Pvalues (see Supplementary Table S2 for data detail). The NFKB complex is a key node in these networks.

Supplementary Fig. S4. Gene set enrichment analysis (GSEA) for NFKB.



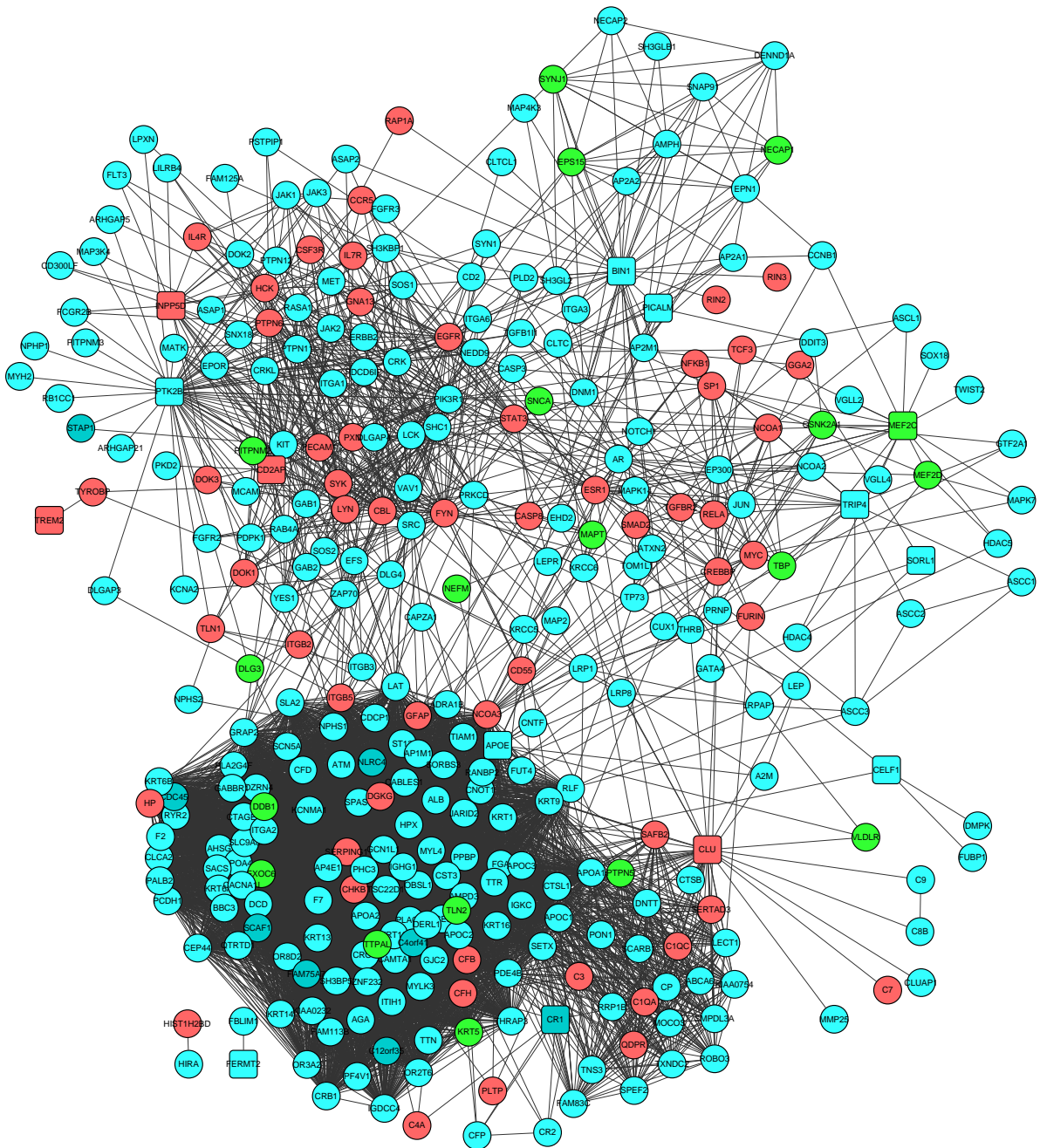
Supplementary Figure S4. Gene set enrichment analysis (GSEA) for NFKB. GSEA confirms the NFKB geneset containing up regulated LOAD DGEs is enriched in old people. Microarray data for ageing (GSE53890) were analysed using GSEA software to identify significant gene sets. The enrichment plot on the left shows the distribution of genes in the set that are correlated with the old or young phenotype. The heatmap on the right shows where the gene expression is relatively high (red) or low (blue) for each gene in the indicated sample.

Supplementary Figure S5: Protein-protein interaction network for the top 30 most significantly expressed genes in LOAD and their first neighbours.



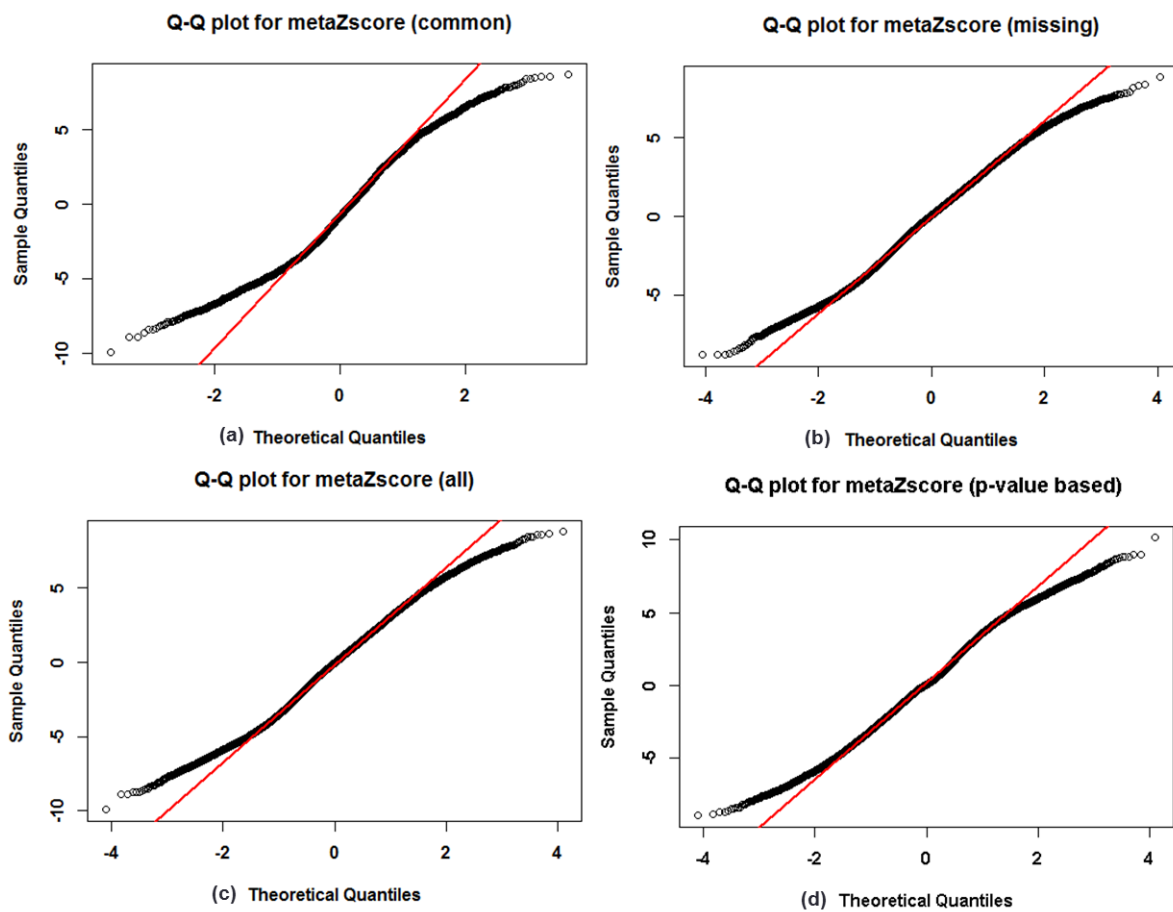
Supplementary Figure S5. Protein-protein interaction network for the top 30 most significantly expressed genes in LOAD and their first neighbours. Among the top 30 DEGs, 16 (octagons, red/green indicates up/down regulation) mapped to the human PPI and their first neighbour. This first neighbour network (FBN) contains 175 nodes and 998 edges. Three GWAS genes are included (squares): INPP5D and CLU are up-regulated DEGs, CR1 is not a DEG. CLU is linked to 32 genes including five DEGs: C1QA, C1QC, QDPR, SERTAD3 and SAFB2. Both CLU and C1QA are ageing relevant genes. NFKBIA, up-regulated, connects to 64 genes in this sub-network including 13 up-regulated DEGs and 10 down-regulated DEGs. For other hubs see Supplementary Table S10.

Supplementary Figure S6: Protein-protein interaction network for the 23 known LOAD GWAS genes and their first neighbours



Supplementary Figure S6: Protein-protein interaction network for the 23 known LOAD GWAS genes and their first neighbours. 14 out of 23 GWAS hits (square shaped) were mapped to PPI, their FBN contains 332 nodes and 7692 edges with average 23 neighbours per node higher than the ratio of connections in whole human PPI (OR=5.29, 95%CI 4.64~5.82, pvalue < 2.2e-16). 78 nodes are DEGs (59 up and 19 down, OR=1.45 with 95%CI 1.11~1.89, pvalue=6.82E-3) including 2 top 30DEGs. TYROBP is the 8th most significant DEGs in this sub-network, links to SYK, TREM2 and ZAP70. APOE is the most top hub (124 FBs), PTK2B is the second top hub with 55 FBs. See Supplementary Table S11

Supplementary Figure S7. Normal Q-Q plot for the meta-analysis



Supplementary Figure S7. Normal Q-Q plot for the meta-analysis. Q-Q plot of the metaZscore calculated for those 3838 common genes across six studies (a); and those missing in at least one study (b); all 23530 genes (c). The distributions are approximated to normal distribution with two fat tails. Clearly the normality of the overall metaZscore is improved by merging data from those incompleting genes (missed in at least one study) to common genes. metaZscore of sample-size weighted P-value combined meta-analysis has similar normality (d).

Supplementary Table S1. Number of samples and genes included in our meta-analysis.

| Platform | Study | EntrezGene | Case | Control | Sum |
|----------|----------|------------|------|---------|-----|
| GPL570 | GSE5281 | 13424 | 23 | 9 | 32 |
| GPL570 | GSE48350 | 14903 | 21 | 23 | 44 |
| GPL2700 | GSE15222 | 3995 | 30 | 37 | 67 |
| GPL4372 | GSE33000 | 21576 | 249 | 88 | 337 |
| GPL4372 | GSE44770 | 21576 | 116 | 39 | 155 |
| GPL6244 | GSE36980 | 18922 | 11 | 16 | 27 |
| Total | 6 | 23530 | 450 | 212 | 662 |

Supplementary Table S2. The full list of 3124 DEGs in an excel file.

Supplementary Table S3. Top co-expression modules with enriched DEGs. Zhang et al. used 1,647 post mortem brain tissues from LOAD patients and non-demented subjects to build the gene co-expression regulatory network, and 20 top modules were identified. Fisher test revealed that half of these modules were enriched with DEGs identified in our meta-analysis.

| Module | Rank | Function | EntrezGene* | DEGs | ratio | fisher.pvalue | OR |
|--------------|------|---|-------------|------|-------|---------------|-------|
| Yellow | 1 | immune and microglia | 952 | 444 | 0.47 | 4.93E-146 | 6.49 |
| Pink | 2 | glutathione transferase | 529 | 78 | 0.15 | 1.73E-01 | 1.13 |
| Gray 1 | 3 | cell junction | 43 | 1 | 0.02 | 9.98E-01 | 0.16 |
| Seashell | 4 | coated vesicle | 229 | 91 | 0.4 | 1.09E-23 | 4.41 |
| Red 3 | 5 | ribosome | 46 | 3 | 0.07 | 9.54E-01 | 0.46 |
| Green yellow | 6 | unfolded protein | 569 | 145 | 0.25 | 2.06E-15 | 2.29 |
| Red | 7 | nerve myelination and oligodendrocytes | 786 | 86 | 0.11 | 9.80E-01 | 0.8 |
| Gold 2 | 8 | axon growth repulsion | 67 | 12 | 0.18 | 1.72E-01 | 1.43 |
| Tan | 9 | extracellular matrix and choroid plexus cells | 597 | 137 | 0.23 | 4.81E-11 | 1.99 |
| Gold 3 | 10 | dynein complex | 65 | 6 | 0.09 | 8.78E-01 | 0.66 |
| Light yellow | 11 | mRNA cleavage | 276 | 43 | 0.16 | 1.48E-01 | 1.21 |
| Brown 2 | 12 | olfactory perception | 53 | 3 | 0.06 | 9.78E-01 | 0.39 |
| Dark cyan | 13 | steroid biosynthesis | 84 | 34 | 0.4 | 5.29E-10 | 4.48 |
| Khaki | 14 | GABA biosynthesis and astrocytes | 229 | 28 | 0.12 | 7.10E-01 | 0.91 |
| Grey 60 | 15 | Ser/Thr kinase receptor | 401 | 125 | 0.31 | 5.71E-21 | 3.04 |
| Purple | 16 | synaptic transmission and neurons | 665 | 224 | 0.34 | 8.89E-43 | 3.5 |
| Green 4 | 17 | cell cycle | 54 | 0 | 0 | 1.00E+00 | 0 |
| Honey dew | 18 | muscle contraction | 121 | 33 | 0.27 | 3.23E-05 | 2.46 |
| Red 2 | 19 | zinc homeostasis | 73 | 47 | 0.64 | 5.45E-24 | 11.97 |
| Beige | 20 | glucose homeostasis | 73 | 16 | 0.22 | 2.81E-02 | 1.84 |

*genes without EntrezGene ID were excluded.

