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Supplementary Data

Characteristic Transformation of Blood Transcriptome in Alzheimer's Disease

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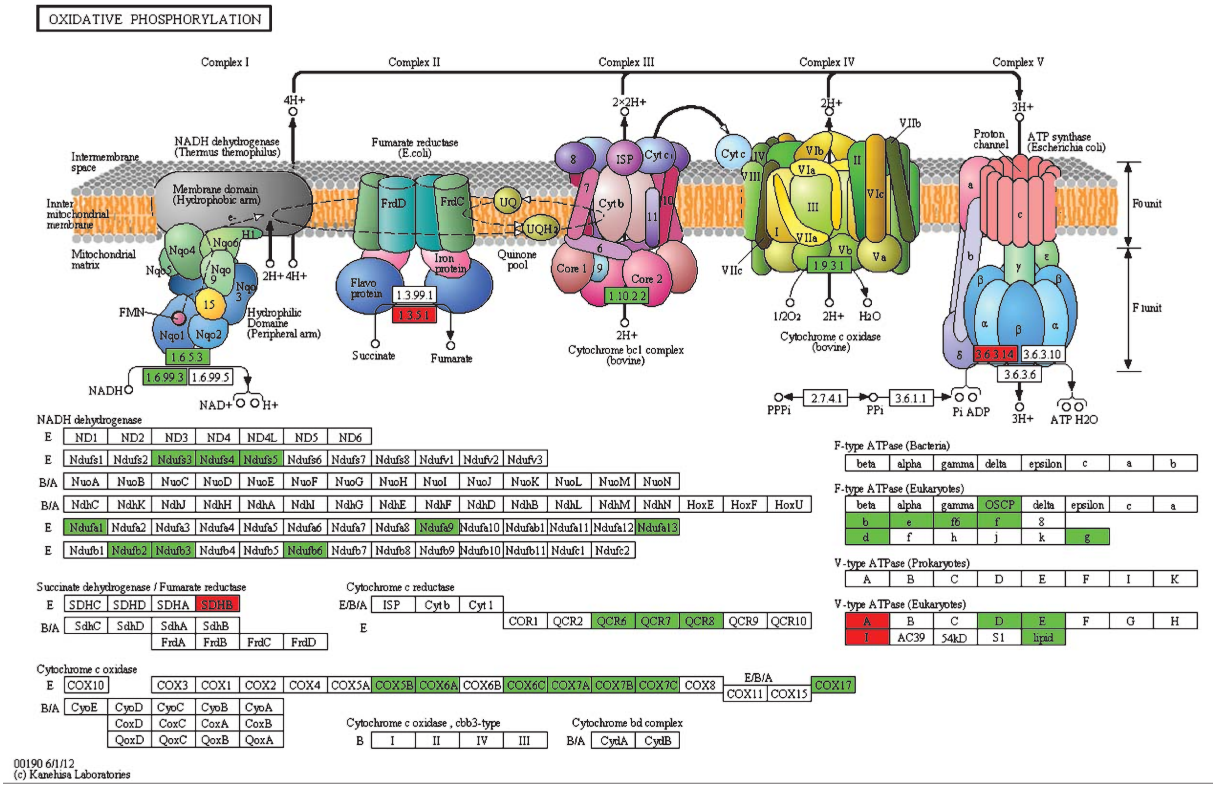
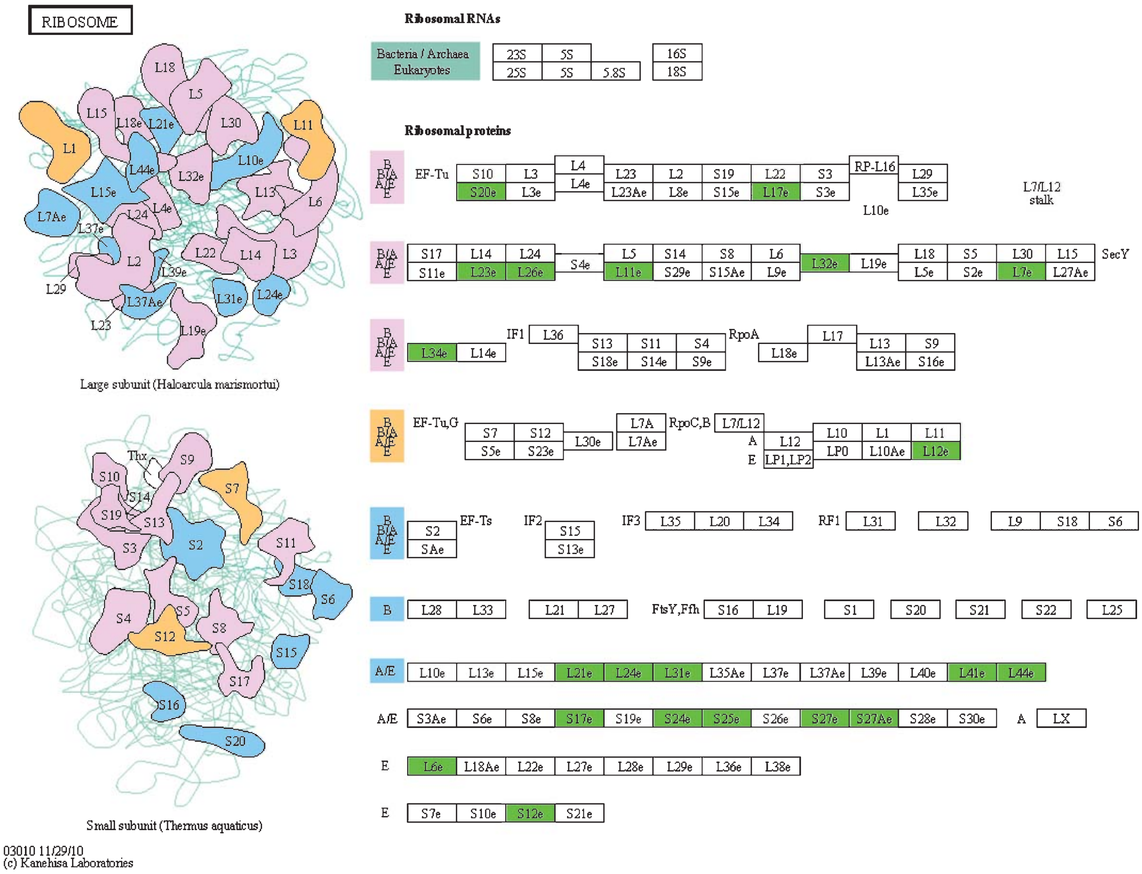
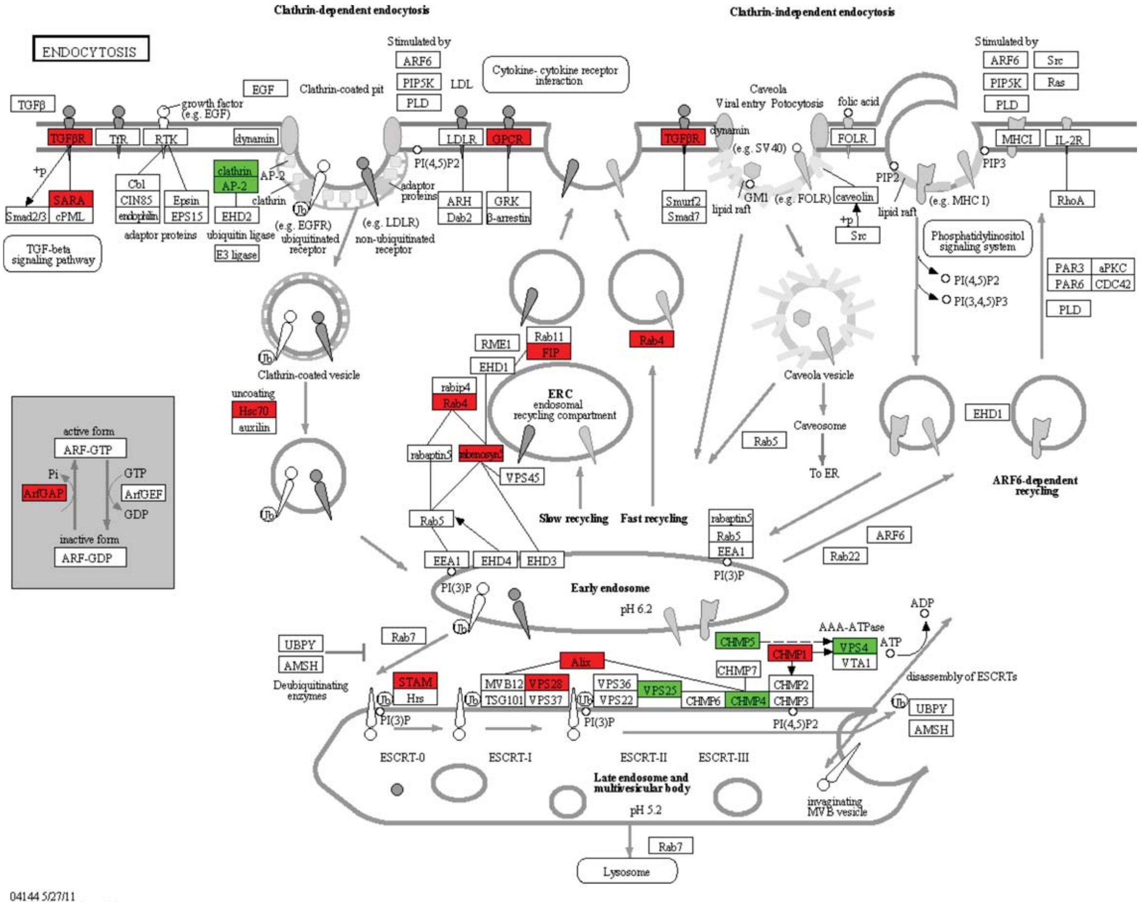


