

Supplementary information

Enhancing mitochondrial proteostasis reduces amyloid- β proteotoxicity

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Supplementary Table 1. GSEA (Prefrontal cortex, Hallmark Gene Set, GN327-328)

Enrichment	Gene set	Size	ES	NES	NOM p-val	FDR q-val	FWER p-val	Rank at max
Upregulated	HALLMARK_P53_PATHWAY	188	0.46	1.77	0.011	0.209	0.084	5989
Upregulated	HALLMARK_INTERFERON_GAMMA_RESPONSE	191	0.59	1.73	0.034	0.147	0.115	4260
Upregulated	HALLMARK_IL6_JAK_STAT3_SIGNALING	87	0.61	1.72	0.022	0.108	0.125	4534
Upregulated	HALLMARK_INFLAMMATORY_RESPONSE	194	0.53	1.70	0.037	0.101	0.148	7297
Upregulated	HALLMARK_IL2_STAT5_SIGNALING	184	0.46	1.69	0.023	0.085	0.158	6692
Upregulated	HALLMARK_COMPLEMENT	197	0.46	1.66	0.047	0.091	0.200	5503
Upregulated	HALLMARK_COAGULATION	138	0.47	1.65	0.026	0.087	0.209	8601
Upregulated	HALLMARK_HYPOXIA	194	0.44	1.63	0.040	0.090	0.240	6455
Upregulated	HALLMARK_INTERFERON_ALPHA_RESPONSE	92	0.62	1.63	0.076	0.082	0.244	4556
Upregulated	HALLMARK_WNT_BETA_CATENIN_SIGNALING	41	0.45	1.54	0.043	0.136	0.371	5292
Upregulated	HALLMARK_EPITHELIAL_MESENCHYMAL_TRANSITION	196	0.49	1.54	0.084	0.126	0.377	9219
Upregulated	HALLMARK_ALLOGRAFT_REJECTION	197	0.43	1.53	0.072	0.120	0.388	4251
Upregulated	HALLMARK_TNFA_SIGNALING_VIA_NFKB	192	0.51	1.53	0.097	0.110	0.388	6307
Upregulated	HALLMARK_ESTROGEN_RESPONSE_EARLY	188	0.37	1.52	0.037	0.107	0.393	5160
Upregulated	HALLMARK_TGF_BETA_SIGNALING	52	0.50	1.51	0.081	0.104	0.405	7212
Upregulated	HALLMARK_NOTCH_SIGNALING	31	0.45	1.50	0.061	0.104	0.420	4966
Upregulated	HALLMARK_APICAL_SURFACE	43	0.41	1.50	0.043	0.101	0.424	3227
Upregulated	HALLMARK_APOPTOSIS	159	0.41	1.48	0.104	0.106	0.456	4291
Upregulated	HALLMARK_ESTROGEN_RESPONSE_LATE	196	0.34	1.42	0.077	0.145	0.565	6455
Upregulated	HALLMARK_MYOGENESIS	196	0.36	1.41	0.090	0.147	0.588	7436
Downregulated	HALLMARK_OXIDATIVE_PHOSPHORYLATION	196	-0.65	-1.82	0.008	0.058	0.076	5220
Downregulated	HALLMARK_SPERMATOGENESIS	126	-0.42	-1.71	0.006	0.089	0.170	7846
Downregulated	HALLMARK_MYC_TARGETS_V1	185	-0.48	-1.45	0.140	0.342	0.515	5995
Downregulated	HALLMARK_PANCREAS_BETA_CELLS	40	-0.38	-1.38	0.091	0.359	0.605	2754
Downregulated	HALLMARK_FATTY_ACID_METABOLISM	152	-0.34	-1.29	0.149	0.421	0.716	5372
Downregulated	HALLMARK_PROTEIN_SECRETION	94	-0.39	-1.26	0.252	0.401	0.752	6166
Downregulated	HALLMARK_DNA_REPAIR	142	-0.30	-1.17	0.262	0.478	0.839	6972
Downregulated	HALLMARK_MYC_TARGETS_V2	51	-0.38	-1.17	0.287	0.423	0.841	7167
Downregulated	HALLMARK_MTORC1_SIGNALING	193	-0.33	-1.16	0.284	0.387	0.846	5953
Downregulated	HALLMARK_REACTIVE_OXIGEN_SPECIES_PATHWAY	45	-0.33	-1.08	0.347	0.457	0.911	5220
Downregulated	HALLMARK_PI3K_AKT_MTOR_SIGNALING	96	-0.26	-1.04	0.387	0.470	0.933	4105
Downregulated	HALLMARK_UNFOLDED_PROTEIN_RESPONSE	108	-0.28	-1.01	0.419	0.466	0.944	5055
Downregulated	HALLMARK_E2F_TARGETS	181	-0.28	-0.88	0.567	0.604	0.977	5119
Downregulated	HALLMARK_HEDGEHOG_SIGNALING	36	-0.26	-0.86	0.633	0.592	0.982	5382
Downregulated	HALLMARK_G2M_CHECKPOINT	187	-0.21	-0.73	0.749	0.751	0.995	5309

Supplementary Table 2. GSEA (Prefrontal cortex, Reactome Gene Set, GN327-328)