Supplementary Table S4. The top 30 DEGs mapped to six different brain regions in AD. GSE5281 contains six brain regions: hippocampus (HIP); entorhinal cortex (EC); medial temporal gyrus (MTG); posterior cingulate (PC); primary visual cortex (PVC), and superior frontal gyrus (SFG). DEGs in each region were identified by limma and then the top meta-analysis DEGs were mapped. C1QA did not present in GSE5281.

| GSE5281 | | HIP | | | EC | | | MTG | | |
|------------|-----------|-------|----------|-----------|-------|----------|-----------|-------|----------|-----------|
| EntrezGene | Symbol | logFC | P.Value | adj.P.Val | logFC | P.Value | adj.P.Val | logFC | P.Value | adj.P.Val |
| 63974 | NEUROD6 | -0.57 | 2.51E-01 | 3.96E-01 | -0.83 | 9.12E-05 | 7.11E-04 | -1.24 | 3.60E-05 | 3.08E-04 |
| 51538 | ZCCHC17 | -0.93 | 6.62E-05 | 1.09E-03 | -0.94 | 3.00E-05 | 2.94E-04 | -1.75 | 3.99E-09 | 8.24E-07 |
| 5475 | PPEF1 | -0.05 | 7.80E-01 | 8.58E-01 | -1.16 | 5.43E-03 | 1.90E-02 | -1.07 | 4.31E-04 | 2.18E-03 |
| 63905 | MANBAL | -1.25 | 1.07E-06 | 6.23E-05 | -1.74 | 6.10E-11 | 3.69E-08 | -0.87 | 4.06E-04 | 2.08E-03 |
| 627 | BDNF | -1.28 | 1.54E-02 | 5.25E-02 | -0.38 | 3.71E-01 | 5.07E-01 | -1.31 | 1.00E-05 | 1.14E-04 |
| 1392 | CRH | -0.65 | 1.06E-01 | 2.16E-01 | -0.04 | 9.12E-01 | 9.46E-01 | -0.73 | 9.98E-05 | 6.85E-04 |
| 3707 | ITPKB | 1.23 | 2.02E-02 | 6.39E-02 | 3.45 | 4.34E-09 | 4.26E-07 | 3.07 | 4.92E-09 | 9.07E-07 |
| 388341 | FAM211A | -0.86 | 3.79E-04 | 3.65E-03 | -0.45 | 2.52E-03 | 1.02E-02 | -0.25 | 1.91E-01 | 2.90E-01 |
| 2289 | FKBP5 | -0.66 | 9.88E-03 | 3.80E-02 | 1.37 | 6.51E-03 | 2.20E-02 | 1.07 | 1.14E-02 | 3.04E-02 |
| 64231 | MS4A6A | 0.46 | 5.27E-02 | 1.29E-01 | 1.02 | 2.66E-03 | 1.07E-02 | 0.67 | 3.63E-02 | 7.75E-02 |
| 78991 | PCYOX1L | -1.22 | 4.10E-07 | 3.28E-05 | -1.31 | 5.07E-06 | 7.52E-05 | -1.98 | 3.07E-08 | 2.32E-06 |
| 1846 | DUSP4 | -1.95 | 5.22E-04 | 4.56E-03 | 0.05 | 7.04E-01 | 7.98E-01 | -0.52 | 3.23E-02 | 7.04E-02 |
| 7108 | TM7SF2 | -0.74 | 1.94E-03 | 1.15E-02 | -1.14 | 3.29E-08 | 1.77E-06 | -1.23 | 5.95E-06 | 7.73E-05 |
| 6405 | SEMA3F | 0.95 | 3.41E-03 | 1.74E-02 | 0.57 | 1.51E-01 | 2.59E-01 | 1.87 | 6.89E-07 | 1.67E-05 |
| 9322 | TRIP10 | 0.47 | 1.72E-03 | 1.06E-02 | 0.49 | 1.90E-02 | 5.18E-02 | 0.74 | 1.59E-05 | 1.64E-04 |
| 10184 | LHFPL2 | -0.47 | 6.52E-02 | 1.51E-01 | 0.74 | 5.08E-03 | 1.80E-02 | 0.12 | 6.14E-01 | 7.10E-01 |
| 9315 | NREP | -0.72 | 1.81E-03 | 1.10E-02 | 0.47 | 1.07E-01 | 2.00E-01 | -1.55 | 9.08E-10 | 4.38E-07 |
| 381 | ARF5 | -1.06 | 5.42E-06 | 1.90E-04 | -0.10 | 6.15E-01 | 7.27E-01 | -0.49 | 1.60E-02 | 4.00E-02 |
| 84620 | ST6GAL2 | -0.61 | 4.41E-02 | 1.13E-01 | -2.06 | 7.53E-10 | 1.35E-07 | -0.41 | 4.18E-02 | 8.69E-02 |
| 56261 | GPCPD1 | -0.63 | 6.90E-04 | 5.55E-03 | 0.58 | 3.53E-04 | 2.11E-03 | -0.77 | 1.07E-02 | 2.89E-02 |
| 79930 | DOK3 | 0.85 | 5.89E-04 | 4.96E-03 | -0.40 | 1.13E-01 | 2.08E-01 | 0.52 | 1.77E-02 | 4.33E-02 |
| 3754 | KCNF1 | -0.24 | 1.13E-01 | 2.26E-01 | -1.11 | 6.80E-05 | 5.61E-04 | -1.06 | 5.45E-05 | 4.25E-04 |
| 4792 | NFKBIA | 1.24 | 2.24E-03 | 1.27E-02 | 2.58 | 6.25E-08 | 2.76E-06 | 1.70 | 1.88E-07 | 6.82E-06 |
| 29906 | ST8SIA5 | -0.47 | 5.09E-02 | 1.26E-01 | -0.34 | 4.44E-02 | 1.01E-01 | -0.76 | 1.06E-03 | 4.51E-03 |
| 26471 | NUPR1 | 0.24 | 2.49E-01 | 3.95E-01 | -0.03 | 8.71E-01 | 9.19E-01 | 0.61 | 9.30E-03 | 2.58E-02 |
| 1802 | DPH2 | -0.10 | 4.91E-01 | 6.33E-01 | -1.07 | 7.68E-06 | 1.04E-04 | -0.21 | 2.34E-01 | 3.40E-01 |
| 887 | CCKBR | -0.50 | 3.22E-02 | 9.01E-02 | -1.44 | 4.34E-05 | 3.94E-04 | -1.71 | 8.61E-07 | 1.92E-05 |
| 26524 | LATS2 | 1.73 | 9.60E-04 | 7.01E-03 | 2.13 | 9.38E-06 | 1.21E-04 | 2.40 | 2.56E-07 | 8.46E-06 |
| 3017 | HIST1H2BD | 0.31 | 2.73E-01 | 4.21E-01 | 0.04 | 7.74E-01 | 8.50E-01 | 0.32 | 1.68E-01 | 2.62E-01 |
| GSE5281 | | PC | | | PVC | | | SFG | | |
| EntrezGene | Symbol | logFC | P.Value | adj.P.Val | logFC | P.Value | adj.P.Val | logFC | P.Value | adj.P.Val |
| 63974 | NEUROD6 | -0.53 | 9.86E-02 | 1.88E-01 | 0.11 | 6.10E-01 | 7.77E-01 | -1.18 | 4.37E-06 | 6.74E-04 |
| 51538 | ZCCHC17 | -0.60 | 3.32E-03 | 1.58E-02 | -0.40 | 4.79E-02 | 1.94E-01 | -0.62 | 3.64E-04 | 7.31E-03 |
| 5475 | PPEF1 | -1.45 | 1.28E-04 | 1.79E-03 | -0.14 | 2.50E-01 | 4.68E-01 | -0.78 | 3.96E-03 | 3.05E-02 |
| 63905 | MANBAL | -1.09 | 4.63E-04 | 4.20E-03 | -0.45 | 2.92E-02 | 1.56E-01 | -0.28 | 2.56E-01 | 4.42E-01 |
| 627 | BDNF | -1.03 | 1.03E-03 | 7.01E-03 | -0.59 | 4.51E-02 | 1.88E-01 | -0.84 | 3.04E-04 | 6.66E-03 |
| 1392 | CRH | -1.16 | 2.06E-02 | 5.91E-02 | -0.64 | 5.94E-02 | 2.14E-01 | -0.68 | 2.14E-02 | 8.95E-02 |
| 3707 | ITPKB | 1.13 | 9.35E-04 | 6.58E-03 | 1.40 | 3.88E-04 | 5.61E-02 | 2.36 | 2.22E-07 | 1.74E-04 |
| 388341 | FAM211A | -0.51 | 9.28E-03 | 3.32E-02 | -0.16 | 3.04E-01 | 5.20E-01 | -0.30 | 5.01E-02 | 1.55E-01 |
| 2289 | FKBP5 | -0.56 | 2.49E-02 | 6.78E-02 | 0.61 | 3.79E-02 | 1.74E-01 | 0.74 | 2.14E-02 | 8.94E-02 |
| 64231 | MS4A6A | 0.40 | 8.17E-02 | 1.64E-01 | 0.47 | 1.45E-02 | 1.20E-01 | 0.25 | 3.62E-01 | 5.52E-01 |
| 78991 | PCYOX1L | -1.24 | 9.13E-04 | 6.49E-03 | -1.15 | 1.31E-04 | 4.53E-02 | -1.20 | 1.37E-04 | 4.11E-03 |
| 1846 | DUSP4 | -0.39 | 4.69E-02 | 1.08E-01 | -0.93 | 1.89E-03 | 7.35E-02 | -0.42 | 5.20E-03 | 3.61E-02 |
| 7108 | TM7SF2 | -0.24 | 2.19E-01 | 3.40E-01 | -0.02 | 8.95E-01 | 9.49E-01 | -0.66 | 5.64E-04 | 9.38E-03 |
| 6405 | SEMA3F | 1.72 | 1.28E-07 | 3.79E-05 | 0.97 | 6.21E-03 | 9.57E-02 | 0.67 | 3.63E-02 | 1.26E-01 |
| 9322 | TRIP10 | 0.54 | 1.11E-02 | 3.77E-02 | 0.49 | 9.74E-03 | 1.06E-01 | 0.45 | 4.60E-03 | 3.34E-02 |
| 10184 | LHFPL2 | 0.16 | 3.47E-01 | 4.78E-01 | 0.45 | 5.66E-02 | 2.09E-01 | 0.55 | 1.28E-02 | 6.40E-02 |
| 9315 | NREP | -0.68 | 5.61E-04 | 4.73E-03 | -0.66 | 4.21E-02 | 1.82E-01 | -0.82 | 5.72E-04 | 9.46E-03 |
| 381 | ARF5 | -0.20 | 3.72E-01 | 5.02E-01 | -0.01 | 9.78E-01 | 9.89E-01 | -0.96 | 1.09E-06 | 3.63E-04 |
| 84620 | ST6GAL2 | -1.20 | 7.16E-04 | 5.54E-03 | -1.20 | 2.25E-03 | 7.67E-02 | -0.45 | 4.07E-02 | 1.36E-01 |
| 56261 | GPCPD1 | -0.61 | 1.91E-02 | 5.60E-02 | -0.85 | 4.50E-03 | 8.94E-02 | -0.88 | 5.55E-04 | 9.29E-03 |
| 79930 | DOK3 | 0.87 | 2.98E-04 | 3.10E-03 | 0.99 | 9.67E-05 | 4.49E-02 | 0.40 | 4.03E-02 | 1.35E-01 |
| 3754 | KCNF1 | -0.74 | 4.51E-03 | 1.97E-02 | -0.19 | 2.21E-01 | 4.34E-01 | -0.69 | 1.25E-04 | 3.89E-03 |
| 4792 | NFKBIA | 0.92 | 1.42E-02 | 4.52E-02 | 0.72 | 1.22E-02 | 1.13E-01 | 1.25 | 1.06E-04 | 3.57E-03 |
| 29906 | ST8SIA5 | -0.93 | 2.68E-04 | 2.91E-03 | -0.37 | 2.36E-02 | 1.43E-01 | -0.67 | 1.80E-03 | 1.88E-02 |
| 26471 | NUPR1 | 0.22 | 2.83E-01 | 4.12E-01 | 0.44 | 3.84E-02 | 1.75E-01 | 1.13 | 3.58E-06 | 6.22E-04 |
| 1802 | DPH2 | 0.19 | 1.41E-01 | 2.45E-01 | 0.19 | 1.90E-01 | 3.99E-01 | -0.18 | 2.34E-01 | 4.18E-01 |

| | | | | | | | | | | |
|-------|-----------|-------|----------|----------|-------|----------|----------|-------|----------|----------|
| 887 | CCKBR | -0.95 | 2.14E-03 | 1.17E-02 | -0.72 | 1.56E-03 | 6.96E-02 | -0.72 | 8.22E-03 | 4.81E-02 |
| 26524 | LATS2 | 1.23 | 2.55E-03 | 1.32E-02 | 1.02 | 6.36E-03 | 9.60E-02 | 1.84 | 5.05E-06 | 7.18E-04 |
| 3017 | HIST1H2BD | 0.47 | 7.21E-02 | 1.49E-01 | 0.34 | 1.49E-01 | 3.46E-01 | 0.41 | 1.11E-01 | 2.59E-01 |

