

SUPPLEMENTAL MATERIALS

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eMETHODS

List of 21 administered neuropsychological tests.

Two tests, the Mini-Mental State Examination and Complex Ideational Material, were used only for diagnostic purposes. The remaining 19 tests used for making global cognition score included immediate and delayed recall of the East Boston Story and Logical Memory Story A, Word List Memory, Recall, and Recognition (episodic memory); Symbol Digit Modalities Test, Number Comparison, Stroop Color and Word Test (perceptual speed); Boston Naming Test, Verbal Fluency, Word Reading (semantic memory); Digit Span Forward and Backward, and Digit Ordering (working memory); Judgement of Line Orientation and Standard Progressive Matrices (visuospatial ability).

Assessment of neurodegenerative and cerebrovascular diseases pathologies other than Alzheimer's disease.

Lewy bodies. Seven brain regions were examined using immunohistochemical methods with an antibody against α -synuclein. In this study, Lewy bodies were summarized using a dichotomous variable indicating presence of Lewy bodies in any brain region.

Transactive response DNA binding protein-43 (TDP-43). TDP-43 was assessed in 6 brain regions using an antibody against phosphorylated TDP-43¹. TDP-43 burden was summarized as none, present in amygdala, present in amygdala plus hippocampus, and extension to neocortex., In this study, we examined presence of TDP-43 in the hippocampus or neocortex as the outcome of interest because these stages of TDP-43 are associated with dementia².

Hippocampal sclerosis. Coronal sections from mid-hippocampus were examined for presence of hippocampal sclerosis, which was defined as severe neuronal loss and gliosis in CA1 region or subiculum¹.

Macroinfarcts. Slabs from the fixed brain hemisphere were examined without microscope for presence of infarcts³. Suspected lesions were confirmed microscopically. As the primary outcome of the study was cognitive decline development over years of follow up, we only examined chronic macroinfarcts³. Microscopically, chronic macroinfarcts were defined as cavities surrounded by fibrillary gliosis and including few macrophages⁴. In this study, macroinfarcts were summarized using a dichotomous (present/absent) variable.

Microinfarcts. Tissue sections from 9 brain regions were examined for the presence of microinfarcts. Like macroinfarcts, only chronic microinfarcts were examined in this study that were seen as either cavities or as a scar-like lesion with possible pial surface invagination⁴. In this study, a dichotomous variable (present/absent) was used to summarize microinfarcts.

Atherosclerosis. Large vessels of the Circle of Willis were examined for the presence and severity of atherosclerosis, which was scored based on the number of vessels involved and severity of atherosclerosis in each vessel¹. In this study, the outcome of interest was presence of moderate to severe atherosclerosis as was used in previous studies⁵.

Arteriolosclerosis. Small arterioles of basal ganglia were examined for concentric hyaline thickening and narrowing of lumen. Dependent on the number of arterioles involved, vessel wall thickening, and degree of lumen stenosis in each vessel, arteriolosclerosis was scored¹. For this