Enrichment	Gene set	Size	ES	NES	NOM p-val	FDR q-val	FWER p-val	Rank at max
Upregulated	REACTOME_AMINO_ACID_TRANSPORT_ACROSS_THE_PLASMA_MEMBRANE	30	0.61	1.77	0.004	1.000	0.443	3744
Upregulated	REACTOME_INTEGRIN_CELL_SURFACE_INTERACTIONS	77	0.62	1.77	0.010	0.642	0.452	7259
Upregulated	REACTOME_SIGNALING_BY_ILS	101	0.48	1.75	0.027	0.554	0.523	5726
Upregulated	REACTOME_ANTIGEN_ACTIVATES_B_CELL_RECEPTOR_LEADING_TO_GENERATION_OF_SECOND_MESSENGERS	29	0.57	1.74	0.024	0.436	0.542	4955
Upregulated	REACTOME_INNATE_IMMUNE_SYSTEM	236	0.44	1.73	0.016	0.392	0.569	6330
Upregulated	REACTOME_CELL_SURFACE_INTERACTIONS_AT_THE_VASCULAR_WALL	85	0.53	1.72	0.028	0.349	0.584	7059
Upregulated	REACTOME_INTEGRIN_ALPHAIIIB_BETA3_SIGNALING	26	0.57	1.72	0.010	0.303	0.585	4885
Upregulated	REACTOME_COMPLEMENT_CASCADE	29	0.70	1.72	0.020	0.276	0.598	5627
Upregulated	REACTOME_YAP1_AND_WWTR1_TAZ_STIMULATED_GENE_EXPRESSION	23	0.65	1.70	0.008	0.277	0.636	4431
Upregulated	REACTOME_GPVI_MEDIATED_ACTIVATION_CASCADE	30	0.57	1.68	0.033	0.303	0.689	5503
Upregulated	REACTOME_PRE_NOTCH_TRANSCRIPTION_AND_TRANSLATION	24	0.59	1.67	0.020	0.310	0.717	5992
Upregulated	REACTOME_TRAF6_MEDIATED_IRF7_ACTIVATION	28	0.53	1.64	0.017	0.370	0.781	8204
Upregulated	REACTOME_TOLL_RECEPTOR_CASCADES	106	0.44	1.64	0.051	0.347	0.784	6330
Upregulated	REACTOME_TRAF6_MEDIATED_NFKB_ACTIVATION	20	0.64	1.63	0.021	0.342	0.795	9459
Upregulated	REACTOME_RNA_POL_I_PROMOTER_OPENING	56	0.60	1.62	0.049	0.332	0.805	10207
Upregulated	REACTOME_CHONDROITIN_SULFATE_DERMATAN_SULFATE_METABOLISM	39	0.54	1.62	0.032	0.312	0.807	4760
Upregulated	REACTOME_SMAD2_SMAD3_SMAD4_HETEROTRIMER_REGULATES_TRANSCRIPTION	25	0.57	1.61	0.053	0.337	0.832	6301
Upregulated	REACTOME_GROWTH_HORMONE_RECEPTOR_SIGNALING	23	0.57	1.60	0.037	0.326	0.837	10693
Upregulated	REACTOME_RIP_MEDIATED_NFKB_ACTIVATION_VIA_DAI	17	0.64	1.60	0.023	0.314	0.840	9459
Upregulated	REACTOME_ACTIVATED_TLR4_SIGNALLING	84	0.41	1.60	0.041	0.306	0.846	6330
Downregulated	REACTOME_MITOCHONDRIAL_PROTEIN_IMPORT	47	-0.68	-1.92	0.002	0.295	0.147	4436
Downregulated	REACTOME_TCA_CYCLE_AND_RESPIRATORY_ELECTRON_TRANSPORT	113	-0.68	-1.79	0.008	0.686	0.389	6319
Downregulated	REACTOME_NEUROTRANSMITTER_RELEASE_CYCLE	34	-0.61	-1.77	0.004	0.580	0.451	4429
Downregulated	REACTOME_ION_CHANNEL_TRANSPORT	54	-0.54	-1.77	0.008	0.439	0.452	5726
Downregulated	REACTOME_RESPIRATORY_ELECTRON_TRANSPORT	62	-0.77	-1.76	0.006	0.360	0.456	6869
Downregulated	REACTOME_RESPIRATORY_ELECTRON_TRANSPORT_ATP_SYNTHESIS_BY_CHEMIOSMOTIC_COUPLING_AND_HEAT_PRODUCTION_BY_UNCOUPLING_PROTEINS	78	-0.74	-1.76	0.012	0.320	0.467	5162
Downregulated	REACTOME_REGULATION_OF_INSULIN_SECRETION	88	-0.41	-1.72	0.000	0.379	0.545	4549
Downregulated	REACTOME_INSULIN_SYNTHESIS_AND_PROCESSING	20	-0.64	-1.70	0.014	0.411	0.616	4257
Downregulated	REACTOME_TRANSMISSION_ACROSS_CHEMICAL_SYNAPSES	182	-0.46	-1.68	0.013	0.424	0.654	6112
Downregulated	REACTOME_INSULIN_RECEPTOR_RECYCLING	23	-0.55	-1.68	0.028	0.382	0.654	4528
Downregulated	REACTOME_LIGAND_GATED_ION_CHANNEL_TRANSPORT	21	-0.73	-1.68	0.012	0.348	0.655	6498
Downregulated	REACTOME_RNA_POL_III_TRANSCRIPTION_TERMINATION	19	-0.65	-1.68	0.013	0.322	0.658	5095
Downregulated	REACTOME_GLYCONEOGENESIS	31	-0.56	-1.68	0.039	0.302	0.664	4436
Downregulated	REACTOME_RNA_POL_III_TRANSCRIPTION_INITIATION_FROM_TYPE_3_PROMOTER	25	-0.58	-1.68	0.013	0.285	0.666	5095
Downregulated	REACTOME_CA_DEPENDENT_EVENTS	29	-0.56	-1.68	0.010	0.270	0.668	4790
Downregulated	REACTOME_AMINE_LIGAND_BINDING_RECEPTORS	36	-0.55	-1.67	0.014	0.264	0.677	5009
Downregulated	REACTOME_GABA_SYNTHESIS_RELEASE_REUPTAKE_AND_DEGRADATION	17	-0.76	-1.67	0.008	0.252	0.683	4429