Supplementary Table S5. GWAS genes in our meta-analysis. The 23 known GWAS genes in AD, seven of which were identified as DEGs

| EntrezGene | Symbol | metaZscore | metaPval | avgFC | Effect [#] | BonfPval | Braak* | atrophy* |
|------------|----------|------------|----------|-------|---------------------|----------|--------|----------|
| 64231 | MS4A6A | 8.57 | 0 | 1.43 | +++++ | 0 | 0.62 | 0.51 |
| 23607 | CD2AP | 6.73 | 1.73E-11 | 1.15 | ++?+++ | 4.08E-07 | 0.68 | 0.57 |
| 3635 | INPP5D | 6.64 | 3.20E-11 | 1.25 | ?+?+++ | 7.52E-07 | 0.66 | 0.56 |
| 4208 | MEF2C | -6.56 | 5.32E-11 | 0.73 | ----- | 1.25E-06 | -0.65 | -0.51 |
| 1191 | CLU | 6.23 | 4.75E-10 | 1.31 | ++?+- | 1.12E-05 | 0.62 | 0.46 |
| 54209 | TREM2 | 6.02 | 1.76E-09 | 1.26 | ?++++ | 4.13E-05 | | |
| 10347 | ABCA7 | 5.32 | 1.05E-07 | 1.13 | ++?+++ | 2.47E-03 | | |
| 9325 | TRIP4 | 4.27 | 1.97E-05 | 1.08 | ++?+- | 4.64E-01 | 0.64 | 0.57 |
| 23646 | PLD3 | -3.77 | 1.60E-04 | 0.84 | --?-- | 1 | -0.64 | -0.57 |
| 10979 | FERMT2 | 3.35 | 7.98E-04 | 1.21 | +---- | 1 | 0.6 | 0.49 |
| 51314 | TXNDC3 | 3.2 | 1.38E-03 | 1.10 | ???+++ | 1 | | |
| 6653 | SORL1 | -2.97 | 2.93E-03 | 0.89 | ---+ | 1 | | |
| 1378 | CR1 | 2.63 | 8.52E-03 | 1.03 | -+?+++ | 1 | | |
| 10658 | CELF1 | 1.86 | 6.23E-02 | 0.95 | --?+++ | 1 | | 0.48 |
| 123041 | SLC24A4 | 1.77 | 7.68E-02 | 1.11 | ++?+++ | 1 | | |
| 2041 | EPHA1 | 1.35 | 1.76E-01 | 1.01 | ???+- | 1 | | |
| 55063 | ZCWPW1 | 1.31 | 1.91E-01 | 1.01 | -+?+- | 1 | | |
| 8301 | PICALM | -1.22 | 2.23E-01 | 0.95 | +?--+ | 1 | | |
| 348 | APOE | 1.13 | 2.57E-01 | 1.12 | +?-++ | 1 | | |
| 57091 | CASS4 | -0.38 | 7.01E-01 | 1.02 | ?+?-- | 1 | | |
| 2185 | PTK2B | 0.38 | 7.06E-01 | 0.99 | --?+++ | 1 | | -0.41 |
| 274 | BIN1 | -0.31 | 7.55E-01 | 0.96 | --?++ | 1 | | |
| 3127 | HLA_DRB5 | 0.32 | 4.29E-01 | 1.43 | ???+- | 1 | | |

*data from Zhang et.al¹; # "+/-/?" indicates up/down and missing

Supplementary Table S6. IPA canonical pathway analysis for LOAD including significant pathways identified by upregulated and downregulated DEGs.

| Supplementary Table S4. | | | | | |
|--|------|------------------|-------|---------|----------|
| Ingenuity Canonical Pathways | DEGs | Genes In Pathway | Ratio | z.score | adjPval |
| Pathways from up-regulated DEGs | | | | | |
| Production of Nitric Oxide and Reactive Oxygen Species in Macrophages | 44 | 180 | 0.244 | 4.938 | 1.26E-12 |
| NF-κB Signalling | 41 | 173 | 0.237 | 5.154 | 1.26E-11 |
| Role of Macrophages, Fibroblasts and Endothelial Cells in Rheumatoid Arthritis | 56 | 298 | 0.188 | | 1.26E-11 |
| LXR/RXR Activation | 33 | 121 | 0.273 | -3.182 | 3.16E-11 |
| IL-8 Signalling | 40 | 183 | 0.219 | 6 | 2.09E-10 |

| | | | | | |
|--|----|-----|-------|--------|----------|
| B Cell Receptor Signalling | 39 | 176 | 0.222 | | 2.09E-10 |
| IL-10 Signalling | 23 | 69 | 0.333 | | 7.76E-10 |
| IL-6 Signalling | 30 | 116 | 0.259 | 5.385 | 8.32E-10 |
| Complement System | 16 | 33 | 0.485 | 0.832 | 1.02E-09 |
| Acute Phase Response Signalling | 36 | 169 | 0.213 | 4.747 | 2.82E-09 |
| Dendritic Cell Maturation | 37 | 179 | 0.207 | | 3.55E-09 |
| Hepatic Fibrosis / Hepatic Stellate Cell Activation | 38 | 197 | 0.193 | | 1.51E-08 |
| Role of Pattern Recognition Receptors in Recognition of Bacteria and Viruses | 29 | 127 | 0.228 | 4.69 | 2.82E-08 |
| Molecular Mechanisms of Cancer | 55 | 364 | 0.151 | | 3.47E-08 |
| PPAR Signalling | 24 | 94 | 0.255 | -3.266 | 6.31E-08 |
| Toll-like Receptor Signalling | 21 | 74 | 0.284 | 3.357 | 6.92E-08 |
| Tec Kinase Signalling | 32 | 158 | 0.203 | 5.196 | 6.92E-08 |
| Type I Diabetes Mellitus Signalling | 26 | 110 | 0.236 | 4.243 | 6.92E-08 |
| TREM1 Signalling | 21 | 75 | 0.28 | 4.583 | 8.32E-08 |
| PI3K Signalling in B Lymphocytes | 28 | 128 | 0.219 | 4.707 | 1.00E-07 |
| Death Receptor Signalling | 23 | 92 | 0.25 | 2.711 | 1.51E-07 |
| Role of Osteoblasts, Osteoclasts and Chondrocytes in Rheumatoid Arthritis | 38 | 218 | 0.174 | | 1.82E-07 |
| p38 MAPK Signalling | 26 | 117 | 0.222 | 4.082 | 2.14E-07 |
| Role of NFAT in Regulation of the Immune Response | 32 | 171 | 0.187 | 4.583 | 3.72E-07 |
| Leukocyte Extravasation Signalling | 35 | 198 | 0.177 | 2.858 | 3.72E-07 |
| iNOS Signalling | 15 | 44 | 0.341 | 3.873 | 5.37E-07 |
| Atherosclerosis Signalling | 26 | 123 | 0.211 | | 5.37E-07 |
| Acute Myeloid Leukemia Signalling | 20 | 77 | 0.26 | 3.3 | 5.37E-07 |
| T Helper Cell Differentiation | 19 | 71 | 0.268 | | 6.76E-07 |
| CD28 Signalling in T Helper Cells | 25 | 118 | 0.212 | 3.3 | 8.71E-07 |
| Hepatic Cholestasis | 30 | 162 | 0.185 | | 1.05E-06 |
| Crosstalk between Dendritic Cells and Natural Killer Cells | 21 | 89 | 0.236 | | 1.32E-06 |
| Signalling by Rho Family GTPases | 37 | 234 | 0.158 | 5.568 | 2.29E-06 |
| Fcy Receptor-mediated Phagocytosis in Macrophages and Monocytes | 21 | 93 | 0.226 | 4.146 | 2.63E-06 |
| Chronic Myeloid Leukemia Signalling | 21 | 93 | 0.226 | | 2.63E-06 |
| PPAR α /RXR α Activation | 31 | 179 | 0.173 | -4.025 | 2.63E-06 |
| IL-12 Signalling and Production in Macrophages | 26 | 135 | 0.193 | | 2.75E-06 |
| PKC θ Signalling in T Lymphocytes | 24 | 118 | 0.203 | 4.899 | 2.75E-06 |
| PTEN Signalling | 24 | 118 | 0.203 | -3.411 | 2.75E-06 |
| HIPPO Signalling | 20 | 86 | 0.233 | 0 | 2.75E-06 |
| Regulation of IL-2 Expression in Activated and Anergic T Lymphocytes | 19 | 79 | 0.241 | | 3.02E-06 |
| HMGB1 Signalling | 24 | 120 | 0.2 | 4.796 | 3.55E-06 |
| Apoptosis Signalling | 20 | 89 | 0.225 | -0.447 | 4.57E-06 |
| TWEAK Signalling | 12 | 34 | 0.353 | 2.309 | 5.13E-06 |
| Granulocyte Adhesion and Diapedesis | 30 | 178 | 0.169 | | 5.37E-06 |
| IL-4 Signalling | 18 | 76 | 0.237 | | 6.76E-06 |
| fMLP Signalling in Neutrophils | 22 | 108 | 0.204 | 4.025 | 6.76E-06 |
| IL-17A Signalling in Fibroblasts | 12 | 35 | 0.343 | | 6.76E-06 |
| Phospholipase C Signalling | 36 | 238 | 0.151 | 5.385 | 7.41E-06 |
| G α q Signalling | 26 | 147 | 0.177 | 4.379 | 1.17E-05 |
| Altered T Cell and B Cell Signalling in Rheumatoid Arthritis | 19 | 88 | 0.216 | | 1.41E-05 |
| RANK Signalling in Osteoclasts | 19 | 88 | 0.216 | | 1.41E-05 |
| Colorectal Cancer Metastasis Signalling | 35 | 236 | 0.148 | 5.292 | 1.41E-05 |
| ERK/MAPK Signalling | 30 | 188 | 0.16 | 3.651 | 1.45E-05 |
| HGF Signalling | 21 | 105 | 0.2 | 3.771 | 1.45E-05 |
| LPS-stimulated MAPK Signalling | 17 | 73 | 0.233 | 3.5 | 1.51E-05 |
| Glucocorticoid Receptor Signalling | 37 | 261 | 0.142 | | 2.00E-05 |
| Estrogen-Dependent Breast Cancer Signalling | 15 | 62 | 0.242 | 3.606 | 3.55E-05 |
| Germ Cell-Sertoli Cell Junction Signalling | 26 | 160 | 0.163 | | 5.13E-05 |
| PI3K/AKT Signalling | 22 | 123 | 0.179 | 1.342 | 5.25E-05 |
| Glioma Invasiveness Signalling | 14 | 57 | 0.246 | 2.673 | 5.75E-05 |
| Pancreatic Adenocarcinoma Signalling | 20 | 106 | 0.189 | 3.207 | 5.75E-05 |
| NF- κ B Activation by Viruses | 16 | 73 | 0.219 | 3.873 | 6.17E-05 |
| STAT3 Pathway | 16 | 73 | 0.219 | | 6.17E-05 |
| NGF Signalling | 20 | 107 | 0.187 | 4.472 | 6.31E-05 |
| Antigen Presentation Pathway | 11 | 37 | 0.297 | | 6.92E-05 |
| iCOS-iCOSL Signalling in T Helper Cells | 20 | 108 | 0.185 | 2.496 | 7.08E-05 |
| IL-1 Signalling | 18 | 91 | 0.198 | 3.742 | 7.41E-05 |
| Erythropoietin Signalling | 15 | 67 | 0.224 | | 8.13E-05 |