Supplementary Figure 1. Perturbation of oxidative phosphorylation (KEGG map) in the study by Hodges and coworkers. Genes are painted red for up-regulation or green for down-regulation. For details regarding the KEGG maps please refer to the KEGG website.



Supplementary Figure 2. Perturbation of ribosome (KEGG map) in the study by Hodges and coworkers.



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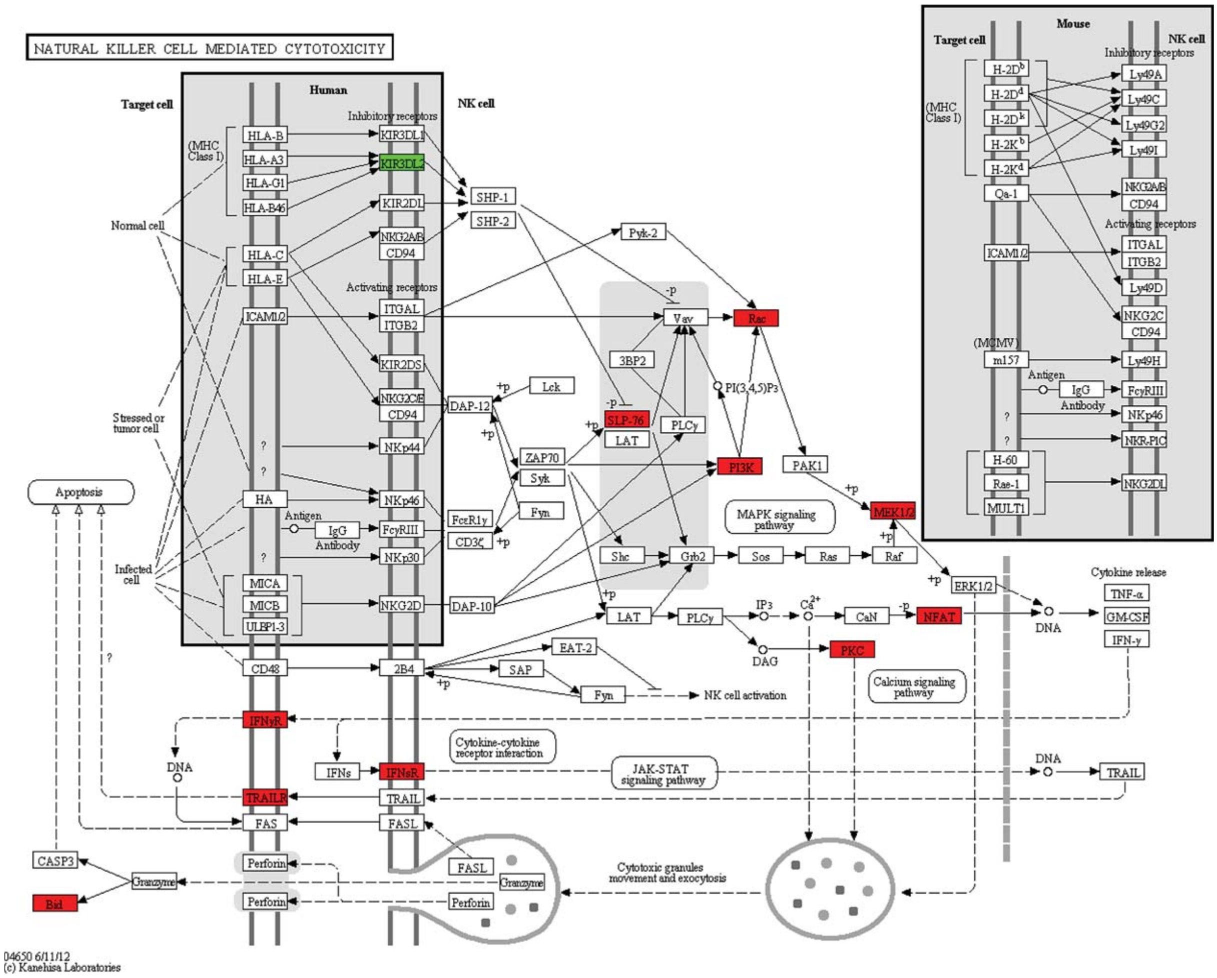
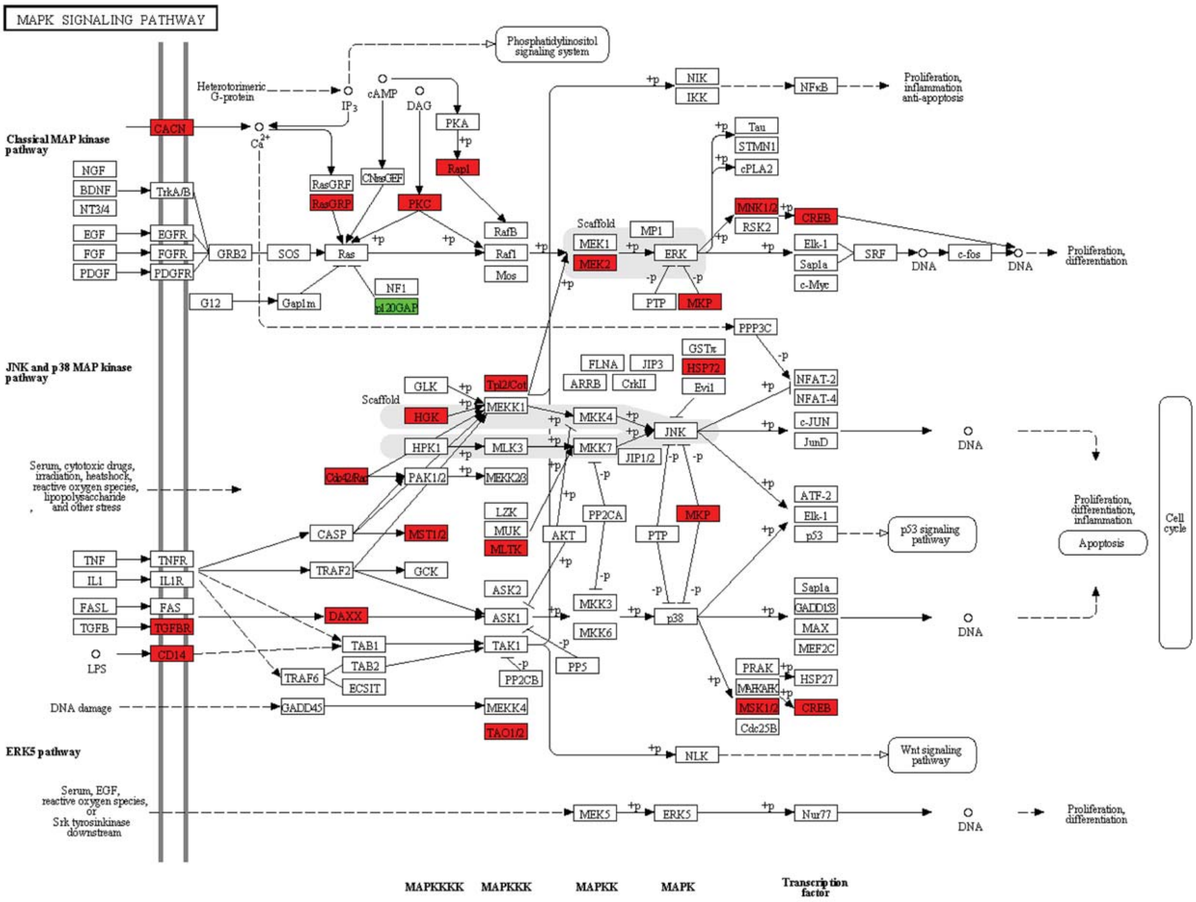
Supplementary Figure 3. Perturbation of endocytosis (KEGG map) in the study by Hodges and coworkers.