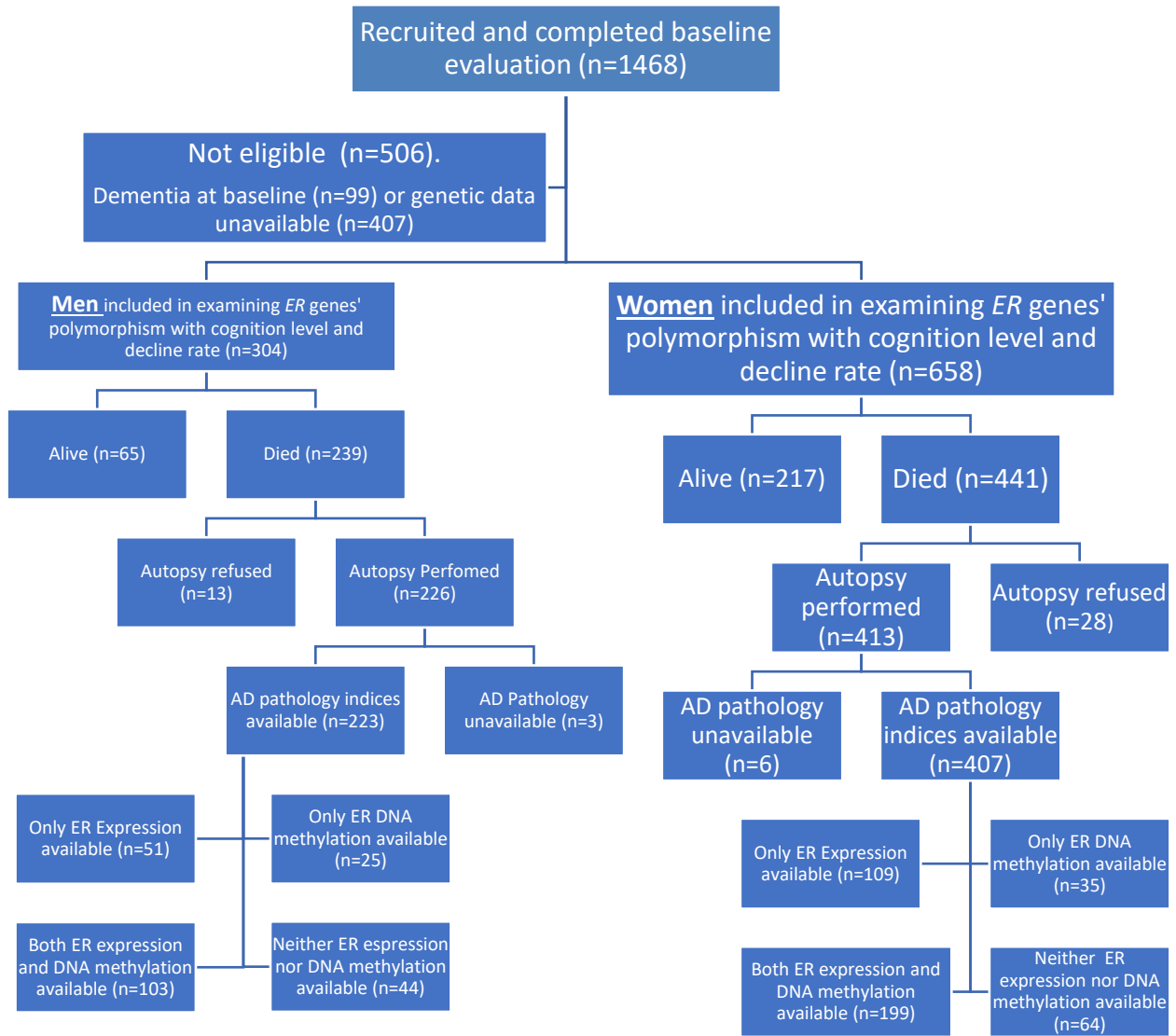
study, the outcome of interest was presence of moderate to severe arteriolosclerosis as was use in previous studies⁵.

Cerebral amyloid angiopathy (CAA). Examining parenchymal and meningeal vessels in 4 brain regions, CAA was assessed using immunohistochemical methods with antibodies against amyloid- β . CAA presence and severity was scored based on the extent of amyloid- β deposition in each vessel and number of vessels involved¹. For this study, the outcome of interest was presence of moderate to severe CAA⁵.