| | | | | | |
|---|----|-----|-------|--------|----------|
| RAR Activation | 27 | 176 | 0.153 | | 8.51E-05 |
| Role of RIG1-like Receptors in Antiviral Innate Immunity | 12 | 45 | 0.267 | 3.162 | 8.91E-05 |
| Induction of Apoptosis by HIV1 | 14 | 60 | 0.233 | 2.673 | 9.12E-05 |
| Macropinocytosis Signalling | 15 | 68 | 0.221 | 3 | 9.33E-05 |
| Axonal Guidance Signalling | 50 | 435 | 0.115 | | 1.23E-04 |
| Role of IL-17A in Arthritis | 13 | 54 | 0.241 | | 1.23E-04 |
| Rac Signalling | 19 | 104 | 0.183 | 4.243 | 1.26E-04 |
| Thrombin Signalling | 28 | 190 | 0.147 | 5 | 1.29E-04 |
| Role of PKR in Interferon Induction and Antiviral Response | 11 | 40 | 0.275 | | 1.35E-04 |
| Cardiac Hypertrophy Signalling | 31 | 223 | 0.139 | 4.811 | 1.35E-04 |
| RhoGDI Signalling | 26 | 173 | 0.15 | -3.71 | 1.55E-04 |
| T Cell Receptor Signalling | 18 | 97 | 0.186 | | 1.55E-04 |
| Regulation of the Epithelial-Mesenchymal Transition Pathway | 27 | 184 | 0.147 | | 1.66E-04 |
| IL-17 Signalling | 15 | 72 | 0.208 | | 1.66E-04 |
| JAK/Stat Signalling | 15 | 72 | 0.208 | 1.807 | 1.66E-04 |
| TNFR1 Signalling | 12 | 49 | 0.245 | 2.714 | 1.91E-04 |
| Glioblastoma Multiforme Signalling | 23 | 146 | 0.158 | 3.545 | 1.95E-04 |
| Sphingosine-1-phosphate Signalling | 19 | 109 | 0.174 | 3.742 | 2.19E-04 |
| TNFR2 Signalling | 9 | 29 | 0.31 | 2.121 | 2.29E-04 |
| IL-15 Signalling | 14 | 66 | 0.212 | | 2.34E-04 |
| Role of Tissue Factor in Cancer | 19 | 110 | 0.173 | | 2.40E-04 |
| Interferon Signalling | 10 | 36 | 0.278 | 1.414 | 2.45E-04 |
| Aryl Hydrocarbon Receptor Signalling | 22 | 140 | 0.157 | 3.153 | 2.75E-04 |
| Role of IL-17F in Allergic Inflammatory Airway Diseases | 11 | 44 | 0.25 | | 2.95E-04 |
| Integrin Signalling | 28 | 201 | 0.139 | 4.811 | 2.95E-04 |
| CD27 Signalling in Lymphocytes | 12 | 52 | 0.231 | | 3.16E-04 |
| Role of JAK1, JAK2 and TYK2 in Interferon Signalling | 8 | 24 | 0.333 | | 3.16E-04 |
| Mouse Embryonic Stem Cell Pluripotency | 17 | 95 | 0.179 | 3.638 | 3.39E-04 |
| Protein Kinase A Signalling | 44 | 383 | 0.115 | | 3.39E-04 |
| April Mediated Signalling | 10 | 38 | 0.263 | 2.53 | 3.72E-04 |
| Ephrin Receptor Signalling | 25 | 174 | 0.144 | | 3.72E-04 |
| Human Embryonic Stem Cell Pluripotency | 21 | 134 | 0.157 | | 3.80E-04 |
| Lymphotoxin β Receptor Signalling | 12 | 54 | 0.222 | 2.53 | 4.37E-04 |
| PEDF Signalling | 14 | 71 | 0.197 | 3.051 | 4.68E-04 |
| 14-3-3-mediated Signalling | 19 | 117 | 0.162 | | 4.90E-04 |
| Caveolar-mediated Endocytosis Signalling | 14 | 72 | 0.194 | | 5.37E-04 |
| Antiproliferative Role of TOB in T Cell Signalling | 8 | 26 | 0.308 | | 5.50E-04 |
| B Cell Activating Factor Signalling | 10 | 40 | 0.25 | 3 | 5.50E-04 |
| IL-17A Signalling in Airway Cells | 13 | 64 | 0.203 | | 5.75E-04 |
| Prolactin Signalling | 14 | 73 | 0.192 | 3.464 | 6.03E-04 |
| Prostate Cancer Signalling | 15 | 82 | 0.183 | | 6.17E-04 |
| Factors Promoting Cardiogenesis in Vertebrates | 16 | 92 | 0.174 | | 6.92E-04 |
| Oncostatin M Signalling | 9 | 34 | 0.265 | 3 | 7.08E-04 |
| Angiopoietin Signalling | 13 | 66 | 0.197 | 0.905 | 7.59E-04 |
| ILK Signalling | 25 | 187 | 0.134 | 4.379 | 9.55E-04 |
| TGF- β Signalling | 15 | 87 | 0.172 | 0.832 | 1.15E-03 |
| GM-CSF Signalling | 12 | 62 | 0.194 | 3.464 | 1.51E-03 |
| IL-3 Signalling | 13 | 71 | 0.183 | 1.941 | 1.55E-03 |
| Telomerase Signalling | 16 | 99 | 0.162 | 2.309 | 1.55E-03 |
| P2Y Purigenic Receptor Signalling Pathway | 18 | 119 | 0.151 | 3.5 | 1.58E-03 |
| Natural Killer Cell Signalling | 17 | 110 | 0.155 | | 1.74E-03 |
| Actin Cytoskeleton Signalling | 27 | 218 | 0.124 | | 1.82E-03 |
| LPS/IL-1 Mediated Inhibition of RXR Function | 27 | 218 | 0.124 | 1.147 | 1.95E-03 |
| Actin Nucleation by ARP-WASP Complex | 11 | 56 | 0.196 | 3.317 | 2.19E-03 |
| Wnt/Ca+ pathway | 11 | 56 | 0.196 | 3.317 | 2.19E-03 |
| CD40 Signalling | 12 | 65 | 0.185 | 2.714 | 2.24E-03 |
| Nur77 Signalling in T Lymphocytes | 11 | 57 | 0.193 | | 2.45E-03 |
| ErbB2-ErbB3 Signalling | 11 | 57 | 0.193 | | 2.45E-03 |
| MIF-mediated Glucocorticoid Regulation | 8 | 33 | 0.242 | 2.828 | 2.69E-03 |
| Xenobiotic Metabolism Signalling | 31 | 270 | 0.115 | | 2.75E-03 |
| HER-2 Signalling in Breast Cancer | 13 | 76 | 0.171 | | 2.75E-03 |
| Role of IL-17A in Psoriasis | 5 | 13 | 0.385 | | 2.75E-03 |
| PDGF Signalling | 13 | 77 | 0.169 | 3.606 | 3.09E-03 |
| FAK Signalling | 14 | 87 | 0.161 | | 3.16E-03 |
| Type II Diabetes Mellitus Signalling | 17 | 117 | 0.145 | | 3.16E-03 |
| IL-9 Signalling | 8 | 34 | 0.235 | 2.121 | 3.16E-03 |
| B Cell Development | 8 | 34 | 0.235 | | 3.16E-03 |
| VDR/RXR Activation | 13 | 78 | 0.167 | -1.897 | 3.39E-03 |

| | | | | | |
|--|------|------------------|-------|---------|----------|
| Neuregulin Signalling | 14 | 88 | 0.159 | 3.464 | 3.47E-03 |
| IL-15 Production | 7 | 27 | 0.259 | | 3.47E-03 |
| p53 Signalling | 15 | 98 | 0.153 | 0 | 3.47E-03 |
| p70S6K Signalling | 17 | 119 | 0.143 | 3.153 | 3.72E-03 |
| CXCR4 Signalling | 20 | 152 | 0.132 | 4.243 | 3.98E-03 |
| Ceramide Signalling | 13 | 80 | 0.163 | 2.496 | 4.07E-03 |
| Small Cell Lung Cancer Signalling | 12 | 71 | 0.169 | | 4.37E-03 |
| Cholecystokinin/Gastrin-mediated Signalling | 15 | 101 | 0.149 | 3.873 | 4.57E-03 |
| Communication between Innate and Adaptive Immune Cells | 14 | 91 | 0.154 | | 4.57E-03 |
| Paxillin Signalling | 15 | 102 | 0.147 | 2.121 | 5.01E-03 |
| Agranulocyte Adhesion and Diapedesis | 23 | 189 | 0.122 | | 5.01E-03 |
| Sertoli Cell-Sertoli Cell Junction Signalling | 22 | 177 | 0.124 | | 5.13E-03 |
| Epithelial Adherens Junction Signalling | 19 | 146 | 0.13 | | 5.62E-03 |
| Calcium-induced T Lymphocyte Apoptosis | 11 | 64 | 0.172 | 2.828 | 5.62E-03 |
| MSP-RON Signalling Pathway | 9 | 46 | 0.196 | | 5.62E-03 |
| Breast Cancer Regulation by Stathmin1 | 23 | 192 | 0.12 | | 5.62E-03 |
| FLT3 Signalling in Hematopoietic Progenitor Cells | 12 | 74 | 0.162 | | 5.89E-03 |
| TR/RXR Activation | 13 | 85 | 0.153 | | 6.61E-03 |
| Extrinsic Prothrombin Activation Pathway | 5 | 16 | 0.312 | 0 | 6.61E-03 |
| 4-1BB Signalling in T Lymphocytes | 7 | 31 | 0.226 | 2.449 | 7.24E-03 |
| Graft-versus-Host Disease Signalling | 9 | 48 | 0.188 | | 7.41E-03 |
| Antioxidant Action of Vitamin C | 14 | 97 | 0.144 | -3.464 | 7.76E-03 |
| GNRH Signalling | 17 | 129 | 0.132 | 2.668 | 7.76E-03 |
| MIF Regulation of Innate Immunity | 8 | 41 | 0.195 | 2.828 | 9.55E-03 |
| Virus Entry via Endocytic Pathways | 13 | 89 | 0.146 | | 9.55E-03 |
| OX40 Signalling Pathway | 13 | 89 | 0.146 | 1.342 | 9.55E-03 |
| Growth Hormone Signalling | 11 | 69 | 0.159 | 2.53 | 9.55E-03 |
| Reelin Signalling in Neurons | 12 | 79 | 0.152 | | 9.55E-03 |
| Pathways from down-regulated DEGs | | | | | |
| Ingenuity Canonical Pathways | DEGs | Genes In Pathway | Ratio | z.score | adjPval |
| Mitochondrial Dysfunction | 37 | 172 | 0.215 | | 2.24E-06 |
| Oxidative Phosphorylation | 24 | 110 | 0.218 | | 4.27E-04 |
| Aspartate Degradation II | 5 | 7 | 0.714 | | 7.24E-03 |

Supplementary Table S7. IPA canonical pathway analysis including upregulated and downregulated DEGs in ageing.

| Supplementary table S5. IPA for ageing | | | | | |
|--|------|------------------|-------|---------|----------|
| Ingenuity Canonical Pathways | DEGs | Genes In Pathway | Ratio | z.score | adjPval |
| Pathways for up regulated DEGs | | | | | |
| EIF2 Signalling | 41 | 169 | 0.243 | 5.196 | 1.05E-10 |
| Germ Cell-Sertoli Cell Junction Signalling | 30 | 154 | 0.195 | | 1.58E-05 |
| mTOR Signalling | 33 | 181 | 0.182 | | 1.58E-05 |
| Semaphorin Signalling in Neurons | 16 | 52 | 0.308 | | 1.62E-05 |
| Integrin Signalling | 34 | 194 | 0.175 | 5.303 | 1.66E-05 |
| Signalling by Rho Family GTPases | 37 | 231 | 0.16 | 5.112 | 4.17E-05 |
| STAT3 Pathway | 18 | 73 | 0.247 | | 6.17E-05 |
| RhoA Signalling | 23 | 118 | 0.195 | 3.71 | 1.55E-04 |
| RhoGDI Signalling | 29 | 172 | 0.169 | -4.379 | 1.62E-04 |
| Adipogenesis pathway | 23 | 120 | 0.192 | | 1.66E-04 |
| ILK Signalling | 29 | 181 | 0.16 | 4.536 | 3.72E-04 |
| Molecular Mechanisms of Cancer | 46 | 359 | 0.128 | | 5.01E-04 |
| Leukocyte Extravasation Signalling | 29 | 191 | 0.152 | 2.683 | 8.91E-04 |
| Actin Nucleation by ARP-WASP Complex | 13 | 56 | 0.232 | 3.606 | 1.95E-03 |
| Fatty Acid ??-oxidation I | 9 | 29 | 0.31 | | 2.24E-03 |
| IL-8 Signalling | 27 | 182 | 0.148 | 5.099 | 2.24E-03 |
| Regulation of Cellular Mechanics by Calpain Protease | 12 | 54 | 0.222 | 1.89 | 4.68E-03 |
| Ephrin Receptor Signalling | 25 | 172 | 0.145 | | 4.68E-03 |
| Dopamine Degradation | 7 | 20 | 0.35 | | 4.79E-03 |
| Caveolar-mediated Endocytosis Signalling | 14 | 71 | 0.197 | | 4.79E-03 |