Supplementary Figure 4. Perturbation of natural killer cell mediated cytotoxicity (KEGG map) in the study by Hodges and coworkers.



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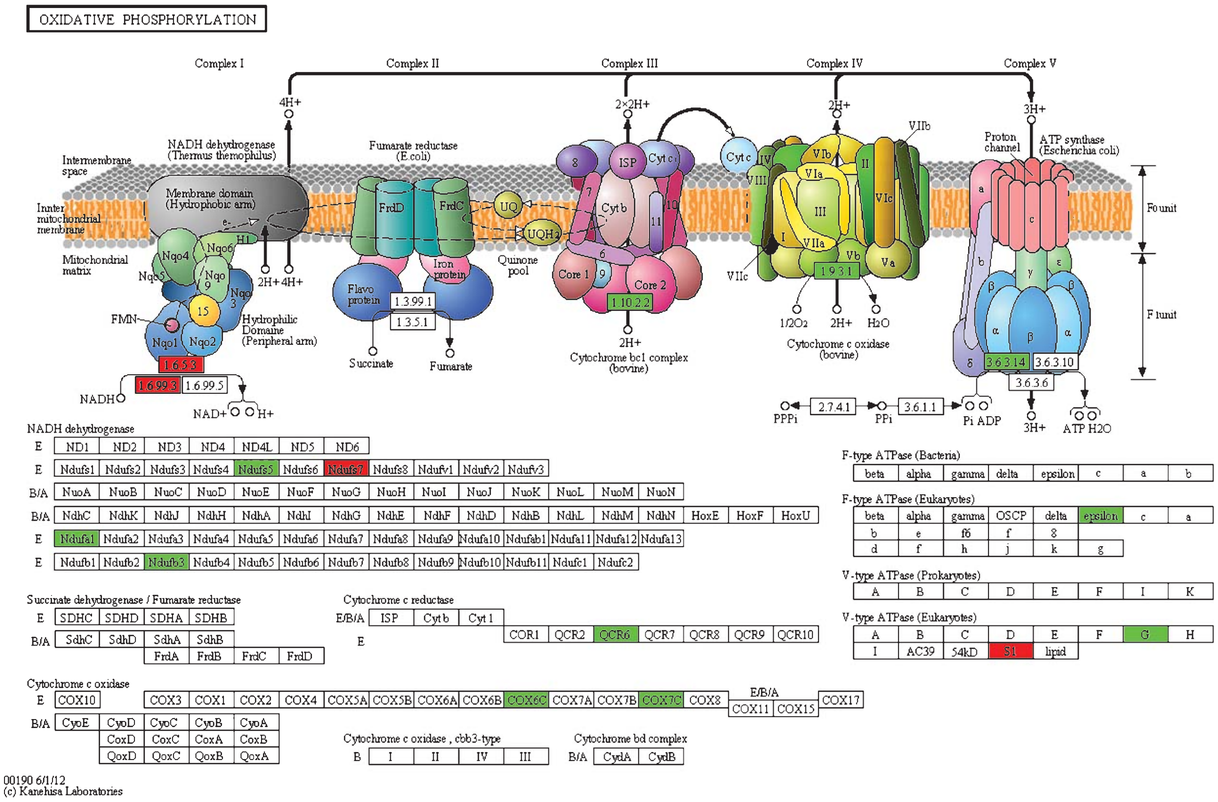
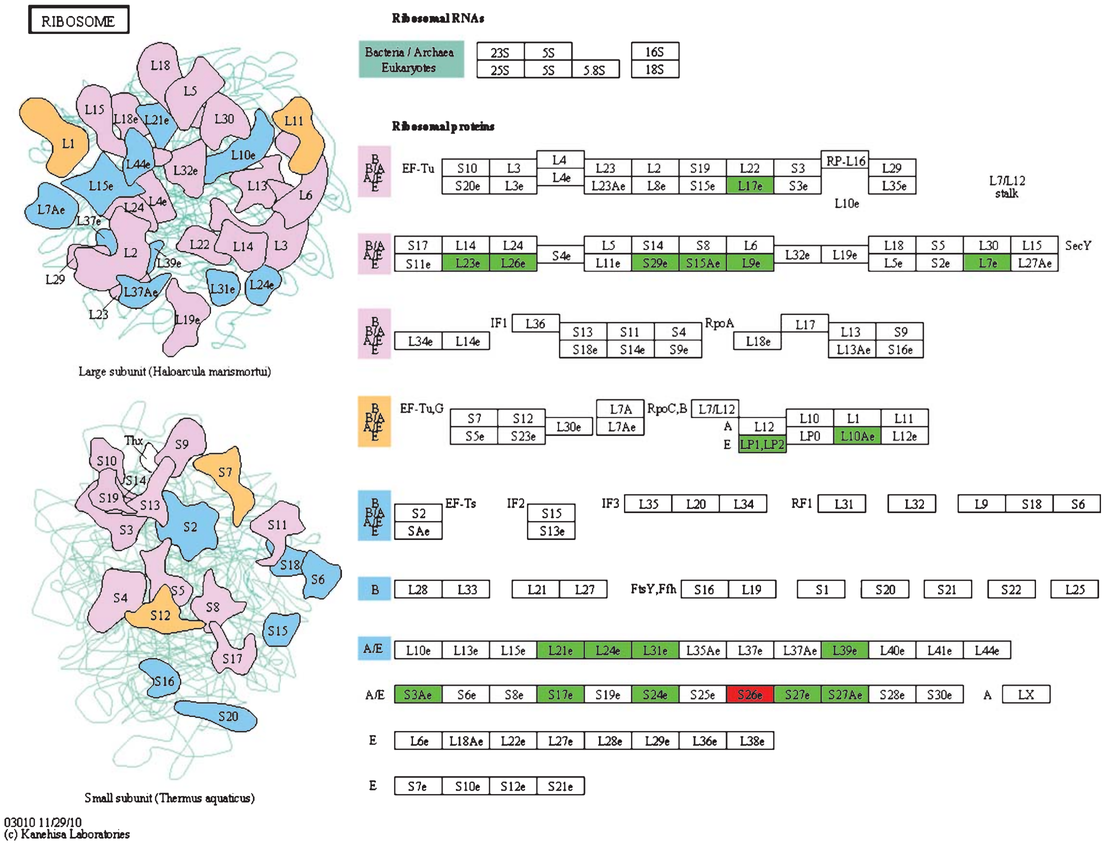
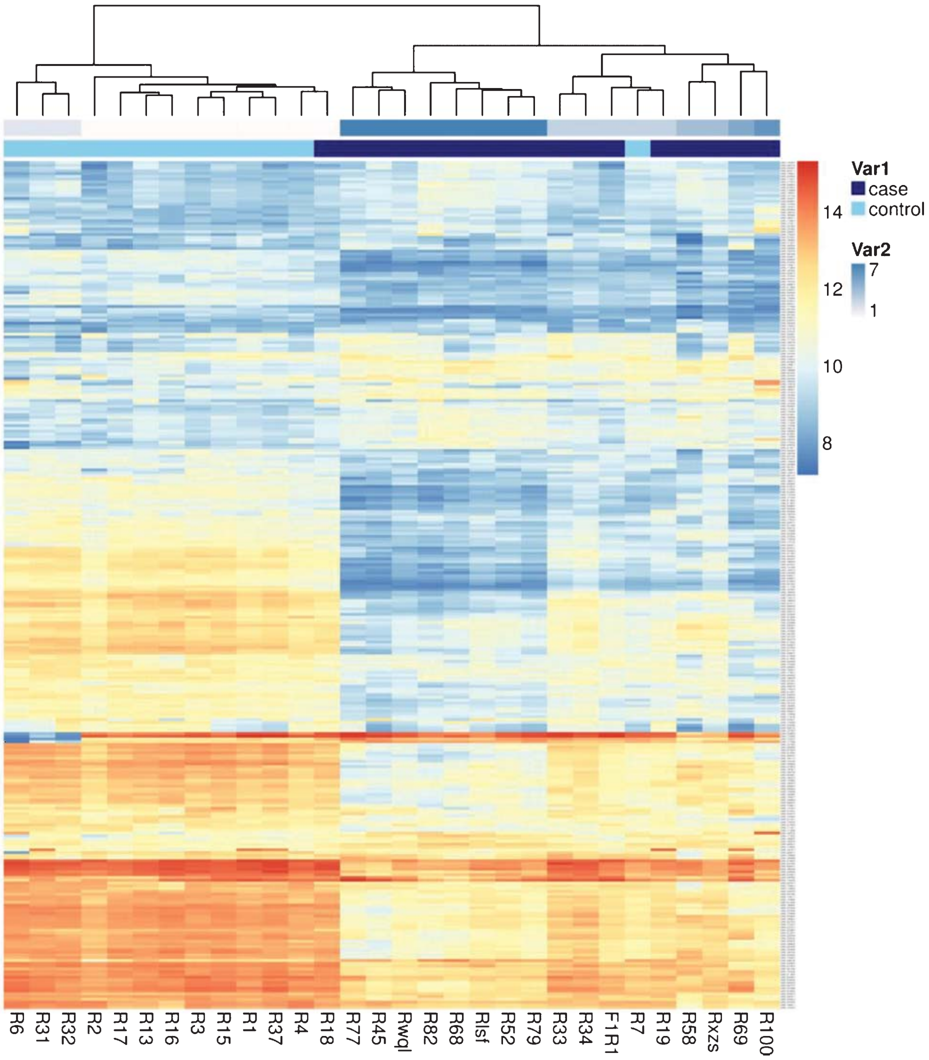
Supplementary Figure 5. Perturbation of MAPK signaling pathway (KEGG map) in the study by Hodges and coworkers.