Downregulated	REACTOME_GABA_RECEPTOR_ACTIVATION	51	-0.48	-1.67	0.021	0.242	0.685	4629
Downregulated	REACTOME_RNA_POL_III_TRANSCRIPTION	31	-0.54	-1.67	0.016	0.231	0.688	5095
Downregulated	REACTOME_INTEGRATION_OF_ENERGY_METABOLISM	114	-0.38	-1.67	0.000	0.220	0.689	4183

Supplementary Table 3. List of Human genes used for GSEA (Oxidative Phosphorylation, GN327-328)

Gene Name	Rank in gene list	Running ES	Core enrichment
TCIRG1	238	9.47E-04	No
ATP6V0E1	273	0.007746442	No
CASP7	305	0.014505365	No
BDH2	564	0.014140344	No
SLC25A20	624	0.019433038	No
ACADVL	748	0.022662003	No
ABCB7	758	0.02919176	No
BAX	1507	0.013326788	No
CPT1A	2268	-0.003545472	No
HADHA	2534	-0.00624248	No
PDK4	2802	-0.009186301	No
ACAA1	2943	-0.008525506	No
HADHB	2992	-0.005222628	No
ALDH6A1	3746	-0.022787208	No
OGDH	3954	-0.024606545	No
CYB5R3	4443	-0.034821402	No
null	4768	-0.04042752	No
SUPV3L1	5004	-0.04355653	No
POLR2F	5638	-0.058490362	No
ACAA2	5707	-0.057049196	No
ECH1	5873	-0.058487084	No
DLST	6272	-0.06683774	No
MAOB	7349	-0.09524228	No
ATP5D	7980	-0.11088957	No
POR	8123	-0.112415165	No
RHOT1	9204	-0.14148025	No
ATP6V0B	9283	-0.14148046	No
MTRR	9593	-0.14826742	No
CYB5A	9681	-0.14863075	No
FXN	10122	-0.15936103	No
IDH1	10745	-0.17552482	No
ETFDH	13614	-0.25755665	No
MTRF1	13924	-0.26537377	No
ATP5G2	14482	-0.28051037	No
GLUD1	17371	-0.36396435	No
DECR1	17493	-0.3671173	No
SURF1	17679	-0.3721663	No
ECHS1	17956	-0.3799227	No
NDUFS8	18012	-0.38127485	No
PMPCA	18297	-0.38934627	No
ACAT1	18573	-0.39721522	No
IDH3G	19139	-0.4135997	No

SDHC	19375	-0.42035037	No
NDUFS1	20241	-0.4451744	No
RHOT2	20701	-0.45810148	No
MRPS15	21063	-0.46809044	No
SDHA	21092	-0.46840557	No
NDUFA2	23108	-0.5258305	No
MRPL34	24546	-0.5660229	No
COX17	24722	-0.5695249	No
ETFB	24792	-0.5699227	No
ATP5I	25170	-0.5791359	No
IDH2	25279	-0.58050066	No
ETFA	25492	-0.5848	No
ACADM	25582	-0.5854947	No
BCKDHA	25744	-0.5882201	No
SLC25A11	25891	-0.59046113	No
UQCRB	26392	-0.6027919	No
RETSAT	26417	-0.60129106	No
ATP5E	26472	-0.600633	No
COX11	27478	-0.62713176	No
NDUFS7	27775	-0.63291025	No
NDUFS4	28009	-0.6367495	No
MRPS12	28236	-0.6402649	No
NDUFA3	28325	-0.6397288	No
SUCLG1	28333	-0.63683784	No
TIMM9	28347	-0.63411564	No
NDUFC1	28382	-0.63198406	No
FDX1	28687	-0.63753635	No
COX6A1	28868	-0.6393904	No
CS	29250	-0.6468447	No
GPX4	29424	-0.648152	Yes
SDHD	29482	-0.6460534	Yes
UQCRC2	29629	-0.646455	Yes
OXA1L	29690	-0.64432424	Yes
NDUFA1	29751	-0.6421554	Yes
PRDX3	29882	-0.6419338	Yes
NDUFB4	29902	-0.63847554	Yes
HTRA2	29967	-0.63629013	Yes
LDHA	29982	-0.63264626	Yes
ATP6V0C	30116	-0.6323709	Yes
LDHB	30140	-0.6288906	Yes
SLC25A12	30208	-0.626635	Yes
COX7C	30235	-0.6231672	Yes
MRPL11	30279	-0.62016	Yes
ACO2	30333	-0.617402	Yes
null	30358	-0.6137867	Yes
NDUFB7	30513	-0.6138337	Yes
GRPEL1	30653	-0.6133473	Yes
IDH3B	30742	-0.6113163	Yes