| | | | | | |
|--|------|------------------|-------|---------|----------|
| Glioma Invasiveness Signalling | 12 | 57 | 0.211 | 2.887 | 6.76E-03 |
| Regulation of eIF4 and p70S6K Signalling | 21 | 140 | 0.15 | 1.633 | 7.41E-03 |
| Tryptophan Degradation X (Mammalian, via Tryptamine) | 6 | 16 | 0.375 | | 7.41E-03 |
| Putrescine Degradation III | 6 | 16 | 0.375 | | 7.41E-03 |
| Epithelial Adherens Junction Signalling | 21 | 141 | 0.149 | | 7.59E-03 |
| Aryl Hydrocarbon Receptor Signalling | 20 | 133 | 0.15 | 2.496 | 8.51E-03 |
| FAK Signalling | 15 | 86 | 0.174 | | 8.51E-03 |
| Clathrin-mediated Endocytosis Signalling | 25 | 184 | 0.136 | | 8.51E-03 |
| Ethanol Degradation IV | 6 | 17 | 0.353 | | 8.91E-03 |
| Pathways for down regulated DEGs | | | | | |
| Ingenuity.Canonical.Pathways | DEGs | Genes In pathway | Ratio | z.score | adjPval |
| Breast Cancer Regulation by Stathmin1 | 43 | 188 | 0.229 | | 1.35E-06 |
| Dopamine-DARPP32 Feedback in cAMP Signalling | 38 | 157 | 0.242 | -2.785 | 1.35E-06 |
| Oxidative Phosphorylation | 28 | 96 | 0.292 | | 1.35E-06 |
| Signalling by Rho Family GTPases | 48 | 231 | 0.208 | -5.667 | 1.82E-06 |
| Huntington's Disease Signalling | 47 | 225 | 0.209 | | 1.82E-06 |
| Mitochondrial Dysfunction | 37 | 157 | 0.236 | | 1.82E-06 |
| Protein Ubiquitination Pathway | 50 | 251 | 0.199 | | 2.40E-06 |
| Role of NFAT in Cardiac Hypertrophy | 39 | 174 | 0.224 | | 2.40E-06 |
| Rac Signalling | 28 | 103 | 0.272 | -5.099 | 2.40E-06 |
| Axonal Guidance Signalling | 71 | 420 | 0.169 | | 3.31E-06 |
| G Beta Gamma Signalling | 25 | 88 | 0.284 | | 3.98E-06 |
| CDK5 Signalling | 26 | 98 | 0.265 | -2.353 | 9.12E-06 |
| Ephrin Receptor Signalling | 36 | 172 | 0.209 | | 2.95E-05 |
| Corticotropin Releasing Hormone Signalling | 26 | 105 | 0.248 | | 3.39E-05 |
| fMLP Signalling in Neutrophils | 26 | 107 | 0.243 | -4.796 | 4.17E-05 |
| GNRH Signalling | 29 | 127 | 0.228 | -5.385 | 4.17E-05 |
| CREB Signalling in Neurons | 35 | 169 | 0.207 | -5 | 4.17E-05 |
| 14-3-3-mediated Signalling | 27 | 114 | 0.237 | | 4.17E-05 |
| Synaptic Long Term Potentiation | 27 | 116 | 0.233 | | 5.62E-05 |
| CXCR4 Signalling | 32 | 151 | 0.212 | -4.2 | 5.89E-05 |
| Renin-Angiotensin Signalling | 25 | 108 | 0.231 | -5 | 1.32E-04 |
| IL-1 Signalling | 22 | 91 | 0.242 | -3.638 | 2.14E-04 |
| GABA Receptor Signalling | 18 | 66 | 0.273 | | 2.19E-04 |
| ??-Adrenergic Signalling | 21 | 85 | 0.247 | -2.5 | 2.19E-04 |
| Cardiac Hypertrophy Signalling | 39 | 218 | 0.179 | -5.145 | 2.95E-04 |
| RhoGDI Signalling | 33 | 172 | 0.192 | 4.899 | 2.95E-04 |
| CCR5 Signalling in Macrophages | 17 | 62 | 0.274 | | 3.02E-04 |
| IGF-1 Signalling | 22 | 96 | 0.229 | -2.668 | 4.17E-04 |
| Myc Mediated Apoptosis Signalling | 16 | 58 | 0.276 | | 4.47E-04 |
| Synaptic Long Term Depression | 27 | 132 | 0.205 | -2.887 | 4.47E-04 |
| HIPPO Signalling | 20 | 85 | 0.235 | 3.464 | 5.75E-04 |
| Cholecystokinin/Gastrin-mediated Signalling | 22 | 99 | 0.222 | -4.69 | 6.03E-04 |
| Androgen Signalling | 23 | 110 | 0.209 | -3 | 1.07E-03 |
| p70S6K Signalling | 24 | 118 | 0.203 | -1.606 | 1.17E-03 |
| CCR3 Signalling in Eosinophils | 23 | 111 | 0.207 | | 1.17E-03 |
| Gap Junction Signalling | 28 | 149 | 0.188 | | 1.32E-03 |
| Aldosterone Signalling in Epithelial Cells | 28 | 150 | 0.187 | | 1.45E-03 |
| ErbB Signalling | 19 | 85 | 0.224 | | 1.48E-03 |
| Neuropathic Pain Signalling In Dorsal Horn Neurons | 21 | 99 | 0.212 | -4.583 | 1.48E-03 |
| Protein Kinase A Signalling | 54 | 365 | 0.148 | | 1.48E-03 |
| UVC-Induced MAPK Signalling | 12 | 42 | 0.286 | -3.464 | 2.19E-03 |
| Nitric Oxide Signalling in the Cardiovascular System | 20 | 95 | 0.211 | -3.441 | 2.19E-03 |
| Melatonin Signalling | 16 | 68 | 0.235 | -2.5 | 2.40E-03 |
| P2Y Purigenic Receptor Signalling Pathway | 23 | 118 | 0.195 | -4.025 | 2.45E-03 |
| Glutamate Receptor Signalling | 14 | 56 | 0.25 | -2.449 | 2.82E-03 |
| NRF2-mediated Oxidative Stress Response | 30 | 175 | 0.171 | -4 | 3.24E-03 |
| Cdc42 Signalling | 23 | 121 | 0.19 | | 3.39E-03 |
| Clathrin-mediated Endocytosis Signalling | 31 | 185 | 0.168 | | 3.39E-03 |
| Remodeling of Epithelial Adherens Junctions | 15 | 64 | 0.234 | -2.828 | 3.39E-03 |
| G??q Signalling | 26 | 145 | 0.179 | -3.962 | 3.55E-03 |
| CD28 Signalling in T Helper Cells | 21 | 107 | 0.196 | -4.146 | 3.55E-03 |
| Reelin Signalling in Neurons | 17 | 79 | 0.215 | | 3.89E-03 |
| UVB-Induced MAPK Signalling | 13 | 52 | 0.25 | -3.606 | 3.89E-03 |
| Molecular Mechanisms of Cancer | 51 | 359 | 0.142 | | 3.89E-03 |
| Relaxin Signalling | 24 | 132 | 0.182 | | 4.17E-03 |

| | | | | | |
|---|----|-----|-------|--------|----------|
| Cardiac ??-adrenergic Signalling | 24 | 132 | 0.182 | -0.243 | 4.17E-03 |
| LPS-stimulated MAPK Signalling | 16 | 73 | 0.219 | -4 | 4.17E-03 |
| Ephrin B Signalling | 16 | 73 | 0.219 | -1.89 | 4.17E-03 |
| BMP Signalling pathway | 16 | 74 | 0.216 | | 4.79E-03 |
| Role of NFAT in Regulation of the Immune Response | 27 | 158 | 0.171 | -3.578 | 5.01E-03 |
| ERK/MAPK Signalling | 30 | 183 | 0.164 | -1.225 | 5.25E-03 |
| ERK5 Signalling | 14 | 61 | 0.23 | -2.828 | 5.25E-03 |
| PI3K/AKT Signalling | 22 | 120 | 0.183 | -0.853 | 5.62E-03 |
| Amyloid Processing | 12 | 50 | 0.24 | -2.449 | 7.76E-03 |
| Parkinson's Signalling | 6 | 15 | 0.4 | | 8.13E-03 |
| Inhibition of Angiogenesis by TSP1 | 9 | 32 | 0.281 | -2.646 | 9.33E-03 |

Supplementary Table S8. Gene set enrichment analysis (GSEA) for ageing with KEGG pathways. FDR q value (FDR, false discovery rate); FWER p value (FWER, family wise-error rate); ES (enrichment score) and NES (normalized enrichment score).

| Supplementary Table S6. Gene set enrichment analysis for ageing | | | | | | |
|---|------|------|------|-----------|-----------|------------|
| NAME | SIZE | ES | NES | NOM p-val | FDR q-val | FWER p-val |
| Enrichment in Old | | | | | | |
| RIBOSOME | 76 | 0.49 | 5.01 | 0 | 0 | 0 |
| UPDEGS_NOROS | 35 | 0.67 | 4.73 | 0 | 0 | 0 |
| UPDEGS_NFKB | 35 | 0.55 | 3.82 | 0 | 0 | 0 |
| COMPLEMENT_AND_COAGULATION_CASCADES | 36 | 0.50 | 3.52 | 0 | 0 | 0 |
| LEISHMANIA_INFECTION | 46 | 0.40 | 3.23 | 0 | 0 | 0 |
| CELL_ADHESION_MOLECULES_CAMS | 89 | 0.29 | 3.17 | 0 | 0 | 0 |
| ALLOGRAFT_REJECTION | 22 | 0.55 | 3.05 | 0 | 0 | 0 |
| GRAFT_VERSUS_HOST_DISEASE | 23 | 0.53 | 2.99 | 2.01E-03 | 1.59E-04 | 0.001 |
| SYSTEMIC_LUPUS_ERYTHEMATOSUS | 51 | 0.34 | 2.84 | 0 | 1.42E-04 | 0.001 |
| CYTOKINE_CYTOKINE_RECEPTOR_INTERACTION | 110 | 0.22 | 2.61 | 0 | 1.07E-03 | 0.009 |
| HEMATOPOIETIC_CELL_LINEAGE | 34 | 0.37 | 2.57 | 0 | 1.62E-03 | 0.015 |
| ASTHMA | 13 | 0.57 | 2.48 | 0 | 1.80E-03 | 0.018 |
| FOCAL_ADHESION | 148 | 0.18 | 2.46 | 0 | 1.75E-03 | 0.019 |
| TYPE_I_DIABETES_MELLITUS | 29 | 0.37 | 2.42 | 0 | 2.14E-03 | 0.025 |
| NOTCH_SIGNALLING_PATHWAY | 37 | 0.34 | 2.42 | 0 | 2.23E-03 | 0.028 |
| SMALL_CELL_LUNG_CANCER | 61 | 0.26 | 2.41 | 0 | 2.09E-03 | 0.028 |
| ECM_RECEPTOR_INTERACTION | 51 | 0.28 | 2.35 | 2.01E-03 | 3.23E-03 | 0.046 |
| AUTOIMMUNE_THYROID_DISEASE | 29 | 0.36 | 2.34 | 0 | 3.40E-03 | 0.051 |
| ANTIGEN_PROCESSING_AND_PRESENTATION | 51 | 0.28 | 2.32 | 4.01E-03 | 3.66E-03 | 0.058 |
| PROSTATE_CANCER | 74 | 0.23 | 2.31 | 0 | 3.47E-03 | 0.058 |
| CHRONIC_MYELOID_LEUKEMIA | 62 | 0.24 | 2.26 | 0 | 5.03E-03 | 0.086 |
| NATURAL_KILLER_CELL_MEDIATED_CYTOTOXICITY | 83 | 0.20 | 2.20 | 0 | 7.14E-03 | 0.126 |
| MAPK_SIGNALLING_PATHWAY | 190 | 0.13 | 2.17 | 0 | 8.29E-03 | 0.152 |
| LYSINE_DEGRADATION | 36 | 0.30 | 2.14 | 0 | 9.98E-03 | 0.185 |
| PPAR_SIGNALLING_PATHWAY | 41 | 0.28 | 2.09 | 2.04E-03 | 1.27E-02 | 0.236 |
| REGULATION_OF_ACTIN_CYTOSKELETON | 146 | 0.15 | 2.09 | 6.00E-03 | 1.23E-02 | 0.238 |
| INTESTINAL_IMMUNE_NETWORK_FOR_IGA_PRODUCTION | 25 | 0.35 | 2.09 | 2.06E-03 | 1.23E-02 | 0.244 |
| LEUKOCYTE_TRANSENDOTHELIAL_MIGRATION | 74 | 0.20 | 2.01 | 7.71E-03 | 1.95E-02 | 0.372 |
| VIRAL_MYOCARDITIS | 52 | 0.23 | 1.94 | 1.02E-02 | 2.83E-02 | 0.502 |
| FATTY_ACID_METABOLISM | 33 | 0.28 | 1.90 | 8.42E-03 | 3.48E-02 | 0.592 |
| PATHWAYS_IN_CANCER | 228 | 0.11 | 1.87 | 6.25E-03 | 4.03E-02 | 0.654 |
| TGF_BETA_SIGNALLING_PATHWAY | 55 | 0.20 | 1.78 | 1.61E-02 | 6.21E-02 | 0.822 |
| ADHERENS_JUNCTION | 67 | 0.18 | 1.75 | 2.20E-02 | 7.10E-02 | 0.869 |
| NON_SMALL_CELL_LUNG_CANCER | 45 | 0.21 | 1.75 | 2.22E-02 | 6.95E-02 | 0.874 |
| ARRHYTHMOGENIC_RIGHT_VENTRICULAR_CARDIOMYOPATHY_ARVC | 56 | 0.19 | 1.69 | 2.47E-02 | 8.73E-02 | 0.933 |
| B_CELL_RECEPTOR_SIGNALLING_PATHWAY | 55 | 0.19 | 1.65 | 3.35E-02 | 1.02E-01 | 0.962 |
| PANCREATIC_CANCER | 58 | 0.19 | 1.65 | 2.85E-02 | 1.01E-01 | 0.963 |
| TIGHT_JUNCTION | 91 | 0.15 | 1.65 | 2.59E-02 | 1.01E-01 | 0.966 |
| TRYPTOPHAN_METABOLISM | 26 | 0.26 | 1.59 | 4.72E-02 | 1.31E-01 | 0.983 |

| VALINE_LEUCINE_AND_Isoleucine_DEGRADATION | | | | | | | 40 | 0.21 | 1.54 | 5.40E-02 | 1.58E-01 | 0.998 |
|---|------|-------|-------|-----------|-----------|------------|----|------|------|----------|----------|-------|
| Enrichment in Young | | | | | | | | | | | | |
| NAME | SIZE | ES | NES | NOM p-val | FDR q-val | FWER p-val | | | | | | |
| OXIDATIVE_PHOSPHORYLATION | 98 | -0.42 | -4.97 | 0 | 0 | 0 | | | | | | |
| PARKINSONS_DISEASE | 98 | -0.40 | -4.70 | 0 | 0 | 0 | | | | | | |
| HUNTINGTONS_DISEASE | 147 | -0.27 | -3.77 | 0 | 0 | 0 | | | | | | |
| ALZHEIMERS_DISEASE | 131 | -0.27 | -3.49 | 0 | 0 | 0 | | | | | | |
| DNDEGS_MITODYS | 36 | -0.47 | -3.37 | 0 | 0 | 0 | | | | | | |
| DNDEGS_OXPPOS | 24 | -0.51 | -2.95 | 0 | 0 | 0 | | | | | | |
| NEUROACTIVE_LIGAND_RECEPTOR_INTERACTION | 119 | -0.21 | -2.74 | 0 | 0 | 0 | | | | | | |
| CARDIAC_MUSCLE_CONTRACTION | 55 | -0.30 | -2.63 | 0 | 3.17E-04 | 0.003 | | | | | | |
| PROTEASOME | 39 | -0.32 | -2.37 | 0 | 3.17E-03 | 0.036 | | | | | | |
| CALCIUM_SIGNALLING_PATHWAY | 115 | -0.18 | -2.19 | 0 | 1.03E-02 | 0.123 | | | | | | |
| OLFACTORY_TRANSDUCTION | 36 | -0.29 | -2.10 | 2.02E-03 | 1.80E-02 | 0.218 | | | | | | |
| AMINOACYL_TRNA_BIOSYNTHESIS | 29 | -0.32 | -2.08 | 0 | 1.76E-02 | 0.229 | | | | | | |
| REGULATION_OF_AUTOPHAGY | 22 | -0.37 | -2.07 | 0 | 1.74E-02 | 0.243 | | | | | | |
| RNA_POLYMERASE | 27 | -0.32 | -2.01 | 4.24E-03 | 2.50E-02 | 0.356 | | | | | | |
| EPITHELIAL_CELL_SIGNALLING_IN_HELICOBACTER_PYLORI_INFECTION | 53 | -0.22 | -1.90 | 1.66E-02 | 4.67E-02 | 0.586 | | | | | | |
| SPLICEOSOME | 90 | -0.17 | -1.89 | 5.98E-03 | 4.50E-02 | 0.595 | | | | | | |
| GLYCOSAMINOGLYCAN_BIOSYNTHESIS_HEPARAN_SULFATE | 21 | -0.32 | -1.76 | 2.12E-02 | 8.58E-02 | 0.839 | | | | | | |
| UBIQUITIN_MEDIATED_PROTEOLYSIS | 106 | -0.14 | -1.71 | 2.10E-02 | 1.03E-01 | 0.897 | | | | | | |
| RIBOFLAVIN_METABOLISM | 11 | -0.42 | -1.66 | 2.98E-02 | 1.22E-01 | 0.939 | | | | | | |
| GLYCOPHINGOLIPID_BIOSYNTHESIS_LACTO_AND_NEOLACTO_SERIES | 19 | -0.30 | -1.60 | 4.97E-02 | 1.56E-01 | 0.973 | | | | | | |