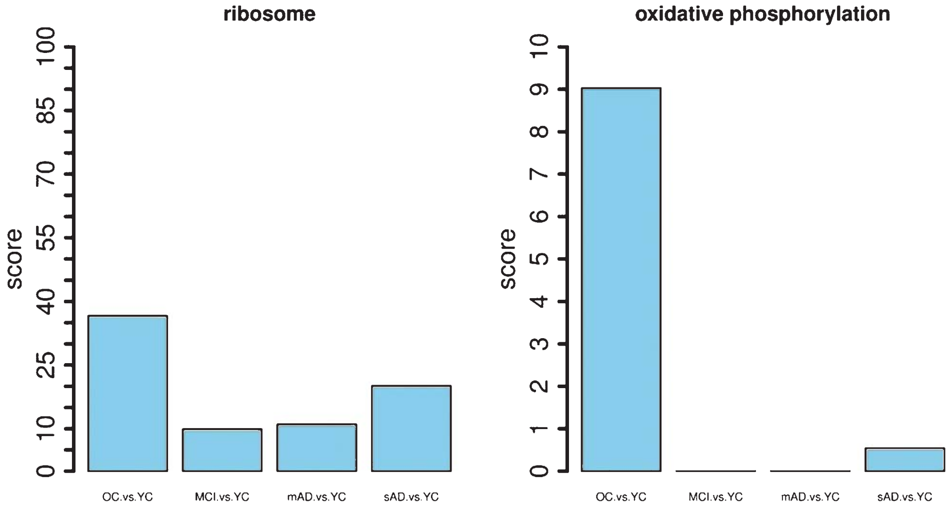
Supplementary Figure 6. Perturbation of oxidative phosphorylation (KEGG map) in our experiment.



Supplementary Figure 7. Perturbation of ribosome (KEGG map) in our experiment.



Supplementary Figure 8. Classification of the MCI patients and normal elderly controls in our experiment. The expression value of the probes for differentially expressed genes were used in the automatic clustering of the 17 MCI samples (dark blue bar at the top) and 13 control samples (light blue bar). Sample IDs are shown at the bottom.



Supplementary Figure 9. Dynamic perturbation of blood transcriptome during the progression of AD. The enrichment scores are converted from p-values of functional enrichment for ribosome or oxidative phosphorylation. The normal elderly controls and three stages of the disease (MCI, mAD and sAD) are compared with young controls separately. Please note the different scales of scores for the two functional categories.

Supplementary Table 1A

. Original datasets for blood transcriptome studies under various disease conditions examined in this work

	Diseases	GEO	Platform	Case\Control	Date	Tissue
Neurological	Alzheimer's disease (AD)	GSE4229	GPL1211	18\22	2006	PBMC
		GSE6613	GPL96	23\22	2006	blood
	Parkinson's disease (PD)	GSE6613	GPL96	50\22	2006	blood
	Huntington's disease (HD)	GSE1751	GPL96	12\14	2007	blood
		GSE8762	GPL570	12\10	2008	lymphocyte
	Autism (ATS)	GSE6575	GPL570	18\12	2006	whole blood
		GSE26415	GPL6480	21\42	2011	whole blood
		GSE25507	GPL570	82\64	2010	leukocyte
	Biopolar Disorder (BP)	GSE39653	GPL10558	8\24	2012	PBMC
	Scizophrenia (SZ)	GSE38481	GPL6883	15\22	2012	whole blood
		GSE38484	GPL6947	106\96	2012	whole blood
	Multiple Sclerosis (MS)	GSE21942	GPL570	12\15	2011	PBMC
		GSE17048	GPL6947	99\45	2009	whole blood
	Narcoleptic (N)	GSE21592	GPL571	10\10	2010	whole blood
	Major depressive disorder (MDD)	GSE19738	GPL6848	33\34	2010	whole blood
		GSE32280	GPL570	8\8	2012	lymphocyte
	Subsyndromal symptomatic depression (SSD)	GSE32280	GPL570	8\8	2012	lymphocyte
Cancer	Breast caner (BC)	GSE27562	GPL570	37\31	2011	PBMCs
	Colorectal cancer (CRC)	GSE10715	GPL570	7\11	2009	PB
	Lung adenocarcinoma (LA)	GSE20189	GPL571	73\80	2011	whole blood
Metabolic	Obesity (O)	E-MTAB-54	GPL570	49\25	2010	blood
	Diabete (D)	GSE9006	GPL96	12\24	2007	PBMC
Autoimmunity	Systemic lupus erythematosus (SLE)	GSE11907	GPL96	108\10	2008	PBMC
Infection	Septic shock (SS)	GSE26440	GPL570	98\32	2011	whole blood
Cardiovascular	Ischemic stroke (IS)	GSE22255	GPL570	20\20	2010	PBMC
Inflammation	Arthritis (A)	GSE13501	GPL570	45\59	2008	PBMC
	Ankylosing spondylitis (AS)	GSE25101	GPL6947	16\16	2010	whole blood