VDAC1	30870	-0.61032826	Yes
COX8A	30985	-0.6088688	Yes
ATP5J2	30991	-0.6042391	Yes
COX5B	31298	-0.6081189	Yes
ATP6V1C1	31322	-0.6037657	Yes
MRPL35	31339	-0.59919184	Yes
BRP44L	31343	-0.5942391	Yes
NDUFB8	31454	-0.5923202	Yes
PHYH	31604	-0.5914238	Yes
SUCLA2	31649	-0.5874463	Yes
COX7A2L	31698	-0.58355296	Yes
NQO2	31899	-0.58390963	Yes
SLC25A6	31958	-0.58008903	Yes
TIMM13	31987	-0.5753724	Yes
IDH3A	32186	-0.5754219	Yes
ATP5O	32240	-0.5712174	Yes
NDUFB3	32292	-0.56691796	Yes
ALAS1	32305	-0.56147695	Yes
TIMM10	32339	-0.5566143	Yes
COX6B1	32379	-0.55188733	Yes
NDUFB1	32395	-0.54645103	Yes
null	32425	-0.5413895	Yes
NDUFB2	32426	-0.5354847	Yes
PHB2	32434	-0.52977943	Yes
ACADSB	32435	-0.52387094	Yes
NNT	32455	-0.51849234	Yes
NDUFS2	32456	-0.5125621	Yes
ATP6V1G1	32542	-0.50899106	Yes
NDUFV2	32558	-0.50337034	Yes
DLD	32690	-0.50101745	Yes
COX5A	32723	-0.49576384	Yes
COX15	32755	-0.4904478	Yes
COX10	32831	-0.48634717	Yes
VDAC3	32879	-0.48138762	Yes
UQCRC1	32903	-0.47570786	Yes
ATP5F1	32906	-0.46941715	Yes
HCCS	32973	-0.46491614	Yes
null	33020	-0.45978478	Yes
SDHB	33023	-0.4533721	Yes
COX7B	33040	-0.44735762	Yes
TIMM50	33064	-0.44151887	Yes
NDUFV1	33147	-0.43730906	Yes
MRPS11	33190	-0.43189594	Yes
FH	33223	-0.4261589	Yes
ATP1B1	33259	-0.42047036	Yes
null	33273	-0.4141297	Yes
COX6C	33317	-0.40861037	Yes
GPI	33386	-0.40374428	Yes

TIMM8B	33405	-0.39740607	Yes
ATP6AP1	33435	-0.3913562	Yes
TIMM17A	33445	-0.38471472	Yes
PDHA1	33450	-0.37792483	Yes
MDH1	33473	-0.37162995	Yes
MFN2	33474	-0.3646952	Yes
MTX2	33489	-0.35815784	Yes
PDHX	33495	-0.35135248	Yes
OAT	33503	-0.34459558	Yes
NDUFA8	33534	-0.33846205	Yes
TOMM22	33583	-0.33279976	Yes
MRPS22	33595	-0.32605374	Yes
UQCRFS1	33658	-0.32073495	Yes
MRPS30	33673	-0.31400982	Yes
ATP5G3	33678	-0.30698562	Yes
AFG3L2	33703	-0.30051062	Yes
ATP6V1F	33710	-0.2935041	Yes
ATP6V1H	33715	-0.28643623	Yes
NDUFA9	33730	-0.2796449	Yes
LRPPRC	33744	-0.27281663	Yes
MGST3	33747	-0.26566803	Yes
GOT2	33803	-0.25999585	Yes
ATP5A1	33811	-0.25291687	Yes
CYC1	33821	-0.24588588	Yes
PDHB	33834	-0.238931	Yes
TOMM70A	33847	-0.2319581	Yes
OPA1	33852	-0.22474873	Yes
NDUFB6	33922	-0.2193208	Yes
UQCRQ	33924	-0.21191664	Yes
DLAT	33933	-0.20470312	Yes
ATP6V1D	33959	-0.197935	Yes
UQCRH	33968	-0.19066676	Yes
SLC25A4	34010	-0.1842913	Yes
NDUFAB1	34011	-0.17672525	Yes
NDUFS6	34040	-0.16993845	Yes
COX4I1	34068	-0.16308294	Yes
IMMT	34137	-0.15728046	Yes
MRPL15	34139	-0.14952837	Yes
NDUFA6	34142	-0.14179952	Yes
NDUFS3	34144	-0.13403678	Yes
VDAC2	34145	-0.12623832	Yes
NDUFA4	34147	-0.118468575	Yes
ATP5H	34163	-0.11108551	Yes
NDUFA5	34170	-0.10342472	Yes
ATP5B	34188	-0.09604499	Yes
CYCS	34257	-0.09002689	Yes
NDUFC2	34286	-0.0827958	Yes
COX7A2	34301	-0.07510456	Yes

ATP5L	34350	-0.06827457	Yes
SLC25A5	34382	-0.060870606	Yes
ATP5C1	34389	-0.052717168	Yes
ATP5J	34406	-0.04480607	Yes
NDUFB5	34421	-0.03679262	Yes
ATP6V1E1	34423	-0.028401112	Yes
MDH2	34427	-0.020056587	Yes
NDUFA7	34437	-0.011861139	Yes
SLC25A3	34489	-0.00463875	Yes
ATP5G1	34564	0.002264278	Yes

Supplementary Table 4. List of Human genes used for GSEA (Mitochondrial Protein Import, GN327-328)