Supplementary Table S9. IPA upstream regulator analysis for LOAD

| Supplementary Table S7. IPA upstream regulator analysis for LOAD | | | | | |
|--|------------|---------------------------------|--------------------|--------------------|------------|
| Upstream Regulator | metaZscore | Molecule Type | Activation z-score | p-value of overlap | Bonferroni |
| Upstream Regulator for up regulated DGEs | | | | | |
| lipopolysaccharide | | chemical drug | 9.35 | 9.82E-59 | 1.91E-55 |
| IFNG | | cytokine | 7.646 | 5.24E-50 | 1.02E-46 |
| TNF | | cytokine | 9.099 | 1.14E-44 | 2.21E-41 |
| TGFB1 | | growth factor | 7.692 | 1.17E-43 | 2.27E-40 |
| tretinoin | | chemical - endogenous mammalian | 8.228 | 1.20E-43 | 2.33E-40 |
| dexamethasone | | chemical drug | 5.474 | 9.17E-36 | 1.78E-32 |
| IL6 | | cytokine | 6.526 | 1.11E-29 | 2.15E-26 |
| TP53 | | transcription regulator | 5.11 | 2.11E-28 | 4.09E-25 |
| IL4 | | cytokine | 4.672 | 5.53E-28 | 1.07E-24 |
| IL1B | | cytokine | 7.236 | 6.16E-28 | 1.20E-24 |
| CD40LG | | cytokine | 4.593 | 4.36E-25 | 8.46E-22 |
| NFKB (complex) | | complex | 7.956 | 5.57E-24 | 1.08E-20 |
| cisplatin | | chemical drug | 6.131 | 1.54E-23 | 2.99E-20 |
| IL13 | | cytokine | 3.105 | 3.74E-23 | 7.26E-20 |
| CSF2 | | cytokine | 5.89 | 5.22E-23 | 1.01E-19 |
| poly rI:rC-RNA | | chemical reagent | 7.561 | 6.14E-23 | 1.19E-19 |
| STAT3 | 7.203 | transcription regulator | 6.635 | 7.24E-23 | 1.40E-19 |
| inosine | | chemical - endogenous mammalian | 5.231 | 5.47E-22 | 1.06E-18 |

| | | | | | |
|-------------------------------|--------|--|-------|----------|----------|
| phorbol myristate acetate | | chemical drug | 7.569 | 1.06E-21 | 2.06E-18 |
| TLR4 | 4.861 | transmembrane receptor | 5.504 | 1.22E-21 | 2.37E-18 |
| IL2 | | cytokine | 4.284 | 1.80E-21 | 3.49E-18 |
| camptothecin | | chemical reagent | 3.065 | 1.48E-20 | 2.87E-17 |
| OSM | | cytokine | 5.305 | 2.11E-20 | 4.09E-17 |
| NFKBIA | 8.282 | transcription regulator | 2.419 | 1.41E-19 | 2.74E-16 |
| E. coli B4 lipopolysaccharide | | chemical toxicant | 5.659 | 1.41E-19 | 2.74E-16 |
| STAT1 | | transcription regulator ligand-dependent nuclear receptor | 4.792 | 4.95E-19 | 9.60E-16 |
| NR3C1 | | chemical - endogenous mammalian | 3.069 | 6.98E-19 | 1.35E-15 |
| beta-estradiol | | mammalian | 2.486 | 2.13E-18 | 4.13E-15 |
| F2 | | peptidase | 6.482 | 7.01E-18 | 1.36E-14 |
| indomethacin | | chemical drug | 3.956 | 2.46E-17 | 4.77E-14 |
| PDGF BB | | complex | 5.274 | 4.73E-17 | 9.18E-14 |
| TGM2 | | enzyme | 5.232 | 4.83E-17 | 9.37E-14 |
| lomustine | | chemical drug | 4.572 | 1.48E-16 | 2.87E-13 |
| triamcinolone acetonide | | chemical drug | 2.403 | 3.14E-16 | 6.09E-13 |
| Interferon alpha | | group | 6.051 | 3.91E-16 | 7.59E-13 |
| forskolin | | chemical toxicant | 4.631 | 4.03E-16 | 7.82E-13 |
| E. coli B5 lipopolysaccharide | | chemical - endogenous non-mammalian | 5.859 | 1.01E-15 | 1.96E-12 |
| hexachlorobenzene | | chemical toxicant | 4.888 | 1.26E-15 | 2.44E-12 |
| gentamicin C | | chemical drug | 4.99 | 1.73E-15 | 3.36E-12 |
| CSF3 | | cytokine | 2.294 | 1.85E-15 | 3.59E-12 |
| IGF1 | -6.721 | growth factor | 3.585 | 2.05E-15 | 3.98E-12 |
| fenamic acid | | chemical reagent | 4.706 | 2.10E-15 | 4.07E-12 |
| 2-bromoethylamine | | chemical reagent | 4.656 | 3.72E-15 | 7.22E-12 |
| triamterene | | chemical drug | 4.954 | 6.29E-15 | 1.22E-11 |
| IL15 | 7.395 | cytokine | 3.457 | 6.40E-15 | 1.24E-11 |
| HGF | 6.33 | growth factor | 6.005 | 8.36E-15 | 1.62E-11 |
| vancomycin | | chemical drug | 4.782 | 9.73E-15 | 1.89E-11 |
| IL1 | | group | 5.27 | 1.06E-14 | 2.06E-11 |
| prostaglandin E2 | | chemical - endogenous mammalian | 3.279 | 1.36E-14 | 2.64E-11 |
| TCR | | complex | 2.783 | 2.56E-14 | 4.97E-11 |
| ERBB2 | | kinase | 2.626 | 3.87E-14 | 7.51E-11 |
| hydrogen peroxide | | chemical - endogenous mammalian | 5.876 | 4.21E-14 | 8.17E-11 |
| MYD88 | 4.999 | other | 6.018 | 5.54E-14 | 1.07E-10 |
| SP1 | 4.807 | transcription regulator | 5.769 | 6.06E-14 | 1.18E-10 |
| EGF | | growth factor | 5.055 | 9.97E-14 | 1.93E-10 |
| CSF1 | 5.575 | cytokine | 4.391 | 1.02E-13 | 1.98E-10 |
| FSH | | complex | 2.384 | 1.18E-13 | 2.29E-10 |
| SPI1 | | transcription regulator | 4.962 | 1.22E-13 | 2.37E-10 |
| TNFSF11 | | cytokine | 4.808 | 1.28E-13 | 2.48E-10 |
| thioacetamide | | chemical toxicant | 4.644 | 1.75E-13 | 3.40E-10 |
| doxorubicin | | chemical drug | 5.309 | 1.94E-13 | 3.76E-10 |
| phenacetin | | chemical drug | 4.338 | 2.39E-13 | 4.64E-10 |

| | | | | | |
|------------------------------------|--------|---------------------------------|-------|----------|----------|
| benzyloxycarbonyl-Leu-Leu aldehyde | | chemical - protease inhibitor | 3.317 | 3.05E-13 | 5.92E-10 |
| Ifn | | group | 3.716 | 3.76E-13 | 7.29E-10 |
| allopurinol | | chemical drug | 4.702 | 4.58E-13 | 8.89E-10 |
| Tgf beta | | group | 3.749 | 5.23E-13 | 1.01E-09 |
| IRF1 | 6.649 | transcription regulator | 4.312 | 5.26E-13 | 1.02E-09 |
| bleomycin | | chemical drug | 5.503 | 7.97E-13 | 1.55E-09 |
| PI3K (complex) | | complex | 4.392 | 9.56E-13 | 1.85E-09 |
| trichostatin A | | chemical drug | 4.147 | 1.29E-12 | 2.50E-09 |
| APP | | other | 3.437 | 2.93E-12 | 5.68E-09 |
| MYC | 5.401 | transcription regulator | 2.112 | 3.78E-12 | 7.33E-09 |
| CD40 | | transmembrane receptor | 3.107 | 8.92E-12 | 1.73E-08 |
| ethionine | | chemical toxicant | 4.123 | 9.24E-12 | 1.79E-08 |
| paclitaxel | | chemical drug | 2.036 | 9.82E-12 | 1.91E-08 |
| TNFSF10 | | cytokine | 2.145 | 1.03E-11 | 2.00E-08 |
| IL27 | | cytokine | 4.123 | 1.11E-11 | 2.15E-08 |
| Cg | | complex | 4.911 | 1.16E-11 | 2.25E-08 |
| HIF1A | | transcription regulator | 4.855 | 1.16E-11 | 2.25E-08 |
| RELA | 6.205 | transcription regulator | 4.749 | 1.30E-11 | 2.52E-08 |
| SMARCA4 | | transcription regulator | 3.594 | 1.74E-11 | 3.38E-08 |
| methylprednisolone | | chemical drug | 2.169 | 1.86E-11 | 3.61E-08 |
| STAT4 | -5.665 | transcription regulator | 6.108 | 3.04E-11 | 5.90E-08 |
| TREM1 | | transmembrane receptor | 2.86 | 3.14E-11 | 6.09E-08 |
| IFNA2 | | cytokine | 4.739 | 4.73E-11 | 9.18E-08 |
| JUN | | transcription regulator | 3.981 | 6.27E-11 | 1.22E-07 |
| CXCL12 | | cytokine | 3.411 | 7.88E-11 | 1.53E-07 |
| IL1A | | cytokine | 4.421 | 1.06E-10 | 2.06E-07 |
| captopril | | chemical drug | 2.262 | 1.24E-10 | 2.41E-07 |
| IKBKB | 5.226 | kinase | 3.239 | 1.26E-10 | 2.44E-07 |
| decitabine | | chemical drug | 6.16 | 1.30E-10 | 2.52E-07 |
| arsenic trioxide | | chemical drug | 3.529 | 1.34E-10 | 2.60E-07 |
| AGN194204 | | chemical drug | 4.414 | 1.42E-10 | 2.75E-07 |
| AKT1 | | kinase | 2.358 | 1.47E-10 | 2.85E-07 |
| IL12 (complex) | | complex | 4.071 | 1.48E-10 | 2.87E-07 |
| TICAM1 | | other | 5.255 | 1.56E-10 | 3.03E-07 |
| NFKB1 | 6.131 | transcription regulator | 4.536 | 1.81E-10 | 3.51E-07 |
| dihydrotestosterone | | chemical - endogenous mammalian | 4.382 | 1.95E-10 | 3.78E-07 |
| lactacystin | | chemical - protease inhibitor | 2.847 | 2.04E-10 | 3.96E-07 |
| ETS1 | | transcription regulator | 3.815 | 2.66E-10 | 5.16E-07 |
| LDL | | complex | 3.129 | 2.91E-10 | 5.65E-07 |
| CEBPA | | transcription regulator | 3.34 | 3.32E-10 | 6.44E-07 |
| phenylbutazone | | chemical drug | 4.321 | 4.11E-10 | 7.97E-07 |
| CTNNB1 | | transcription regulator | 4.842 | 4.97E-10 | 9.64E-07 |
| ethanol | | chemical - endogenous mammalian | 3.755 | 5.69E-10 | 1.10E-06 |
| calcitriol | | chemical drug | 2.277 | 7.45E-10 | 1.45E-06 |
| PRL | | cytokine | 3.845 | 8.24E-10 | 1.60E-06 |
| P38 MAPK | | group | 4.482 | 1.08E-09 | 2.10E-06 |