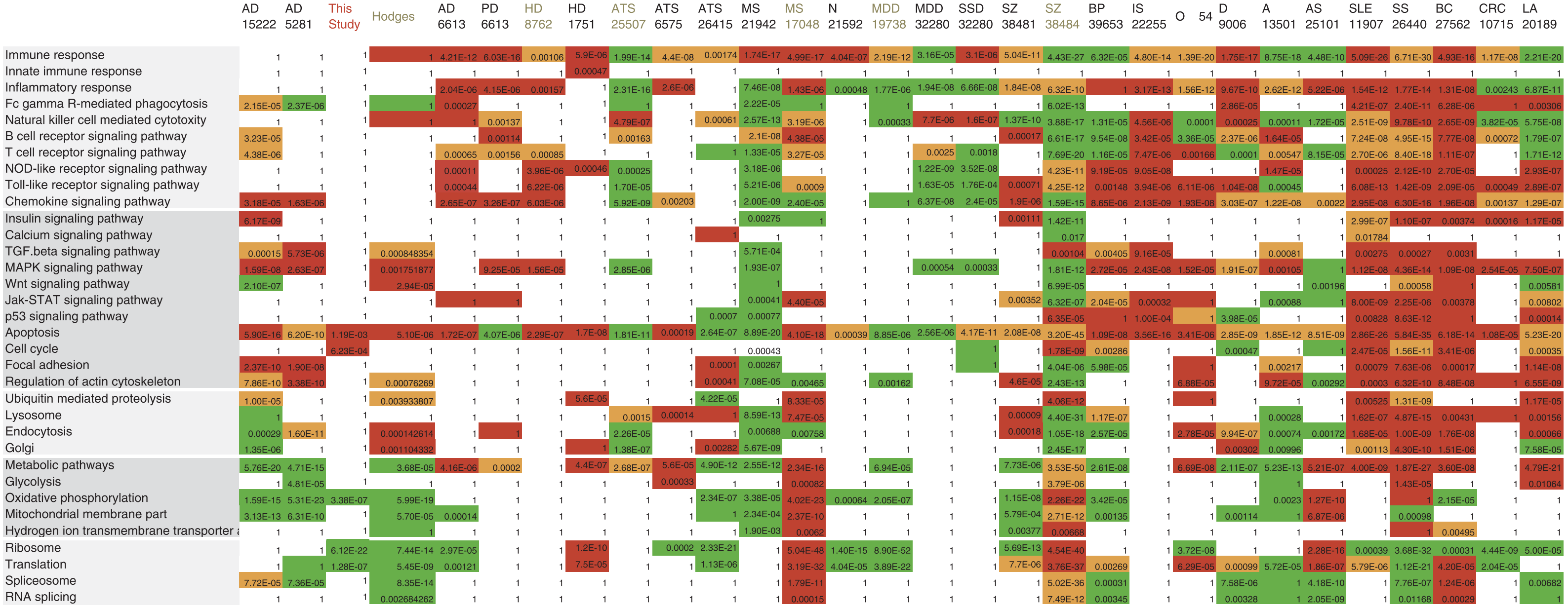
Supplementary Table 1B

. Enriched functional categories in the five published studies on AD blood transcriptome

Functional term	Source	Category
Immune_response	GOBP	Immune response
Innate_immune_response	GOBP	Immune response
Inflammatory_response	GOBP	Immune response
Fc_gamma_R-mediated_phagocytosis	KEGG	Immune response
Natural_killer_cell_mediated_cytotoxity	KEGG	Immune response
B_cell_receptor_signaling_pathway	KEGG	Immune response
T_cell_receptor_signaling_pathway	KEGG	Immune response
NOD-like_receptor_signaling_pathway	KEGG	Immune response
Toll-like_receptor_signaling_pathway	KEGG	Immune response
Chemokine_signaling_pathway	KEGG	Immune response
Insulin_signaling_pathway	KEGG	Survival/death signaling
Calcium_signaling_pathway	KEGG	Survival/death signaling
TGF.beta_signaling_pathway	KEGG	Survival/death signaling
MAPK_signaling_pathway	KEGG	Survival/death signaling
Wnt_signaling_pathway	KEGG	Survival/death signaling
Jak-STAT_signaling_pathway	KEGG	Survival/death signaling
p53_signaling_pathway	KEGG	Survival/death signaling
Apoptosis	GOBP	Survival/death signaling
Cell_cycle	KEGG	Survival/death signaling
Focal_adhesion	KEGG	Survival/death signaling
Regulation_of_actin_cytoskeleton	KEGG	Survival/death signaling
Ubiquitin_mediated_proteolysis	KEGG	Cellular recycling
Endocytosis	KEGG	Cellular recycling
Lysosome	KEGG	Cellular recycling
Golgi	GOCC	Cellular recycling
Metabolic_pathways	KEGG	Energy metabolism
Glycolysis	KEGG	Energy metabolism
Oxidative_phosphorylation	KEGG	Energy metabolism
Mitochondrial_membrane_part	GOCC	Energy metabolism
Hydrogen_ion_transmembrane_transporter_activity	GOMF	Energy metabolism
Ribosome	KEGG	Translation/splicing
Translation	GOBP	Translation/splicing
Spliceosome	KEGG	Translation/splicing
RNA_splicing	GOBP	Translation/splicing

Supplementary Table 1C

Perturbation of selected functional categories in AD and other diseases, the first two columns are for brain transcriptome, the rest are for blood transcriptome