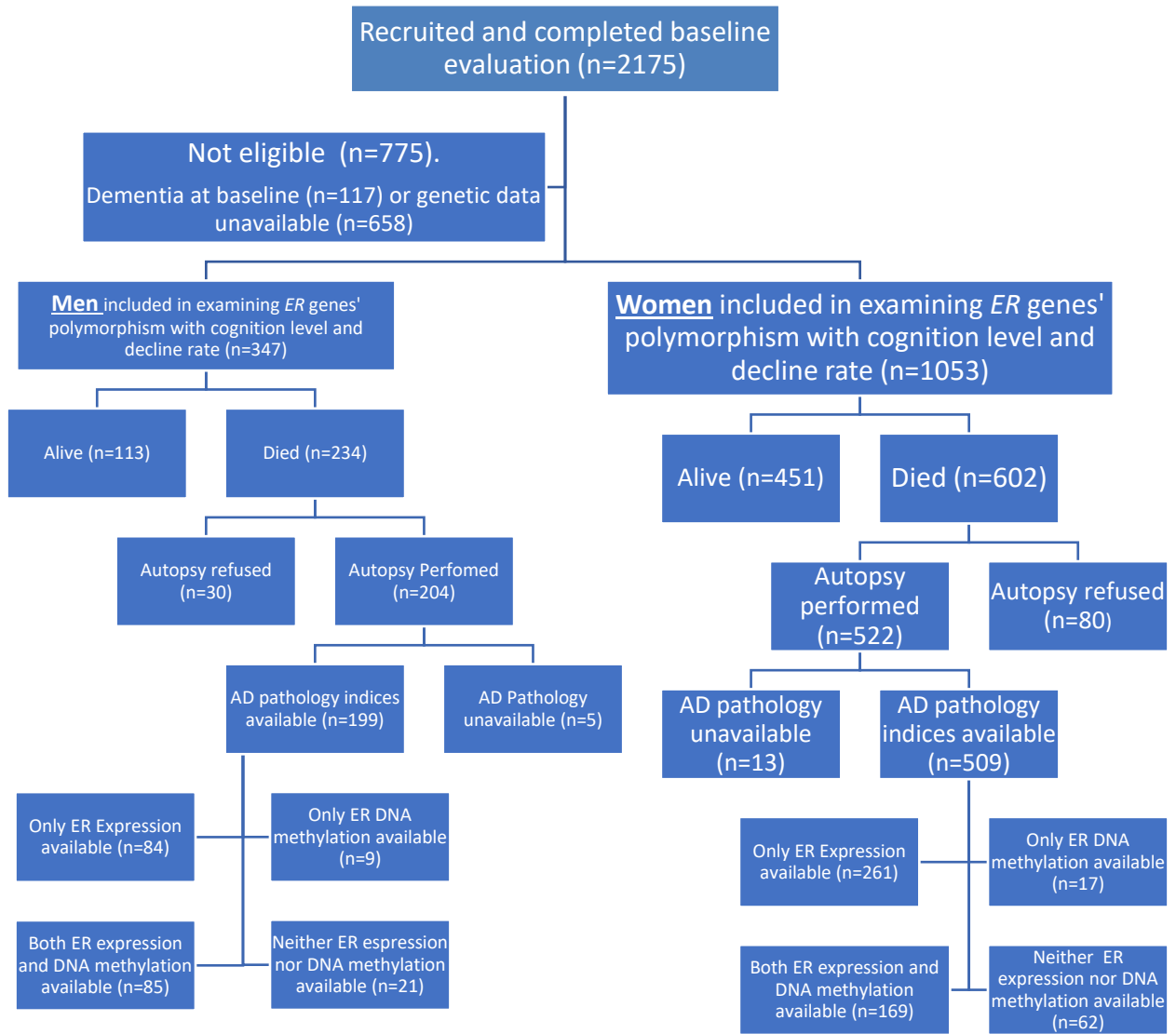
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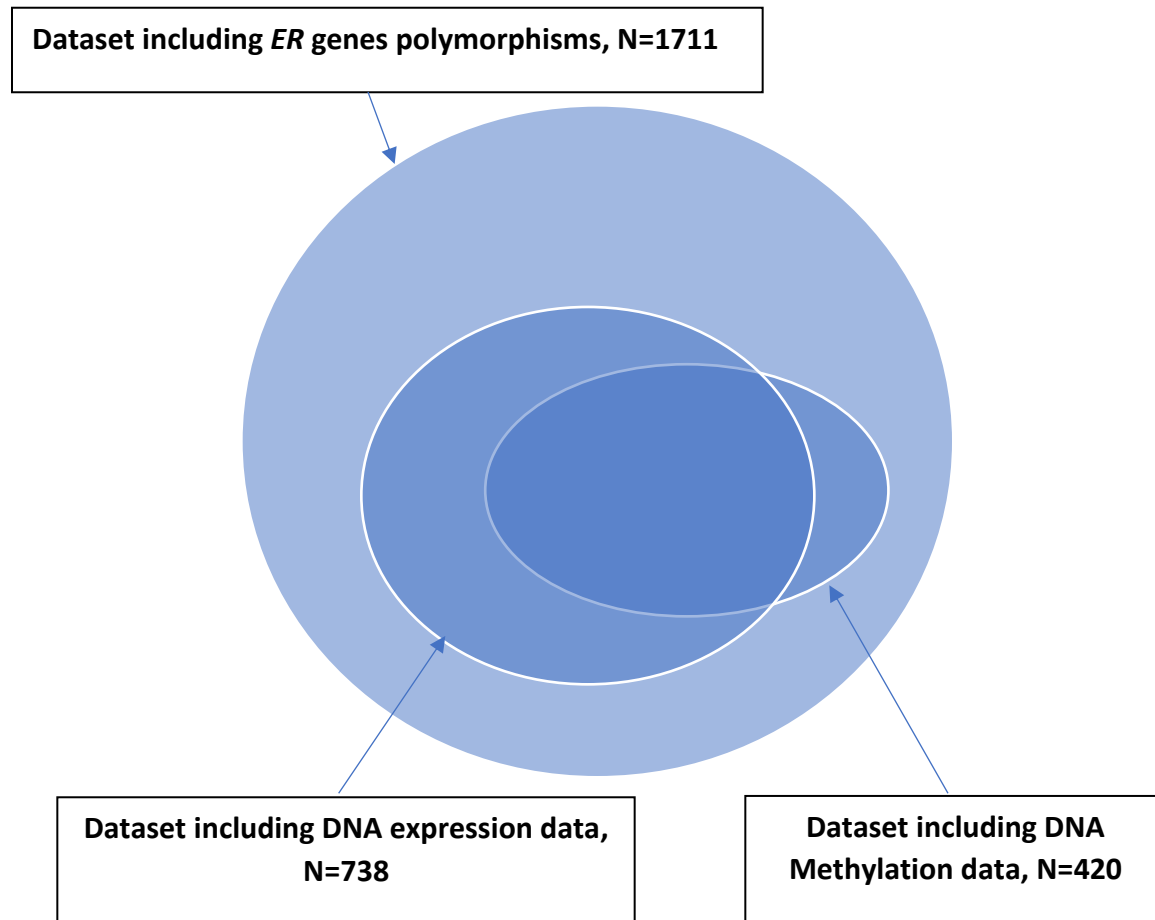
eFigure 1. Flow chart of the Religious Orders Study (ROS) participants included in the current study.