| | | | | | |
|--|--------|-------------------------------------|-------|----------|----------|
| RETNLB | | other | 4.571 | 1.10E-09 | 2.13E-06 |
| TGFA | | growth factor | 2.39 | 1.10E-09 | 2.13E-06 |
| PGR | | ligand-dependent nuclear receptor | 4.038 | 1.32E-09 | 2.56E-06 |
| resiquimod | | chemical drug | 3.402 | 1.35E-09 | 2.62E-06 |
| cardiotoxin | | chemical - other | 5.196 | 1.55E-09 | 3.01E-06 |
| SMAD4 | 5.82 | transcription regulator | 2.593 | 1.64E-09 | 3.18E-06 |
| SYVN1 | | transporter | 4.785 | 1.64E-09 | 3.18E-06 |
| KITLG | | growth factor | 4.636 | 1.68E-09 | 3.26E-06 |
| carbon tetrachloride | | chemical toxicant | 4.197 | 1.88E-09 | 3.65E-06 |
| ERK | | group | 4.427 | 2.72E-09 | 5.28E-06 |
| methotrexate | | chemical drug | 2.372 | 2.81E-09 | 5.45E-06 |
| IL5 | | cytokine | 5.233 | 3.11E-09 | 6.03E-06 |
| AGT | | growth factor | 5.34 | 3.83E-09 | 7.43E-06 |
| Vegf | | group | 6.824 | 5.22E-09 | 1.01E-05 |
| CEBPB | 7.844 | transcription regulator | 2.999 | 5.46E-09 | 1.06E-05 |
| Ifnar | | group | 3.72 | 6.14E-09 | 1.19E-05 |
| ERK1/2 | | group | 3.884 | 6.85E-09 | 1.33E-05 |
| GATA1 | | transcription regulator | 2.035 | 6.94E-09 | 1.35E-05 |
| CAMP | | other | 3.139 | 7.41E-09 | 1.44E-05 |
| TLR3 | | transmembrane receptor | 4.645 | 8.29E-09 | 1.61E-05 |
| carboplatin | | chemical drug | 2.523 | 8.34E-09 | 1.62E-05 |
| IRF8 | | transcription regulator | 2.713 | 9.02E-09 | 1.75E-05 |
| CCL5 | | cytokine | 3.371 | 9.58E-09 | 1.86E-05 |
| IRF7 | 6.129 | transcription regulator | 5.334 | 1.02E-08 | 1.98E-05 |
| SELPLG | 5.971 | other | 3.606 | 1.18E-08 | 2.29E-05 |
| ERG | | transcription regulator | 3.956 | 1.28E-08 | 2.48E-05 |
| TGFBR2 | 5.355 | kinase | 2.358 | 1.39E-08 | 2.70E-05 |
| EGFR | 5.637 | kinase | 2.753 | 1.80E-08 | 3.49E-05 |
| Pam3-Cys-Ser-Lys4 | | chemical reagent | 2.384 | 1.86E-08 | 3.61E-05 |
| peptidoglycan | | chemical - endogenous non-mammalian | 3.366 | 2.28E-08 | 4.42E-05 |
| SRC | | kinase | 2.266 | 2.43E-08 | 4.71E-05 |
| RAF1 | 5.926 | kinase | 5.032 | 2.80E-08 | 5.43E-05 |
| rosiglitazone | | chemical drug | 2.213 | 3.14E-08 | 6.09E-05 |
| HRG | | other | 3.162 | 3.68E-08 | 7.14E-05 |
| 5-O-mycolyl-beta-araf-(1->2)-5-O-mycolyl-alpha-araf-(1->1')-glycerol | | chemical - endogenous non-mammalian | 4.472 | 4.26E-08 | 8.26E-05 |
| TWIST1 | | transcription regulator | 2.248 | 4.93E-08 | 9.56E-05 |
| 4-methylnitrosoamino-1-(3-pyridinyl)-1-butanone | | chemical toxicant | 2.989 | 5.49E-08 | 1.07E-04 |
| MAP3K14 | | kinase | 3.364 | 6.46E-08 | 1.25E-04 |
| lipoteichoic acid | | chemical - endogenous non-mammalian | 3.282 | 6.46E-08 | 1.25E-04 |
| alitretinoin | | chemical drug | 2.022 | 8.84E-08 | 1.71E-04 |
| FGF2 | | growth factor | 3.815 | 1.04E-07 | 2.02E-04 |
| MAPKAPK2 | 7.373 | kinase | 2.743 | 1.16E-07 | 2.25E-04 |
| cyclophosphamide | | chemical drug | 2.031 | 1.20E-07 | 2.33E-04 |
| MAP2K1 | -5.028 | kinase | 3.302 | 1.25E-07 | 2.43E-04 |

| | | | | | |
|---------------------------|--------|-------------------------------------|-------|----------|----------|
| IL18 | 7.009 | cytokine | 3.385 | 1.28E-07 | 2.48E-04 |
| SAMSN1 | 5.64 | other | 4.472 | 1.43E-07 | 2.77E-04 |
| CpG oligonucleotide | | chemical drug | 4.473 | 1.52E-07 | 2.95E-04 |
| D-glucose | | chemical - endogenous mammalian | 2.72 | 1.59E-07 | 3.08E-04 |
| TET2 | | other | 3.606 | 1.71E-07 | 3.32E-04 |
| SELP | | transmembrane receptor | 3.464 | 1.82E-07 | 3.53E-04 |
| Mapk | | group | 2.942 | 1.92E-07 | 3.72E-04 |
| EGR1 | -6.552 | transcription regulator | 3.906 | 2.41E-07 | 4.68E-04 |
| mir-223 | | microRNA | 2.761 | 2.43E-07 | 4.71E-04 |
| SASH1 | 5.975 | other | 4.123 | 3.32E-07 | 6.44E-04 |
| IL3 | | cytokine | 2.995 | 3.32E-07 | 6.44E-04 |
| PRKCE | | kinase | 3.423 | 3.90E-07 | 7.57E-04 |
| EDN1 | | cytokine | 3.987 | 3.94E-07 | 7.64E-04 |
| lipid A | | chemical toxicant | 3.44 | 4.43E-07 | 8.59E-04 |
| SMARCB1 | | transcription regulator | 3.845 | 5.73E-07 | 1.11E-03 |
| EBI3 | 6.463 | cytokine | 2.84 | 5.96E-07 | 1.16E-03 |
| RET | | kinase | 2.729 | 6.26E-07 | 1.21E-03 |
| Tnf (family) | | group | 2.65 | 6.48E-07 | 1.26E-03 |
| bucladesine | | chemical toxicant | 3.522 | 7.34E-07 | 1.42E-03 |
| REL | | transcription regulator | 3.289 | 8.07E-07 | 1.57E-03 |
| motexafin gadolinium | | chemical drug | 2.449 | 8.40E-07 | 1.63E-03 |
| tunicamycin | | chemical - endogenous non-mammalian | 2.559 | 8.68E-07 | 1.68E-03 |
| mycophenolic acid | | chemical drug | 2.714 | 8.86E-07 | 1.72E-03 |
| MET | | kinase | 3.179 | 9.37E-07 | 1.82E-03 |
| NRG1 | -5.386 | growth factor | 2.42 | 1.02E-06 | 1.98E-03 |
| thapsigargin | | chemical toxicant | 3.022 | 1.05E-06 | 2.04E-03 |
| ETS2 | | transcription regulator | 2.959 | 1.13E-06 | 2.19E-03 |
| salmonella minnesota R595 | | chemical - endogenous non-mammalian | 4.307 | 1.14E-06 | 2.21E-03 |
| lipopolysaccharides | | | | | |
| IL17A | | cytokine | 4.532 | 1.30E-06 | 2.52E-03 |
| CD44 | 5.738 | enzyme | 2.676 | 1.34E-06 | 2.60E-03 |
| TYROBP | 7.113 | transmembrane receptor | 2.213 | 1.35E-06 | 2.62E-03 |
| TNFSF12 | | cytokine | 3.957 | 1.38E-06 | 2.68E-03 |
| TLR2 | 6.847 | transmembrane receptor | 3.453 | 1.48E-06 | 2.87E-03 |
| 17-alpha-ethinylestradiol | | chemical drug | 2.037 | 1.48E-06 | 2.87E-03 |
| PTGS2 | | enzyme | 3.364 | 1.68E-06 | 3.26E-03 |
| Akt | | group | 2.14 | 1.87E-06 | 3.63E-03 |
| JAK2 | | kinase | 3.22 | 1.89E-06 | 3.67E-03 |
| ATM | | kinase | 2.105 | 2.06E-06 | 4.00E-03 |
| DETA-NONOate | | chemical reagent | 2.206 | 2.31E-06 | 4.48E-03 |
| AR | | ligand-dependent nuclear receptor | 2.607 | 2.54E-06 | 4.93E-03 |
| tributyrin | | chemical drug | 3.359 | 2.67E-06 | 5.18E-03 |
| MTPN | | transcription regulator | 4.067 | 2.87E-06 | 5.57E-03 |
| hyaluronic acid | | chemical - endogenous mammalian | 2.045 | 3.04E-06 | 5.90E-03 |
| Insulin | | group | 2.29 | 3.07E-06 | 5.96E-03 |

| | | | | | |
|--|------------|-------------------------------------|--------------------|--------------------|-----------|
| E. coli lipopolysaccharide | | chemical - endogenous non-mammalian | 3.175 | 3.28E-06 | 6.36E-03 |
| TLR7 | 6.476 | transmembrane receptor | 3.917 | 3.97E-06 | 7.70E-03 |
| etoposide | | chemical drug | 3.581 | 4.00E-06 | 7.76E-03 |
| vitamin K2 | | chemical drug | 2.8 | 4.54E-06 | 8.81E-03 |
| 5-azacytidine | | chemical drug | 4.115 | 4.88E-06 | 9.47E-03 |
| EIF2AK2 | | kinase | 2.48 | 5.69E-06 | 1.10E-02 |
| LIF | | cytokine | 3.42 | 5.75E-06 | 1.12E-02 |
| Ifn gamma | | complex | 2.517 | 6.71E-06 | 1.30E-02 |
| dimethyl sulfoxide | | chemical drug | 2.848 | 7.24E-06 | 1.40E-02 |
| bromodeoxyuridine | | chemical drug | 3.544 | 7.48E-06 | 1.45E-02 |
| CXCR4 | 6.322 | g-protein coupled receptor | 3.26 | 7.48E-06 | 1.45E-02 |
| NOS2 | | enzyme | 3.971 | 7.55E-06 | 1.46E-02 |
| PTK2 | | kinase | 2.398 | 8.72E-06 | 1.69E-02 |
| IFN alpha/beta | | group | 3.478 | 9.11E-06 | 1.77E-02 |
| TGFB2 | 4.843 | growth factor | 2.236 | 9.23E-06 | 1.79E-02 |
| EPAS1 | | transcription regulator | 2.905 | 1.10E-05 | 2.13E-02 |
| hemozoin | | chemical - endogenous non-mammalian | 2.946 | 1.10E-05 | 2.13E-02 |
| GC-GCR dimer | | complex | 2.621 | 1.36E-05 | 2.64E-02 |
| PRKCD | | kinase | 2.177 | 1.46E-05 | 2.83E-02 |
| 7-ethyl-10-hydroxycamptothecin | | chemical drug | 2.414 | 1.67E-05 | 3.24E-02 |
| VEGFA | | growth factor | 4.577 | 1.93E-05 | 3.74E-02 |
| cobalt chloride | | chemical reagent | 2.998 | 1.94E-05 | 3.76E-02 |
| GLI1 | | transcription regulator | 4.504 | 1.98E-05 | 3.84E-02 |
| TP63 | | transcription regulator | 2.982 | 2.05E-05 | 3.98E-02 |
| pirinixic acid | | chemical toxicant | 2.941 | 2.06E-05 | 4.00E-02 |
| arsenite | | chemical toxicant | 2.299 | 2.11E-05 | 4.09E-02 |
| Gm-csf | | group | 2.239 | 2.14E-05 | 4.15E-02 |
| KLF5 | | transcription regulator | 2.117 | 2.14E-05 | 4.15E-02 |
| NEDD9 | | other | 3.162 | 2.20E-05 | 4.27E-02 |
| Pdgf (complex) | | complex | 3.091 | 2.26E-05 | 4.38E-02 |
| trovafloxacin | | chemical drug | 3.207 | 2.31E-05 | 4.48E-02 |
| reactive oxygen species | | chemical toxicant | 3.832 | 2.48E-05 | 4.81E-02 |
| TNFRSF1A | 7.527 | transmembrane receptor | 2.421 | 2.48E-05 | 4.81E-02 |
| Hbb-b1 | | transporter | 2.335 | 2.56E-05 | 4.97E-02 |
| Upstream Regulator for down regulated DGEs | | | | | |
| Upstream Regulator | metaZscore | Molecule Type | Activation z-score | p-value of overlap | Boferroni |
| REST | | transcription regulator | 3.024 | 8.22E-09 | 1.53E-06 |
| RICTOR | | other | 6 | 2.52E-05 | 4.69E-03 |

Supplementary Table S10. List of 36 target DEGs of RICTOR in LOAD.

| Entrez.Gene | Symbol | metaZscore | metaPval | effect | Bonferroni | BraakR | atrophyR |
|-------------|--------|------------|----------|--------|------------|--------|----------|
| 4711 | NDUFB5 | -7.70 | 1.40E-14 | ----- | 3.29E-10 | -0.67 | -0.52 |
| 4701 | NDUFA7 | -6.94 | 3.90E-12 | --?--+ | 9.17E-08 | -0.66 | -0.56 |
| 516 | ATP5G1 | -6.66 | 2.69E-11 | --?-- | 6.34E-07 | -0.70 | -0.60 |