	AD 15222	AD 5281	This Study	Hodges	AD 6613	PD 6613	HD 8762	HD 1751	ATS 25507	ATS 6575	ATS 26415	MS 21942	MS 17048	N 21592	MDD 19738	MDD 32280	SSD 32280	SZ 38481	SZ 38484	BP 39653	IS 22255	O 54	D 9006	A 13501	AS 25101	SLE 11907	SS 26440	BC 27562	CRC 10715	LA 20189
Immune response	1	1	1	1	4.21E-12	6.03E-16	0.00106	5.9E-06	1.99E-14	4.4E-08	0.00174	1.74E-17	4.99E-17	4.04E-07	2.19E-12	3.16E-05	3.1E-06	5.04E-11	4.43E-27	6.32E-05	4.80E-14	1.39E-20	1.75E-17	8.75E-18	4.48E-10	5.09E-26	6.71E-30	4.93E-16	1.17E-08	2.21E-20
Innate immune response	1	1	1	1	1	1	1	0.00047	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Inflammatory response	1	1	1	1	2.04E-06	4.15E-06	0.00157	1	2.31E-16	2.6E-06	1	7.46E-08	1.43E-06	0.00048	1.77E-06	1.94E-08	6.66E-08	1.84E-08	6.32E-10	1	3.17E-13	1.56E-12	9.67E-10	2.62E-12	5.22E-06	1.54E-12	1.77E-14	1.31E-08	0.00243	6.87E-11
Fc gamma R-mediated phagocytosis	2.15E-05	2.37E-06	1	1	0.00027	1	1	1	1	1	1	2.22E-05	1	1	1	1	1	1	6.02E-13	1	1	1	2.86E-05	1	1	4.21E-07	2.40E-11	6.28E-06	1	0.00306
Natural killer cell mediated cytotoxity	1	1	1	1	1	0.00137	1	1	4.79E-07	1	0.00061	2.57E-13	3.19E-06	1	0.00033	7.7E-06	1.6E-07	1.37E-10	3.88E-17	1.31E-05	4.56E-06	0.0001	0.00025	0.00011	1.72E-05	2.51E-09	9.78E-10	2.65E-09	3.82E-05	5.75E-08
B cell receptor signaling pathway	3.23E-05	1	1	1	1	0.00114	1	1	0.00163	1	1	2.1E-08	4.38E-05	1	1	1	1	0.00017	6.61E-17	9.54E-08	3.42E-05	3.36E-05	2.37E-06	1.64E-05	1	7.24E-08	4.95E-15	7.77E-08	0.00072	1.79E-07
T cell receptor signaling pathway	4.38E-06	1	1	1	0.00065	0.00156	0.00085	1	1	1	1	1.33E-05	3.27E-05	1	1	0.0025	0.0018	1	7.69E-20	1.16E-05	7.47E-06	0.00166	0.0001	0.00547	8.15E-05	2.70E-06	8.40E-18	1.11E-07	1	1.71E-12
NOD-like receptor signaling pathway	1	1	1	1	0.00011	1	3.96E-06	0.00046	0.00025	1	1	3.18E-06	1	1	1	1.22E-09	3.52E-08	1	4.23E-11	9.19E-05	9.05E-08	1	1	1.47E-05	1	0.00025	2.12E-10	2.70E-05	1	2.93E-07
Toll-like receptor signaling pathway	1	1	1	1	0.00044	1	6.22E-06	1	1.70E-05	1	1	5.21E-06	0.0009	1	1	1.63E-05	1.76E-04	0.00071	4.25E-12	0.00148	3.94E-06	6.11E-06	1.04E-08	0.00045	1	6.08E-13	1.42E-09	2.09E-05	0.00049	2.89E-07
Chemokine signaling pathway	3.18E-05	1.63E-06	1	1	2.65E-07	3.26E-07	6.03E-06	1	5.92E-09	0.00203	1	2.00E-09	2.40E-05	1	1	6.37E-08	2.4E-05	1.9E-06	1.59E-15	8.65E-06	2.13E-09	1.93E-08	3.03E-07	1.22E-08	0.0022	2.95E-08	6.30E-16	1.96E-08	0.00137	1.29E-07
Insulin signaling pathway	6.17E-09	1	1	1	1	1	1	1	1	1	1	0.00275	1	1	1	1	1	0.00111	1.42E-11	1	1	1	1	1	1	2.99E-07	1.10E-07	0.00374	0.00016	1.17E-05
Calcium signaling pathway	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0.017	1	1	1	1	1	1	0.01784	1	1	1	1
TGF.beta signaling pathway	0.00015	5.73E-06	1	0.000848354	1	1	1	1	1	1	1	5.71E-04	1	1	1	1	1	1	0.00104	0.00405	9.16E-05	1	1	0.00081	1	0.00275	0.00027	0.0031	1	1
MAPK signaling pathway	1.59E-08	2.63E-07	1	0.001751877	1	9.25E-05	1.56E-05	1	2.85E-06	1	1	1.93E-07	1	1	1	0.00054	0.00033	1	1.81E-12	2.72E-05	2.43E-08	1.52E-05	1.91E-07	0.00105	1	1.12E-08	4.36E-14	1.09E-08	2.54E-05	7.50E-07
Wnt signaling pathway	2.10E-07	1	1	2.94E-05	1	1	1	1	1	1	1	1	1	1	1	1	1	1	6.99E-05	1	1	1	1	1	0.00196	1	0.00058	1	1	0.00581
Jak-STAT signaling pathway	1	1	1	1	1	1	1	1	1	1	1	0.00041	4.40E-05	1	1	1	1	0.00352	6.32E-07	2.04E-05	0.00032	1	1	0.00088	1	8.00E-09	2.25E-06	0.00378	1	0.00802
p53 signaling pathway	1	1	1	1	1	1	1	1	1	1	0.0007	0.00077	1	1	1	1	1	1	6.35E-05	1	1.00E-04	1	3.98E-05	1	1	0.00828	8.63E-12	1	1	0.00014
Apoptosis	5.90E-16	6.20E-10	1.19E-03	5.10E-06	1.72E-07	4.07E-06	2.29E-07	1.7E-08	1.81E-11	0.00019	2.64E-07	8.89E-20	4.10E-18	0.00039	8.85E-06	2.56E-06	4.17E-11	2.08E-08	3.20E-45	1.09E-08	3.56E-16	3.41E-06	2.85E-09	1.85E-12	8.51E-09	2.86E-26	5.84E-35	6.18E-14	1.08E-05	5.23E-20
Cell cycle	1	1	6.23E-04	1	1	1	1	1	1	1	1	0.00043	1	1	1	1	1	1	1.78E-09	0.00286	1	1	0.00047	1	1	2.47E-05	1.56E-11	3.41E-06	1	0.00035
Focal adhesion	2.37E-10	1.90E-08	1	1	1	1	1	1	1	1	0.0001	0.00267	1	1	1	1	1	1	4.04E-06	5.98E-05	1	1	1	0.00217	1	0.00079	7.63E-06	0.00017	1	1.14E-08
Regulation of actin cytoskeleton	7.86E-10	3.38E-10	1	0.00076269	1	1	1	1	1	1	0.00041	7.08E-05	0.00465	1	0.00162	1	1	4.6E-05	2.43E-13	1	1	6.88E-05	1	9.72E-05	0.00292	0.0003	6.32E-10	8.48E-08	1	6.55E-09
Ubiquitin mediated proteolysis	1.00E-05	1	1	0.003933807	1	1	1	5.6E-05	1	1	4.22E-05	1	8.33E-05	1	1	1	1	1	4.06E-12	1	1	1	1	1	1	0.00525	1.31E-09	1	1	1.17E-05
Lysosome	1	1	1	1	1	1	1	1	0.0015	0.00014	1	8.59E-13	7.47E-05	1	1	1	1	0.00009	4.40E-31	1.17E-07	1	1	1	0.00028	1	1.62E-07	4.87E-15	0.00431	1	0.00156
Endocytosis	0.00029	1.60E-11	1	0.000142614	1	1	1	1	2.26E-05	1	1	0.00688	0.00758	1	1	1	1	0.00018	1.05E-18	2.57E-05	1	2.78E-05	9.94E-07	0.00074	0.00172	1.68E-05	1.00E-09	1.76E-08	1	0.00066
Golgi	1.35E-06	1	1	0.001104332	1	1	1	1	1.38E-07	1	0.00282	5.67E-09	1	1	1	1	1	1	2.45E-17	1	1	1	0.00302	0.00996	1	0.00113	4.30E-10	1.51E-06	1	7.58E-05
Metabolic pathways	5.76E-20	4.71E-15	1	3.68E-05	4.16E-06	0.0002	1	4.4E-07	2.68E-07	5.6E-05	4.90E-12	2.55E-12	2.34E-16	1	6.94E-05	1	1	7.73E-06	3.53E-50	2.61E-08	1	6.69E-08	2.11E-07	5.23E-13	5.21E-07	4.00E-09	1.87E-27	3.60E-08	1	4.79E-21
Glycolysis	1	4.81E-05	1	1	1	1	1	1	1	0.00033	1	1	0.00082	1	1	1	1	1	3.79E-06	1	1	1	1	1	1	1	1.43E-05	1	1	0.01064
Oxidative phosphorylation	1.59E-15	5.31E-23	3.38E-07	5.99E-19	1	1	1	1	1	1	2.34E-07	3.38E-05	4.02E-23	0.00064	2.05E-07	1	1	1.15E-08	2.26E-22	3.42E-05	1	1	1	0.0023	1.27E-10	1	1	2.15E-05	1	1
Mitochondrial membrane part	3.13E-13	6.31E-10	1	5.70E-05	0.00014	1	1	1	1	1	1	2.34E-04	2.37E-10	1	1	1	1	5.79E-04	2.71E-12	0.00135	1	1	0.00114	1	6.87E-06	1	0.00098	1	1	1
Hydrogen ion transmembrane transporter a	1	1	1	1	1	1	1	1	1	1	1	1.90E-03	0.0062	1	1	1	1	0.00377	0.00668	1	1	1	1	1	1	1	1	0.00495	1	1
Ribosome	1	1	6.12E-22	7.44E-14	2.97E-05	1	1	1.2E-10	1	0.0002	2.33E-21	1	5.04E-48	1.40E-15	8.90E-52	1	1	5.69E-13	4.54E-40	1	1	3.72E-08	1	1	2.28E-16	0.00039	3.68E-32	0.00031	4.44E-09	5.00E-05
Translation	1	1	1.28E-07	5.45E-09	0.00121	1	1	7.5E-05	1	1	1.13E-06	1	3.19E-32	4.04E-05	3.89E-22	1	1	7.7E-06	3.76E-37	0.00269	1	6.29E-05	0.00099	5.72E-05	1.86E-07	5.79E-06	1.12E-21	4.20E-05	2.04E-05	1
Spliceosome	7.72E-05	7.36E-05	1	8.35E-14	1	1	1	1	1	1	1	1	1.79E-11	1	1	1	1	1	5.02E-36	0.00031	1	1	7.58E-06	1	4.18E-10	1	7.76E-07	1.24E-06	1	0.00682
RNA splicing	1	1	1	0.002684262	1	1	1	1	1	1	1	1	0.00015	1	1	1	1	1	7.49E-12	0.00345	1	1	0.00328	1	2.05E-09	1	0.01168	0.00029	1	1

Note: overall p-values are shown in the cells. Directional dys-regulation is indicated by color, red for up-regulation, green for down-regulation, and yellow for both or neither.