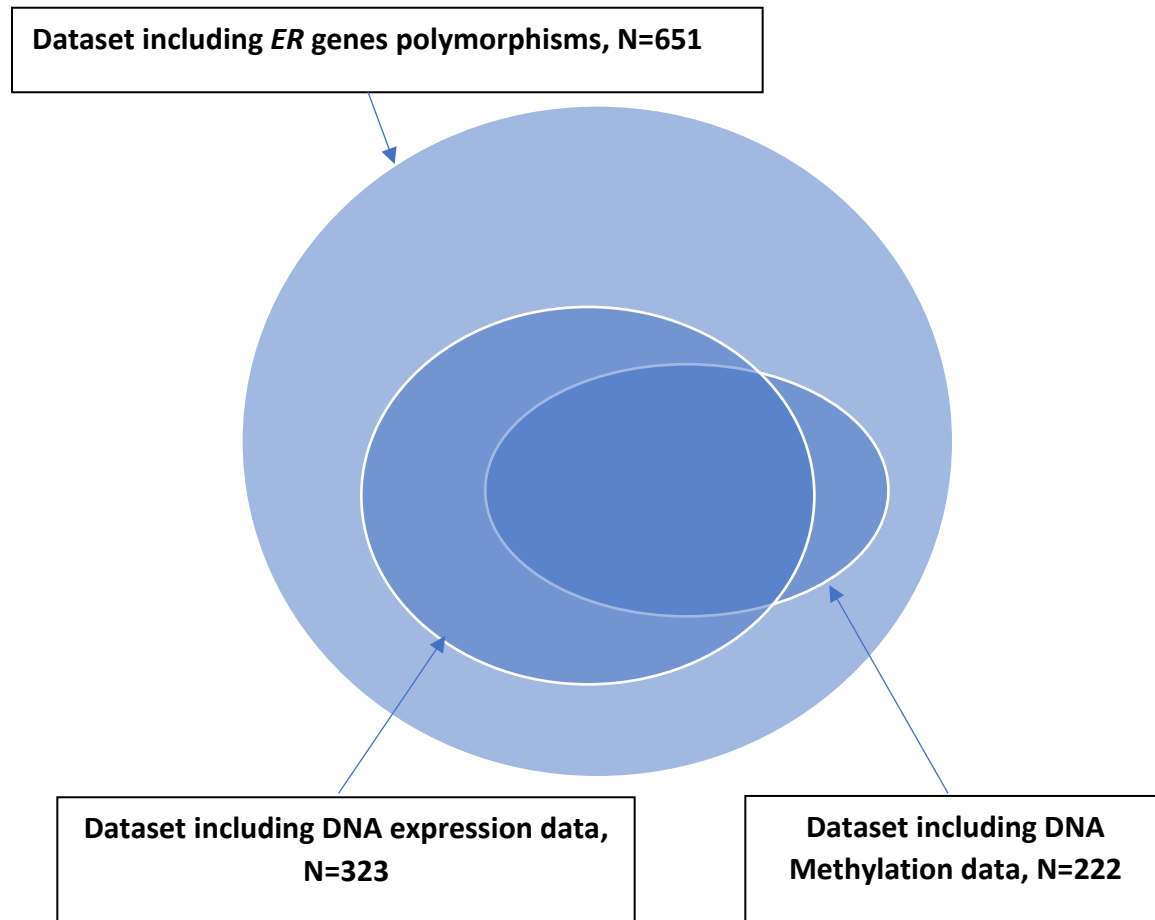
eFigure 2. Flow chart of the Rush Memory and Aging Project (MAP) participants included in the current study.