| | | | | | | | |
|-------|----------|-------|----------|--------|----------|-------|-------|
| 51382 | ATP6V1D | -6.62 | 3.70E-11 | ----- | 8.70E-07 | -0.64 | -0.53 |
| 4704 | NDUFA9 | -6.58 | 4.86E-11 | ----- | 1.14E-06 | -0.67 | -0.50 |
| 1355 | COX15 | -6.52 | 6.94E-11 | --?-- | 1.63E-06 | -0.61 | -0.47 |
| 4723 | NDUFV1 | -6.30 | 2.91E-10 | -----+ | 6.84E-06 | -0.67 | -0.53 |
| 1537 | CYC1 | -6.03 | 1.65E-09 | --?-- | 3.89E-05 | -0.67 | -0.55 |
| 522 | ATP5J | -5.93 | 2.95E-09 | --?-- | 6.94E-05 | -0.69 | -0.54 |
| 5702 | PSMC3 | -5.88 | 4.08E-09 | --?-- | 9.61E-05 | -0.68 | -0.55 |
| 5714 | PSMD8 | -5.69 | 1.31E-08 | ----- | 3.07E-04 | -0.61 | -0.47 |
| 7385 | UQCRC2 | -5.64 | 1.72E-08 | --?--+ | 4.05E-04 | -0.65 | -0.53 |
| 529 | ATP6V1E1 | -5.60 | 2.12E-08 | --?-- | 4.99E-04 | -0.66 | -0.56 |
| 518 | ATP5G3 | -5.54 | 3.02E-08 | --?-- | 7.12E-04 | -0.65 | -0.52 |
| 509 | ATP5C1 | -5.47 | 4.53E-08 | --+-- | 1.06E-03 | -0.64 | -0.52 |
| 9167 | COX7A2L | -5.45 | 5.17E-08 | --?--+ | 1.22E-03 | | -0.46 |
| 5719 | PSMD13 | -5.41 | 6.36E-08 | --+-- | 1.50E-03 | | -0.49 |
| 51187 | RSL24D1 | -5.37 | 7.70E-08 | ----- | 1.81E-03 | | |
| 515 | ATP5F1 | -5.37 | 8.09E-08 | --?-- | 1.90E-03 | -0.61 | -0.48 |
| 534 | ATP6V1G2 | -5.35 | 8.85E-08 | ----- | 2.08E-03 | -0.66 | -0.57 |
| 27089 | UQCRCQ | -5.35 | 8.86E-08 | --?--+ | 2.08E-03 | -0.73 | -0.57 |
| 6171 | RPL41 | -5.23 | 1.66E-07 | --?--+ | 3.90E-03 | -0.70 | -0.52 |
| 4700 | NDUFA6 | -5.22 | 1.82E-07 | --?-- | 4.29E-03 | -0.65 | -0.53 |
| 4712 | NDUFB6 | -5.20 | 1.96E-07 | --+?-- | 4.60E-03 | -0.63 | -0.50 |
| 5718 | PSMD12 | -5.19 | 2.10E-07 | --+?-- | 4.94E-03 | | -0.49 |
| 5686 | PSMA5 | -5.18 | 2.24E-07 | ----- | 5.27E-03 | -0.66 | -0.55 |
| 10632 | ATP5L | -5.14 | 2.74E-07 | --?-- | 6.46E-03 | -0.66 | -0.52 |
| 5695 | PSMB7 | -5.14 | 2.80E-07 | ----- | 6.59E-03 | -0.65 | -0.51 |
| 4722 | NDUFS3 | -5.00 | 5.63E-07 | ----- | 1.32E-02 | -0.67 | -0.53 |
| 51606 | ATP6V1H | -4.96 | 7.10E-07 | --?-- | 1.67E-02 | -0.61 | -0.52 |
| 523 | ATP6V1A | -4.96 | 7.10E-07 | ----- | 1.67E-02 | | -0.45 |
| 4705 | NDUFA10 | -4.94 | 7.74E-07 | -----+ | 1.82E-02 | | -0.45 |
| 1327 | COX4I1 | -4.90 | 9.42E-07 | --+-- | 2.22E-02 | -0.70 | -0.58 |
| 526 | ATP6V1B2 | -4.88 | 1.06E-06 | --?-- | 2.50E-02 | -0.65 | -0.51 |
| 4706 | NDUFAB1 | -4.80 | 1.62E-06 | ----- | 3.82E-02 | -0.65 | -0.51 |
| 1347 | COX7A2 | -4.74 | 2.12E-06 | --+-- | 4.99E-02 | -0.66 | -0.54 |

Supplementary Table S11. IPA upstream regulator analysis for ageing

| Supplementary Table S9. IPA upstream regulator analysis for ageing | | | | | | |
|--|-----------|-----------------------------------|--------------------|--------------------|------------|--|
| Upstream Regulator | Log Ratio | Molecule Type | Activation z-score | p-value of overlap | Bonferroni | |
| Upstream Regulator for up regulated DEGs | | | | | | |
| MYCN | 0.143 | transcription regulator | 3.030 | 4.65E-15 | 3.18E-12 | |
| HRAS | -0.055 | enzyme | 2.332 | 3.92E-12 | 2.68E-09 | |
| tretinoin | | chemical - endogenous mammalian | 5.225 | 3.96E-11 | 2.71E-08 | |
| TGFB1 | 0.839 | growth factor | 4.541 | 4.33E-11 | 2.96E-08 | |
| TP53 | 0.217 | transcription regulator | 5.590 | 6.96E-11 | 4.76E-08 | |
| dexamethasone | | chemical drug | 5.394 | 6.22E-10 | 4.25E-07 | |
| dihydrotestosterone | | chemical - endogenous mammalian | 3.112 | 2.29E-09 | 1.57E-06 | |
| cisplatin | | chemical drug | 3.809 | 1.27E-08 | 8.69E-06 | |
| MITF | 0.332 | transcription regulator | 5.237 | 8.82E-08 | 6.03E-05 | |
| JUN | -0.490 | transcription regulator | 2.598 | 9.97E-08 | 6.82E-05 | |
| AKT1 | 0.225 | kinase | 2.454 | 3.01E-07 | 2.06E-04 | |
| SYVN1 | 0.193 | transporter | 4.574 | 3.05E-07 | 2.09E-04 | |
| motexafin gadolinium | | chemical drug | 2.449 | 4.42E-07 | 3.02E-04 | |
| SMARCA4 | -0.378 | transcription regulator | 3.520 | 5.81E-07 | 3.97E-04 | |
| triamcinolone acetonide | | chemical drug | 2.744 | 1.88E-06 | 1.29E-03 | |
| IFNG | | cytokine | 2.503 | 2.79E-06 | 1.91E-03 | |
| PGR | 0.055 | ligand-dependent nuclear receptor | 4.352 | 5.54E-06 | 3.79E-03 | |
| progesterone | | chemical - endogenous mammalian | 4.791 | 5.70E-06 | 3.90E-03 | |
| FSH | | complex | 2.454 | 5.77E-06 | 3.95E-03 | |
| FN1 | 0.481 | enzyme | 3.393 | 2.39E-05 | 1.63E-02 | |
| PDGF BB | | complex | 4.439 | 2.46E-05 | 1.68E-02 | |

| NR3C1 | -0.521 | ligand-dependent nuclear receptor | 2.517 | 2.52E-05 | 1.72E-02 |
|--|-----------|-----------------------------------|--------------------|--------------------|------------|
| MYOD1 | | transcription regulator | 3.739 | 2.61E-05 | 1.79E-02 |
| ERK | | group | 2.327 | 3.80E-05 | 2.60E-02 |
| LIMS1 | 0.457 | other | 2.224 | 5.00E-05 | 3.42E-02 |
| Insulin | | group | 3.386 | 6.01E-05 | 4.11E-02 |
| Up stream regulators for down regulated DEGs | | | | | |
| Upstream Regulator | Log Ratio | Molecule Type | Activation z-score | p-value of overlap | Bonferroni |
| RICTOR | 0.459 | other | 6.487 | 3.24E-08 | 6.35E-06 |
| CD 437 | | chemical drug | 6.164 | 4.17E-06 | 8.17E-04 |
| REST | 0.410 | transcription regulator | 3.098 | 1.42E-05 | 2.78E-03 |
| topotecan | | chemical drug | 2.501 | 2.11E-04 | 4.14E-02 |

Supplementary Table S12. Number of neighbours for the top DEGs in PPI DEGs network. It contains the number of first neighbours, number of DEG, number of up/down regulated DEGs among the first neighbours (see Supplementary Fig. S4)

| TopDEGs | Neighbours | DEGs | up DEGs | down DEGs |
|-----------|------------|------|---------|-----------|
| NFKBIA | 64 | 23 | 13 | 10 |
| C1QA | 43 | 10 | 9 | 1 |
| TRIP10 | 12 | 6 | 4 | 2 |
| BDNF | 7 | 1 | 1 | 0 |
| DUSP4 | 7 | 1 | 0 | 1 |
| DOK3 | 5 | 4 | 4 | 0 |
| SEMA3F | 4 | 0 | 0 | 0 |
| KCNF1 | 4 | 1 | 0 | 1 |
| ITPKB | 3 | 1 | 0 | 1 |
| CCKBR | 3 | 1 | 0 | 1 |
| CRH | 2 | 0 | 0 | 0 |
| LATS2 | 2 | 1 | 1 | 0 |
| NUPR1 | 2 | 0 | 0 | 0 |
| ZCCHC17 | 2 | 0 | 0 | 0 |
| PPEF1 | 1 | 0 | 0 | 0 |
| HIST1H2BD | 1 | 0 | 0 | 0 |

Supplementary Table S13. Number of neighbours for GWAS hits in the PPI GWAS network. The table shows the number of first neighbours, number of DEGs, and number of up/down regulated DEGs among the first neighbours (see Supplementary Fig. S5)

| GWASAD | Neighbours | DEGs | up DEGs | down DEGs |
|--------|------------|------|---------|-----------|
| APOE | 124 | 18 | 10 | 8 |
| PTK2B | 55 | 16 | 13 | 3 |
| CLU | 44 | 9 | 7 | 2 |
| BIN1 | 32 | 7 | 4 | 3 |
| INPP5D | 22 | 7 | 7 | 0 |
| CD2AP | 19 | 3 | 3 | 0 |
| MEF2C | 19 | 5 | 4 | 1 |
| TRIP4 | 14 | 6 | 5 | 1 |
| CR1 | 9 | 6 | 6 | 0 |
| PICALM | 7 | 1 | 1 | 0 |
| CELF1 | 4 | 0 | 0 | 0 |
| SORL1 | 3 | 2 | 2 | 0 |
| FERMT2 | 1 | 0 | 0 | 0 |
| TREM2 | 1 | 1 | 1 | 0 |

Methods

Data collection and pre-processing

We searched arrayExpress (<https://www.ebi.ac.uk/arrayexpress/>) and GEO (<http://www.ncbi.nlm.nih.gov/geo/>) for all late-onset Alzheimer's disease (LOAD) related mRNA expression studies that included human post mortem brain tissues from super frontal gyrus (SFG) or prefrontal cortex (PFC), both of which are part of the brain frontal lobe. We found and downloaded six profile datasets with GEO accession number of GSE5281, GSE48350, GSE36980, GSE15222, GSE44770 and GSE33000. The GSE5281 and GSE48350 datasets, generated from the Affymatrix HG-U133-plus2 platform (GEO platform ID: GPL570), contained 54675 probesets and have 161 and 252 profiles respectively. We worked on the raw CEL files and completed the normalization using the RMA (Robust Multi-array Average) method implemented in the `affy`² R package (<http://www.bioconductor.org>). Pre-filtering was completed by allowing no more than 10% absent (present/absent call by `affy` `mas5` algorithm) across all samples in each study and probesets with average expression level lower than 3 (after \log_2 transformation) were discarded afterwards. The latest version of probesets annotation file HG-U133_Plus_2.na34.annot.csv was downloaded from Affymetrix NetAffx Analysis Centre (www.affymetrix.com/analysis/index.affx). GSE36980 was generated from the Affymatrix Human Gene 1.0 ST platform (GEO platform ID: GPL6244) with 79 profiles. As with the above datasets, we worked on the raw CEL files to complete transcript level RMA normalization and excluded transcripts with average expression lower than 3. For this dataset, we also carried out probe level present/absent calls using the `oligo`³ R package, i.e., we marked all probes having fewer than 10% absents across samples as good probes and discarded any transcripts that did not contain any good probes. Microarray annotation database package `hugene10sttranscriptcluster.db` in R was used for annotating this dataset. GSE44770 and GSE33000 were both generated from the Rosetta/Merck Human 44k microarray platform (GEO platform ID: GPL4372), containing 39302 probesets and including 230 and 623 case-control profiles respectively. We worked on the processed data without any pre-filtering. GSE15222 was generated from the

Illumina microarray platform (GEO platform ID: GPL2700) and contains 24354 probesets and 363 profiles. We worked on a sub-dataset containing 8650 pre-filtered probesets downloaded from Dr Myer's lab (<http://labs.med.miami.edu/myers>). In this data file, probesets had null values if their relevant detection scores were less than 0.99, and probesets with more than 30% null values were excluded. GSE44770 and GSE33000 contained only PFC tissue; GSE5281, GSE48350, GSE15222 and GSE36980 had multiple tissues. Alzheimer's disease is age-related, so in order to reduce the analysis bias induced by age we only included samples aged between 65 and 95 years old, and discarded any samples without age information. In this study, we only focused on PFC types because we were able to obtain the maximum number of gene expression profiles in this brain region, giving us a total number of 212 controls and 450 cases after age controlling.

We mapped probesets to Entrez Gene IDs (as gene IDs) in each study first, and removed probesets having multiple mapped genes. Furthermore, if a gene has multiple relevant probesets, then the probesets having the biggest absolute estimated effect size would be kept and the rest discarded. Supplementary Table S1 lists the numbers of case and control samples, and the number of unique genes in each study used for the meta-analysis.

We downloaded GSE53890 from GEO which contains 12 young (age < 40 yrs), 17 old (aged between 65 to 95) and other aged gene expression profiles in raw CEL file format generated from the Affymatrix HG-U133-plus2 platform. Similar data processing was completed for this non-AD cohort. After pre-processing, 25264 probesets were left. The limma⁴ R package was used for detecting differentially expressed genes (DEGs) with Benjamini-Hochberg adjusted p-value < 0.01 and expression intensity > 5 (in log₂ space).

GSE5281 contains six brain regions: entorhinal cortex (EC); hippocampus (HIP); medial temporal gyrus (MTG); posterior cingulate (PC); superior frontal gyrus (SFG) and primary visual cortex (PVC). DEGs in each region were identified by limma with the same criteria as above, we mapped the top meta-analysis DEGs to this dataset (see Supplementary Table S4).

References

- 1 Zhang, B. *et al.* Integrated systems approach identifies genetic nodes and networks in late-onset Alzheimer's disease. *Cell* **153**, 707-720, doi:10.1016/j.cell.2013.03.030 (2013).
- 2 Gautier, L., Cope, L., Bolstad, B. M. & Irizarry, R. A. affy--analysis of Affymetrix GeneChip data at the probe level. *Bioinformatics* **20**, 307-315, doi:10.1093/bioinformatics/btg405 (2004).
- 3 Carvalho, B. S. & Irizarry, R. A. A framework for oligonucleotide microarray preprocessing. *Bioinformatics* **26**, 2363-2367, doi:10.1093/bioinformatics/btq431 (2010).
- 4 GK, S. *Limma: linear models for microarray data.* 397-420 (Springer, 2005).