Supplementary Table 2A

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Sample information for each group of patients or controls

	gender ratio (F/M)	age	MMSE	CDR
Young Control (YC)	6/6	26±3.19	30±0	0
Old Control (OC)	7/6	76.46±11.31	29.46±0.66	0
Mild Cognitive Impairment (MCI)	11/6	73.94±10.07	25.12±2.50	0.5
mild to moderate AD (mAD)	4/8	69.17±9.36	14.58±6.43	1 - 2
severe AD (sAD)	10/7	74.75±9.61	9.06±5.60	3
AD (mAD + sAD)	14/15			
patients (MCI + AD)	25/21			

Note: all subjects are Chinese

Supplementary Table 2B

Perturbation of selected functional categories in various sub-groups of AD patients compared to normal elderly controls

	AD.vs.OC			patients.vs.OC			sAD.vs.OC			mAD.vs.OC		
	UP	DN	ALL	UP	DN	ALL	UP	DN	OC2sAD	UP	DN	OC2mAD
immune_response	1	1	1	1	1	1	1	1	1	1	1	1
innate_immune_response	1	1	1	1	1	1	1	1	1	1	1	1
inflammatory_response	1	1	1	1	1	1	1	1	1	1	1	1
Fc_gamma_R-mediated_phagocytosis	1	1	1	1	1	1	1	1	1	1	1	1
natural_killer_cell_mediated_cytotoxity	1	1	1	1	1	1	1	1	1	1	1	1
B_cell_receptor_signaling_pathway	1	1	1	1	1	1	1	1	1	1	1	1
T_cell_receptor_signaling_pathway	1	1	1	1	1	1	1	1	1	1	1	1
NOD-like_receptor_signaling_pathway	1	1	1	1	1	1	1	1	1	1	1	1
Toll-like_receptor_signaling_pathway	1	1	1	0.0007572	1	1	1	1	1	1	1	1
chemokine_signaling_pathway	1	1	1	1	1	1	1	1	1	1	1	1
insulin_signaling_pathway	1	1	1	1	1	1	1	1	1	1	1	1
calcium_signaling_pathway	1	1	1	1	1	1	1	1	1	1	1	1
TGF.beta_signaling_pathway	1	1	1	1	1	1	1	1	1	1	1	1
MAPK_signaling_pathway	1	1	1	1	1	1	1	1	1	1	1	1
Wnt_signaling_pathway	1	1	1	1	1	1	1	1	1	1	1	1
Jak-STAT_signaling_pathway	1	1	1	1	1	1	1	1	1	1	1	1
p53_signaling_pathway	1	1	1	1	1	1	1	1	1	1	1	1
opoptosis	0.0007538	1	0.0011903	1.928E-06	1	7.819E-06	1	1	1	1	1	0.0006349
cell_cycle	0.0002972	1	0.0006234	0.002009	1	1	1	1	1	1	1	1
focal_adhesion	1	1	1	0.000518	1	1	1	1	1	1	1	1
regulation_of_actin_cytoskeleton	1	1	1	0.0007953	1	1	1	1	1	1	1	1
ubiquitin_mediated_proteolysis	1	1	1	1	1	1	1	1	1	1	1	1
lysosome	1	1	1	0.0002116	1	1	1	1	1	1	1	1
endocytosis	1	1	1	1	1	1	1	1	1	1	1	1
golgi	1	1	1	1	1	1	1	1	1	1	1	1
metabolic_pathways	1	1	1	1	1	1	1	1	1	1	1	1
glycolysis	1	1	1	1	1	1	1	1	1	1	1	1
oxidative_phosphorylation	1	3.049E-07	3.383E-07	1	1	9.11E-05	1	1.99E-06	7.671E-07	1	0.0001078	8.37E-05
mitochondrial_membrane_part	1	1	1	1	1	1	1	1	1	1	1	1
hydrogen_ion_transmembrane_transporter_activity	1	1	1	1	1	1	1	1	1	1	1	1
ribosome	1	5.29E-25	6.116E-22	1	1.018E-21	1.625E-17	1	4.548E-19	5.475E-16	1	2.341E-23	1.446E-22
translation	1	3.535E-06	1.283E-07	0.0015645	3.535E-06	2.612E-08	1	1.954E-06	1.543E-06	1	2.671E-08	4.457E-07
spliceosome	1	1	1	1	1	1	1	1	1	1	1	1
RNA_splicing	1	1	1	1	1	1	1	1	1	1	1	1

Supplementary Table 2C
Perturbation of selected functional categories during the disease progression

	MCI.vs.OC			mAD.vs.MCI			sAD.vs.mAD			sAD.vs.MCI			AD.vs.MCI		
	UP	DN	ALL	UP	DN	ALL	UP	DN	ALL	UP	DN	ALL	UP	DN	ALL
immune_response	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
innate_immune_response	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
inflammatory_response	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Fc_gamma_R-mediated_phagocytosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
natural_killer_cell_mediated_cytotoxity	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
B_cell_receptor_signaling_pathway	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
T_cell_receptor_signaling_pathway	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
NOD-like_receptor_signaling_pathway	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Toll-like_receptor_signaling_pathway	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
chemokine_signaling_pathway	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
insulin_signaling_pathway	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
calcium_signaling_pathway	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
TGF.beta_signaling_pathway	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
MAPK_signaling_pathway	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Wnt_signaling_pathway	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Jak-STAT_signaling_pathway	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
p53_signaling_pathway	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
opoptosis	1	1	1	1	1	1	1	1	1	1	0.00152374	1	1	1	1
cell_cycle	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
focal_adhesion	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
regulation_of_actin_cytoskeleton	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
ubiquitin_mediated_proteolysis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
lysosome	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
endocytosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
golgi	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
metabolic_pathways	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
glycolysis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
oxidative_phosphorylation	1	0.0001685	0.0008076	1	1	1	1	1	1	1	1	1	1	1	1
mitochondrial_membrane_part	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
hydrogen_ion_transmembrane_transporter_activity	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
ribosome	1	2.26E-29	1.81E-26	1	0.0006018	0.0006976	2.49E-13	1	2.01E-15	1.157E-17	1	1.2444E-17	8.2312E-15	1	2.2509E-15
translation	1	8.10E-11	2.38E-11	1	1	1	1.50E-06	1	3.43E-06	7.6218E-06	1	3.9026E-05	1.1489E-05	1	3.532E-05
spliceosome	1	1	1	1	1	1	1	1	1	1	5.6537E-06	1	1	1	1
RNA_splicing	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