eFigure 3. Venn diagram of the sample sizes for examining *ER* genes polymorphisms, DNA methylation, and expression levels with the outcomes in women.



eFigure 4. Venn diagram of the sample sizes for examining *ER* genes polymorphisms, DNA methylation, and expression levels with the outcomes in men.



eTable 1. Post hoc comparison of the analytic datasets in their baseline characteristics.

Dataset1	Dataset2	Age	Education	Global cognition	Years of follow up
Women-SNP	Men-SNP	0.479	<0.001	0.565	1.0
	Women-CpG	<0.001	1.0	<0.001	0.009
	Men-CPG	0.133	<0.001	0.120	0.103
	Women-RNA	<0.001	0.720	<0.001	<0.001
	Men-RNA	0.484	<0.001	<0.001	<0.001
Men-SNP	Women-CpG	<0.001	<0.001	0.230	0.110
	Men-CPG	0.009	0.999	0.870	0.283
	Women-RNA	<0.001	<0.001	<0.001	<0.001
	Men-RNA	0.079	0.725	0.054	<0.001
Women-CpG	Men-CPG	0.003	<0.001	0.995	1.0
	Women-RNA	0.721	0.832	0.007	<0.001
	Men-RNA	0.006	<0.001	0.723	<0.001
Men-CPG	Women-RNA	<0.001	<0.001	0.011	<0.001
	Men-RNA	1.0	0.636	0.574	<0.001
Women-RNA	Men-RNA	<0.001	<0.001	0.809	1.0

Cells' parameters are p-values derived from Tukey Tests performed after analysis of variance tests.

eTable 2. SNPs associated with the global cognition level at baseline in women.

<i>ER gene</i>	Chr.	Position	Estimate	SE	Raw P-value	FDR q-value
<i>GPER1</i>	7	1132075	-0.136	0.038	0.0003	0.048
<i>ERI</i>	6	152133351	-0.287	0.039	<0.0001	<0.001
	6	152200749	-0.264	0.041	<0.0001	<0.001
	6	152203279	-0.232	0.039	<0.0001	<0.001
	6	152213352	-0.233	0.039	<0.0001	<0.001
	6	152224736	-0.221	0.039	<0.0001	<0.001
	6	152225233	-0.221	0.039	<0.0001	<0.001
	6	152226922	-0.221	0.039	<0.0001	<0.001
	6	152266043	-0.219	0.039	<0.0001	<0.001
	6	152246865	-0.216	0.039	<0.0001	<0.001
	6	152246866	-0.216	0.039	<0.0001	<0.001
	6	152258509	-0.215	0.039	<0.0001	<0.001
	6	152129588	-0.235	0.044	<0.0001	<0.001
	6	152133187	-0.231	0.045	<0.0001	<0.001
	6	152145916	-0.230	0.045	<0.0001	<0.001
	6	152137648	-0.113	0.023	<0.0001	<0.001
	6	152132609	-0.112	0.023	<0.0001	<0.001
	6	152151863	-0.107	0.022	<0.0001	<0.001
	6	152152193	-0.106	0.022	<0.0001	<0.001
	6	152152988	-0.098	0.022	<0.0001	0.001
	6	152200363	-0.110	0.026	<0.0001	0.002
	6	152007611	-0.103	0.025	<0.0001	0.003
	6	152129746	-0.217	0.057	0.0001	0.010
	6	152262453	-0.110	0.029	0.0002	0.011
	6	152054374	0.069	0.019	0.0002	0.016
	6	152209409	-0.106	0.030	0.0003	0.019
	6	152209815	-0.106	0.030	0.0003	0.019
	6	152212508	-0.106	0.029	0.0003	0.019
	6	152459143	0.085	0.024	0.0003	0.019
	6	152113328	-0.228	0.065	0.0005	0.022
	6	152140464	-0.085	0.024	0.0005	0.022
	6	152173872	-0.194	0.055	0.0004	0.022
	6	152245218	-0.102	0.029	0.0005	0.022
	6	152028479	0.064	0.019	0.0008	0.025
	6	152110601	-0.224	0.065	0.0006	0.025
	6	152113339	-0.225	0.065	0.0005	0.025
	6	152119119	-0.069	0.021	0.0009	0.025
6	152122037	-0.069	0.021	0.0009	0.025	
6	152126824	-0.087	0.025	0.0006	0.025	
6	152139886	-0.083	0.024	0.0007	0.025	
6	152140042	-0.083	0.024	0.0007	0.025	
6	152142956	-0.081	0.024	0.0001	0.025	