Gene Name	Rank in gene list	Running ES	Core enrichment
TAZ	217	0.030715793	No
GFER	3434	-0.04142935	No
MTX1	5400	-0.081726424	No
LDHD	5919	-0.08110618	No
TIMM44	7881	-0.12531078	No
FXN	10122	-0.18051185	No
TIMM17B	12394	-0.23911586	No
TOMM7	16254	-0.34772995	No
HSPD1	16297	-0.3460585	No
null	16983	-0.3636731	No
PMPCA	18297	-0.40081638	No
IDH3G	19139	-0.42504367	No
TIMM22	19267	-0.42849085	No
PMPCB	22167	-0.50860226	No
SLC25A13	24512	-0.5692842	No
COX17	24722	-0.5679506	No
TIMM9	28347	-0.6582189	No
COQ2	28724	-0.65370923	No
CS	29250	-0.65203345	No
SLC25A12	30208	-0.6600675	Yes
TOMM40	30233	-0.64104134	Yes
ACO2	30333	-0.62382615	Yes
CHCHD4	30345	-0.604037	Yes
null	30358	-0.5842345	Yes
BCS1L	30361	-0.56413794	Yes
GRPEL1	30653	-0.5514207	Yes
VDAC1	30870	-0.5358195	Yes
FXC1	31867	-0.53925127	Yes
GRPEL2	31904	-0.51481646	Yes
SLC25A6	31958	-0.49062788	Yes
TIMM13	31987	-0.46559948	Yes
TIMM10	32339	-0.4485465	Yes
SAMM50	32644	-0.4287354	Yes
TIMM50	33064	-0.41044345	Yes
TIMM8B	33405	-0.38821244	Yes
TIMM17A	33445	-0.3570848	Yes
MTX2	33489	-0.3258811	Yes
TOMM22	33583	-0.2955995	Yes
ATP5A1	33811	-0.26813293	Yes
CYC1	33821	-0.23431808	Yes
TOMM70A	33847	-0.20083024	Yes
SLC25A4	34010	-0.17016007	Yes
DNAJC19	34064	-0.1360141	Yes

TOMM20	34149	-0.10197448	Yes
ATP5B	34188	-0.06628301	Yes
TIMM8A	34221	-0.030154238	Yes
ATP5G1	34564	0.002254659	Yes

Supplementary Table 5. List of Human genes used for the gene expression correlation

Gene Name	Gene ID	Description	PCA
<i>BECN1</i>	8678	beclin 1	Mitochondrial Stress
<i>BNIP3</i>	664	BCL2 interacting protein 3	Mitochondrial Stress
<i>CLPP</i>	8192	caseinolytic mitochondrial matrix peptidase proteolytic subunit	Mitochondrial Stress
<i>COX5A</i>			Mitochondrial Stress
<i>CYC1</i>			Mitochondrial Stress
<i>DNM1L</i>			Mitochondrial Stress
<i>HSPA9</i>	3313	heat shock protein family A (Hsp70) member 9	Mitochondrial Stress
<i>HTRA2</i>	27429	HtrA serine peptidase 2	Mitochondrial Stress
<i>LONP1</i>	9361	lon peptidase 1, mitochondrial	Mitochondrial Stress
<i>PARK2</i>	5071	parkin RBR E3 ubiquitin protein ligase	Mitochondrial Stress
<i>PMPCB</i>	9512	peptidase, mitochondrial processing beta subunit	Mitochondrial Stress
<i>TIMM17A</i>	10440	translocase of inner mitochondrial membrane 17 homolog A	Mitochondrial Stress
<i>YME1L1</i>			Mitochondrial Stress
<i>ATF6</i>	22926	activating transcription factor 6	UPR ^{ER}
<i>EIF2A</i>	83939	eukaryotic translation initiation factor 2A	UPR ^{ER}
<i>ERO1LB</i>	56605	endoplasmic reticulum oxidoreductase 1 beta	UPR ^{ER}
<i>ERO1L</i>			UPR ^{ER}
<i>ERN1</i>			UPR ^{ER}
<i>ERN2</i>			UPR ^{ER}
<i>HSPA5</i>	3309	heat shock protein family A (Hsp70) member 5	UPR ^{ER}
<i>TRAF2</i>	7186	TNF receptor associated factor 2	UPR ^{ER}
<i>XBP1</i>	7494	X-box binding protein 1	UPR ^{ER}
<i>CLPB</i>	81570	ClpB homolog, mitochondrial AAA ATPase chaperonin	HSR
<i>DNAJA1</i>	3301	DnaJ heat shock protein family (Hsp40) member A1	HSR
<i>DNAJB1</i>	3337	DnaJ heat shock protein family (Hsp40) member B1	HSR
<i>DNAJC1</i>	64215	DnaJ heat shock protein family (Hsp40) member c1	HSR
<i>HSP90</i>	3320	heat shock protein 90 alpha family class A member 1	HSR
<i>HSPA14</i>	51182	heat shock protein family A (Hsp70) member 14	HSR
<i>HSPA2</i>	3306	heat shock protein family A (Hsp70) member 2	HSR

Supplementary Table 6. Clinical, demographic and neuropathological characteristics of cases by diagnosis group