Supplementary Table 2D

Perturbation of selected functional categories in old compared to young

	OC.vs.YC			mAD.vs.YC			sAD.vs.YC			AD.vs.YC			MCI.vs.YC			patients.vs.YC		
	UP	DN	ALL	UP	DN	ALL	UP	DN	ALL	UP	DN	ALL	UP	DN	ALL	UP	DN	ALL
immune_response	1	0.0027214	0.0053202	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
innate_immune_response	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
inflammatory_response	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Fc_gamma_R-mediated_phagocytosis	1	3.09E-08	2.29E-05	1	1	1	1	5.166E-06	0.0020692	1	8.9879E-06	1	1	1	1	1	0.00019767	1
natural_killer_cell_mediated_cytotoxity	1	0.0074036	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
B_cell_receptor_signaling_pathway	1	4.32E-05	0.000522	1	1	1	1	1	0.0017023	1	1	1	1	1	1	1	1	1
T_cell_receptor_signaling_pathway	1	6.58E-05	0.005373	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
NOD-like_receptor_signaling_pathway	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Toll-like_receptor_signaling_pathway	1	0.0018031	0.0133101	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
chemokine_signaling_pathway	1	8.50E-07	5.09E-06	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
insulin_signaling_pathway	1	0.0003415	0.007079	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
calcium_signaling_pathway	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
TGF.beta_signaling_pathway	1	0.0040937	0.0047576	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
MAPK_signaling_pathway	1	8.22E-06	0.0071596	1	0.0015251	1	1	7.092E-05	1	1	1	1	1	1	1	1	1	1
Wnt_signaling_pathway	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Jak-STAT_signaling_pathway	1	0.0001536	0.005283	1	1	1	1	1	1	1	1	1	1	0.00064044	1	1	1	1
p53_signaling_pathway	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
opoptosis	1	2.04E-06	9.62E-08	1	0.0007884	0.0006131	1	1.711E-08	6.376E-09	0.00129022	6.5529E-05	5.1307E-07	0.00038036	1	0.00010624	1	0.00143879	7.0146E-05
cell_cycle	1	0.000204	0.0012402	1	0.0003068	0.0005382	1	0.0003119	1	1	0.00046834	1	1	1	1	1	0.00093096	1
focal_adhesion	1	6.66E-10	2.50E-06	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
regulation_of_actin_cytoskeleton	1	4.58E-14	4.50E-12	1	0.0004765	1	1	0.0001526	0.0019316	1	0.00011905	1	1	1	1	1	1	1
ubiquitin_mediated_proteolysis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
lysosome	1	3.07E-06	0.0008557	1	1	1	1	0.0012133	1	1	0.00070999	1	1	1	1	1	1	1
endocytosis	1	5.47E-05	0.0016971	1	4.424E-05	0.0002274	1	1.985E-05	0.0003953	1	1.4091E-05	0.00188816	1	1	1	1	8.435E-05	1
golgi	1	0.0019636	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
metabolic_pathways	0.0014522	1	0.0001804	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
glycolysis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
oxidative_phosphorylation	4.58E-14	1	1.56E-12	0.0010103	1	1	1.18E-05	1	0.0005839	1.291E-09	1	1.8844E-07	1	1	1	1.5864E-09	1	7.6708E-08
mitochondrial_membrane_part	1	1	0.001296	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
hydrogen_ion_transmembrane_transporter_a	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
ribosome	5.73E-49	1	3.47E-40	3.82E-18	1	1.391E-14	8.012E-27	1	1.168E-23	1.6054E-33	1	1.4975E-29	1.612E-13	1	3.3644E-13	7.5333E-35	1	7.5803E-32
translation	6.84E-14	0.0004114	7.10E-16	2.916E-05	1	0.0005474	1.191E-10	1	1.126E-10	2.1471E-09	1	6.0447E-09	5.9551E-05	1	7.7781E-05	2.6896E-09	1	1.0265E-08
spliceosome	1	5.09E-06	6.71E-07	1	1	1	1	8.836E-06	0.0015429	1	7.7781E-05	1	1	1	1	1	0.00096967	1
RNA_splicing	1	8.91E-07	5.50E-06	1	1	1	1	1.434E-07	3.037E-05	1	2.975E-06	9.9576E-05	1	1	1	1	0.00079637	1

Supplementary Table 3A

. Datasets for blood transcriptome affected by various lifestyles examined in this study

Factor	GEO	Platform	Case\Control		Date	Tissue	Notes
Exercise	E-GEOD-1140	GPL96	exercise\no	5\5	2007	PBMC	male
	E-GEOD-14642	GPL570	exercise\no	10\10	2009	PBMC	girls
	E-GEOD-11761	GPL570	exercise\no	10\10	2008	PBMC	boys
Sleep loss	GSE37667	GPL570	simulated sleep loss\no	9\9	2012	whole blood	
Social isolation	E-GEOD-7148	GPL96	high isolation\low	7\7	2009	leukocyte	old people
Smoking	E-GEOD-12585	GPL96	heavy smoking\light	10\13	2008	lymphocyte	
Water	E-GEOD-3846	GPL96	12 hours after drinking\baseline	6\6	2005	leukocyte	
Red wine	E-GEOD-3846	GPL96	12 hours after drinking\baseline	6\6	2005	leukocyte	
Grape juice	E-GEOD-3846	GPL96	12 hours after drinking\baseline	4\5	2005	leukocyte	
Bilberry/grape juice	E-MTAB-274	GPL570	after drinking\before	10\10	2011	whole blood	old men(62-67)
High protein breakfast	E-TABM-271	HG-U133A_2	after eating\before	8\8	2008	whole blood	
High carbohybrate breakfast	E-TABM-271	HG-U133A_2	after eating\before	8\8	2008	whole blood	

Supplementary Table 3B

Major functional enrichment in the perturbation of blood transcriptome affected by various lifestyles

			Exercise			Smoking	Social isolation	Sleep loss	Food		Drink			
			Exercise 1140	Exercise 14642	Exercise 11761	Smoking 12585	Isolation 7148	Sleep 37667	Protein 271	Carbohydrate 271	Water 3846	Wine 3846	Juice 3846	Juice 274
Immune response	GOBP	Immune_response	5.04E-29	3.17E-14	1.98E-12	8.76E-10	1	1	7.27E-08	1.72E-08	1	1	1	1
	GOMF	immune_system_process	1.61E-29	7.67E-13	1.74E-12	2.63E-12	1	2.05E-05	3.35E-13	1.11E-10	1	1	1	1
	GOBP	Inflammatory_response	6.99E-12	1.18E-06	2.32E-05	6.33E-09	1	1	1.84E-09	0.00000129	1	1	1	1
	KEGG	B_cell_receptor_signaling_pathway	1	1.04E-08	0.00000023	2.52E-05	1	1	1	1	1	1	1	1
	KEGG	Natural_killer_cell_mediated_cytotoxity	2.85E-13	2.20E-13	2.66E-08	1	1	1	1	1	1	1	1	1
	KEGG	NOD-like_receptor_signaling_pathway	1	1	1	9.91E-06	1	1	1	1	1	1	1	1
	KEGG	Toll-like_receptor_signaling_pathway	0.000000449	1	1	2.45E-08	1	1	1	1	1	1	1	1
	KEGG	Chemokine_signaling_pathway	0.000159008	0.0000521	1	1	1	1	0.0000885	0.000183563	1	1	1	1
	NCI	Calcineurin_regulated_NFAT_dependent_transcription_in_lymphocytes	2.15E-08	3.60E-13	1.34E-09	5.88E-08	0.0001351	1	1	1	1	1	1	1
	NCI	IL12_mediated_signaling_events	8.64E-11	7.08E-13	4.12E-13	5.13E-08	1	1	7.83E-09	0.00000199	1	1	1	1
Survival/death signaling	KEGG	TGF beta_signaling_pathway	1	8.08E-05	1	1	1	1	1	1	1	1	1	1
	KEGG	MAPK_signaling_pathway	1.80E-07	1	1	4.90E-08	1	1	1	1	1	1	1	1
	KEGG	Jak-STAT_signaling_pathway	0.000000117	1	1	1	1	1	1	1	1	1	1	1
	GOBP	Apoptosis	4.99E-10	0.000000523	0.0000378	1	1	1	1	1	1	1	1	1
	GOBP	Cell_cycle	1	1	1	1	1	0.00000818	1	1	1	1	1	1
	KEGG	Focal_adhesion	1	1	1	0.000039	1	1	1	1	1	1	1	1
	GOCC	Cytoskeleton	1	1	1	1	1	0.000243938	1	1	1	1	1	1
	GOBP	response_to_stress	4.26E-11	8.45E-09	3.54E-05	1.32E-09	1	1	0.00000073	1	1	1	1	1