		Clinical Diagnosis			Statistics	
		NCI (n = 8)	MCI (n = 8)	AD (n = 8)	p-value	Pair-wise comparison
Age (years) at death	mean ± SD (range)	89.2 ± 2.6 (84-92)	88.4 ± 3.9 (82-91)	88.9 ± 2.8 (85-92)	0.1	--
Number (%) of males		4 (50%)	4 (50%)	3 (38%)	0.9	--
Years of education	mean ± SD (range)	18.3 ± 2.7 (15-22)	18.7 ± 5.3 (9-23)	17.4 ± 3.6 (13-22)	0.1	--
Number (%) with ApoE ε4 allele		2 (25%)	2 (25%)	4 (50%)	0.01	AD>(NCI,MCI)
MMSE	mean ± SD (range)	27.5 ± 1.7 (25-30)	25.5 ± 3.0 (21-29)	19.7 ± 4.8 (10-26)	0.0008	(NCI,MCI)>AD
Global cognitive score	mean ± SD (range)	0.08 ± 0.3 (-0.2-0.5)	-0.34 ± 0.4 (-1.0-0.4)	-1.2 ± 0.5 (-1.8- -0.4)	0.0006	(NCI,MCI)>AD
Post-mortem interval (hours)	mean ± SD (range)	7.1 ± 3.9 (4.4-12.0)	5.0 ± 3.3 (3.2-8.0)	6.8 ± 3.8 (4.2-14.0)	0.4	--
Distribution of Braak scores	0 I/II III/IV V/VI	0 5 3 0	0 0 8 0	0 0 3 5	0.0005	(MCI,AD)>NCI
NIA Reagan diagnosis (likelihood of AD)	No AD Low Intermediate High	0 7 1 0	0 2 6 0	0 2 4 2	0.0008	(MCI,AD)>NCI
CERAD diagnosis	No AD Possible Probable Definite	1 5 2 0	0 3 5 0	0 2 5 1	0.001	(MCI,AD)>NCI

^aKruskal-Wallis test, with Bonferroni correction for multiple comparisons. ^bFisher's exact test, with Bonferroni correction for multiple comparisons.

Abbreviations: NCI, No Cognitive Impairment; MCI, mild cognitive impairment; AD, Alzheimer's disease; MMSE, Mini-Mental State Exam; NIA, National Institute on Aging; CERAD, Consortium to Establish a Registry for Alzheimer's Disease

Supplementary Table 7. List of qPCR primers used in *C. elegans*

Gene Symbol	Gene ID	Forward	Reverse
<i>act-1</i>	179535	CTACGAACTTCCTGACGGACAAG	CCGGCGGACTCCATAACC
<i>pmp-3</i>	179968	GTTCCCGTGTTCACTCAT	ACACCGTCGAGAAGCTGTAGA
<i>hsp-6</i>	178873	AGAGCCAAGTTCGAGCAGAT	TCTTGAACAGTGGCTTGCAC
<i>hsp-60</i>	175316	GGAAGCCCAAAGATCACAAA	CAGCCTCCTCATTAGCCTTG
<i>ymel-1</i>	176460	CAAAACCTGATCTCGCTGGG	TTCTCAATGTCGGCTCCAGT
<i>clpp-1</i>	174594	TGATAAGTGCAACAGTGCCA	TGATTCTGGAGTTCGGGAGA
<i>lonp-1</i>	172966	CGATGATGGCCATTGTGCAG	CGCTTTGAAACATCAATTTTCATCCA
<i>sqst-1</i>	178139	GATCCTCCGACCACTCCAAA	TGGAAGTGGTGAACGATCA
<i>dct-1</i>	181053	GCAAAAGCCGTCTCAAACCC	ACCCACGATTCTGACATACCA
<i>pdr-1</i>	176816	AGCCACCGAGCGATTGATTGC	GTGGCATTGTTGGGCATCTTCTTG
<i>pink-1</i>	173918	AAGCACCAGAAATTGCGACG	ACGAGATGGGAGTGCTGGTA
<i>cco-1</i>	172832	GCTCGTCTTGCTGGAGATGATCGTT	GGTCGGCGTCGACTCCCTTG
<i>mev-1</i>	260040	ATCGATCGTCACCAAGTCCG	GGAATCCGGAGAGCATCCAG
<i>cyc-1</i>	172582	GTGCCGTGGTTCAAGGAT	TTCACGTCGTACAGAAGC
<i>nduo-1</i>	2565698	AGCGTCATTTATTGGGAAGAAGAC	AAGCTTGCTAATCCATAAATGT
<i>hsp-3</i>	180880	CCATCAGCTCGGAAAGTTCG	TTCCGGTTCCTTATCCTCG
<i>hsp-4</i>	174203	GACATCGAGCGCATGATCAA	CCTTGTCGGCGATTTGAGTT
<i>hsp-16.1</i>	179286	ACCACTATTTCCGTCCAGCT	ATCTTCTGGCTTGAACCTGCG
<i>hsp-16.2</i>	178659	TCCATCTGAGTCTTCTGAGATTGTTA	TGGTTTAAACTGTGAGACGTTGA
<i>hsp-16.41</i>	178660	TGCTCCGTTCTCCATATTCTGA	AGAGACATCGAGTTGAACCGA
<i>hsp-16.48/49</i>	179287	CTCATGCTCCGTTCTCCATT	ACAATCTCTCCAATATTGTCCGA
<i>sod-3</i>	181748	TCTGACATCACTATTGCGGTTT	TTTCTTGCAATATCCCAACCAT
<i>hsp-12.6</i>	177778	AGGGAGATGGAGTTGTCAATG	TTCAATCTCTTTGGGAGGAAG
<i>atfs-1 3'UTR</i>	179922	TCCCTTTGTTACCCAACTGT	TGGGATCGAATACCCGTAACAA
<i>atfs-1</i>	179922	TCCTAGATTGGGAAAATCAACTG	TACCATTCTGCCATGAGTCG

Supplementary Table 8. List of primers used in *M. musculus*

Gene Symbol	Gene ID	Forward	Reverse
<i>Gapdh</i>	14433	TGTGTCCGTCGTGGATCTGA	CCTGCTTCACCACCTTCTTGAT
<i>B2m</i>	12010	ATGGGAAGCCGAACATACTG	CAGTCTCAGTGGGGTGAAT
<i>Hspa9</i>	15526	AATGAGAGCGCTCCTTGCTG	CTGTTCCCCAGTGCCAGAAC
<i>Hsp60</i>	15510	GCTGTAGCTGTTACAATGGGG	TGACTTTGCAACAGTGACCC
<i>Yme1l1</i>	27377	AGGGACCTTGGATTATCTGAACT	TGGGATGTATGCCAATGGGAA
<i>Clpp</i>	53895	TGTTGCGGGAACGCATCGTGT	TAGATGGCCAGGCCCGCAGTT
<i>Lonp1</i>	74142	ATGACCGTCCCGGATGTGT	CCTCCACGATCTTGATAAAGCG
<i>Bnip3</i>	12176	CCTGTGCGAGTTGGGTTC	GAAGTGCAGTTCTACCCAGGAG
<i>Sqstm1</i>	18412	GCTGAAGGAAGCTGCCCTAT	TTGGTCTGTAGGAGCCTGGT
<i>Park2</i>	50873	CCGAATCACCTGACGGTTCA	TCTGGCTGCTTCTGAATCCC
<i>Cox5a</i>	12858	GAGCCCAAATCATTGATGC	TGAGGTCCTGCTTTGTCCTT
<i>Cox2</i>	17709	AACCGAGTCGTTCTGCCAAT	CTAGGGAGGGGACTGCTCAT
<i>Nd1</i>	17716	CAAACACTTATTACAACCCAAGAACA	TCATATTATGGCTATGGGTCAGG
<i>Sdhc</i>	66052	GCTGCGTTCTTGCTGAGACA	ATCTCCTCCTTAGCTGTGGTT
<i>Pink1</i>	68943	GCTTGCCAATCCCTTCTATG	CTCTCGCTGGAGCAGTGAC
<i>Lc3</i>	66734	GTCACCCAGGCGAGTTACC	TTACAGCGGTGCGGCGAAG
<i>hApp</i>	351	GGTTGGCACTGCTCCTG	CAGTCTGCCACAGAACATGG

Supplementary Table 9. List of primers used in human neuroblastoma cells

Gene Symbol	Gene ID	Forward	Reverse
<i>GAPDH</i>	2597	TTGGTATCGTGGAAGGACTC	ACAGTCTTCTGGGTGGCAGT
<i>HSPA9</i>	3313	TGGTGAGCGACTTGTTGGAAT	ATTGGAGGCACGGACAATTTT
<i>HSP60</i>	3329	GGGTAACCGAAGCATTCTGC	CTGCACTCTGTCCCTCACTC
<i>YME1L1</i>	10730	AGGGACCTTGGATTATCTGAACT	TGGGATGTATGCCAATGGGAA
<i>CLPP</i>	8192	AAGCACACCAACAGAGCCT	AAGATGCCAAACTCCTGGG
<i>LONP1</i>	9361	CCCGCGCTTTATCAAGATT	AGAAAGACGCCGACATAAGG
<i>BNIP3</i>	664	AGGGCTCCTGGGTAGAACTG	CCCTGTTGGTATCTTGTGGTG
<i>COX5A</i>	9377	CATTGATGCTGCTTTCGGGG	AGCCCATCCATGCGGTTTAC
<i>ND1</i>	6775098	CCGAATCACCTGACGGTTCA	TCTGGCTGCTTCTGAATCCC

Supplementary Table 10. List of primers used in *H. sapiens*

Gene Symbol	Gene ID	Taqman Probe set
<i>GAPDH</i>	2597	Hs02758991_g1
<i>HSPA9</i>	3313	Hs00269818_m1
<i>HSPD1</i>	3329	Hs01941522_u1
<i>YME1L1</i>	10730	Hs00204609_m1
<i>DNM1L</i>	10059	Hs01552605_m1
<i>BECN1</i>	8678	Hs00186838_m1
<i>SQSTM1</i>	8878	Hs01061917_g1

<i>PARK2</i>	5071	Hs01038322_m1
<i>COX5A</i>	9377	Hs00362067_m1
<i>CYC1</i>	1537	Hs00357718_g1

Supplementary Table 11. List of antibodies

Antibody	Supplier	Reference #	Validation	Species
HSP60	Enzo Life Science	ADI-SPA-806	manufacturer	Mouse
CLPP	Sigma	WH0008192M1	manufacturer	Mouse
GAPDH (14C10)	Cell Signaling	2118S	manufacturer	Mouse
LONP1	Sigma	HPA002192	manufacturer	Mouse
PINK1	Novus Biologicals	BC100-494	manufacturer	Mouse
LC3 A/B	Cell Signaling	4108S	manufacturer	Mouse
SDHB	Abcam	ab110413	manufacturer	Mouse
MTCO1	Abcam	ab14705	manufacturer	Mouse
SQSTM1	BD Transduction Laboratories	610497	manufacturer	Mouse
Phospho SQSTM1	Cell signaling	95967	manufacturer	Mouse
VDAC	Abcam	ab14734	manufacturer	Mouse
Ubiquitin	Enzo Life Science	BML-PW8810-0100	manufacturer	Mouse
β -amyloid,1-16 (6E10)	BioLegend	803002	manufacturer	Mouse, Human
β -amyloid,17-24 (4G8)	BioLegend	800701	manufacturer	Mouse, Human
anti-Oligomer (A11)	Thermo Scientific	AHB0052	manufacturer	Mouse, Human
CLPP (2E1D9)	ProteinTech	66271-1-Ig	manufacturer	Human
GAPDH (2D9)	Origene	TA802519	manufacturer	Human
mtDnaJ (RS13)	Cell Signaling	4775S	manufacturer	Human
Anti-Beta-Amyloid 1-42	Millipore	AB5078P	manufacturer	Human
Actin	Sigma	A5441	manufacturer	Human, mouse, worm
Tubulin	Santa Cruz	Sc-5286	manufacturer	Human, mouse, worm

Supplementary Table 12. List of *C. elegans* strains

Strain	Supplier	Genotype information	Notes
N2	CGC	<i>C. elegans</i> Bristol wild isolate	
CL2122	CGC	dvls15 [(<i>pPD30.38</i>) <i>unc-54</i> + (<i>pCL26</i>) <i>mtl-2::GFP</i>]	Backcrossed 3x in N2
GMC101	CGC	dvls100 [<i>unc-54p::A-beta-1-42::unc-54</i> 3'-UTR + <i>mtl-2p::GFP</i>]	
CB4876	CGC	<i>clk-1(e2519)</i> III	
MQ1333	CGC	<i>nuo-6(qm200)</i> I	
AUW9	Generated <i>in house</i>	[<i>GMC101</i> + epfEx6[<i>atfs-1p::atfs-1</i>]]	Clone 1
AUW10	Generated <i>in house</i>	[<i>GMC101</i> + epfEx7[<i>atfs-1p::atfs-1</i>]]	Clone 2
AUW11	Generated <i>in house</i>	[<i>CL2122</i> + epfEx8[<i>atfs-1p::atfs-1</i>]]	

AUW12	Generated <i>in house</i>	[GMC101 + <i>clk-1(e2519)</i> III]	
AUW13	Generated <i>in house</i>	[GMC101 + <i>nuo-6(qm200)</i> I]	

Supplementary Table 13. List of cloning and sequencing primers used in *C. elegans*

Gene Symbol	Gene ID	Forward	Reverse
<i>atfs-1 promoter</i>	179922	CTAACATGTAAAAATAATAAAAGGACA AAAAAGC	GTAACCGGTTTTGATGGTACTGTTTCAGATGG
<i>atfs-1 CDS</i>	179922	GTTCCCGTGTTTCATCACTCAT	ACACCGTCGAGAAGCTGTAGA
<i>pPD30.38 seq</i>		TTTTGTGATGCTCGTCAGGG	TTAGAAGTCAGAGGCACGGG
<i>atfs-1 seq.1</i>	179922	GGAAGCCCAAAGATCACAAA	TCTAAAGGATTGTCAACGATTTTT
<i>atfs-1 seq.2</i>	179922	CAAAACCTGATCTCGCTGGG	TTCAAAAATATCAGTTTCTTTT
<i>atfs-1 seq.3</i>	179922	TGATAAGTGCACCAAGTGTCCA	GTCAGAATGCACCATGATGTTG
<i>clk-1</i>	175729	TTCAGTGTGGCTGCTTATGC	AAAAGGGACACATTATTGAAATTGTT
<i>clk-1 seq.</i>	175729		ATTATTGAAATTGTTCAAATTTTCTCAG
<i>nuo-6</i>	172438	TGCGATAAAATTGGATATTAACACT	ATTCCGATGGTTGGAGCA
<i>nuo-6 seq.</i>	172438		CGATGGTTGGAGCAAAGAG
<i>atfs-1 RNAi#2</i>	179922	GGGGACAAGTTTGTACAAAAAAGCAG GCTTCGGCTCCCCGCTCTTCC	GGGGACCACTTTGTACAAGAAAGCTGGGTCGAG TTGATTTTCTGATTGAGATGTG

Human datasets for bioinformatics studies

For the *in silico* analysis of human brain expression datasets, we have used two sets of publicly available RNA-seq data: (1) from the Harvard Brain Tissue Resource Center (HBTRC), for human primary visual cortex (GN Accession: GN327) and human prefrontal cortex (GN Accession: GN328), and (2) from the Translational Genomics Research Institute, for the whole brain (GN Accession: GN314). These two datasets are publicly available on GeneNetwork (www.genenetwork.org).

GN327 and GN328 are two sets of publicly available RNA-seq data generated by the Harvard Brain Tissue Resource Center (HBTRC). The 803 participants in this dataset are composed of 388 Alzheimer's disease cases and 195 controls matched for age, gender, and post mortem interval (as well as 220 Huntington's disease cases). Three brain regions including the cerebellum, the visual cortex and the dorsolateral prefrontal cortex from the same individuals were profiled on a custom-made Agilent 44K microarray. Clinical outcomes available include age at onset, age at death, Braak scores and Regional brain enlargement/atrophy. In our study, we have analyzed the visual cortex (GN237) and the prefrontal cortex (GN238).

GN314 is a set generated by Translational Genomics Research Institute. This human brain expression data was obtained from patients with Alzheimer's disease and age-matched elderly control subjects. Samples were recovered from cortical regions of 14 normal elderly

humans (10 males and 4 females) and from 33 AD cases (15 males and 18 females). 6 brain regions were analyzed with about 14 biological replicates per brain region. The brain regions are as the entorhinal, hippocampus, medial temporal gyrus, posterior cingulate, superior frontal gyrus and primary visual cortex. Mean age of cases and controls was 80 years. All samples were run on the Affymetrix U133 Plus 2.0 array.