	6	152146721	-0.081	0.024	0.0001	0.025
	6	152149872	-0.081	0.024	0.0009	0.025
	6	152150923	-0.082	0.024	0.0007	0.025
	6	152151184	-0.083	0.024	0.0006	0.025
	6	152172807	-0.186	0.056	0.0009	0.025
	6	152172859	-0.186	0.056	0.0009	0.025
	6	152172905	-0.185	0.056	0.0009	0.025
	6	152172943	-0.185	0.056	0.0009	0.025
	6	152172950	-0.175	0.052	0.0009	0.025
	6	152173170	-0.184	0.056	0.0009	0.025
	6	152178576	-0.183	0.055	0.0001	0.025
	6	152181094	-0.183	0.055	0.0009	0.025
	6	152187526	-0.184	0.055	0.0008	0.025
	6	152188095	-0.184	0.055	0.0008	0.025
	6	152200639	-0.132	0.039	0.0007	0.025
	6	152349859	-0.142	0.042	0.0008	0.025
	6	152365339	-0.138	0.042	0.0009	0.025
	6	152367853	-0.140	0.042	0.0009	0.025
	6	152369268	-0.140	0.042	0.0008	0.025
	6	152178159	-0.182	0.055	0.0001	0.025
	6	152114301	-0.068	0.021	0.0010	0.025
	6	152176674	-0.182	0.055	0.0010	0.025
	6	152174108	-0.181	0.055	0.0011	0.025
	6	152174127	-0.181	0.055	0.0011	0.025
	6	152175106	-0.181	0.055	0.0011	0.025
	6	152176076	-0.181	0.055	0.0011	0.025
	6	152150924	-0.083	0.026	0.0012	0.028
	6	152034387	0.061	0.019	0.0013	0.028
	6	152114448	-0.067	0.021	0.0013	0.028
	6	152147218	-0.079	0.024	0.0013	0.028
	6	152148098	-0.079	0.024	0.0013	0.028
	6	152175825	-0.176	0.055	0.0014	0.029
	6	152263628	-0.095	0.030	0.0014	0.029
	6	152261146	-0.094	0.030	0.0015	0.032
	6	152149435	-0.081	0.026	0.0017	0.034
	6	152242159	-0.093	0.030	0.0017	0.035
	6	152246042	-0.092	0.029	0.0018	0.035
	6	152263380	-0.091	0.029	0.0019	0.037
	6	152389173	-0.129	0.042	0.0022	0.043
	6	152388479	-0.128	0.042	0.0023	0.044
	6	152007587	-0.071	0.024	0.0025	0.048
ER2	14	64697828	-0.101	0.024	<0.0001	0.018
	14	64738255	-0.188	0.047	<0.0001	0.018
	14	64738264	-0.188	0.047	<0.0001	0.018
	14	64692465	-0.094	0.025	0.0002	0.019
	14	64693871	-0.093	0.025	0.0002	0.019

14	64696817	-0.094	0.025	0.0002	0.019
14	64700739	-0.093	0.025	0.0002	0.019
14	64743130	-0.177	0.048	0.0002	0.019
14	64691456	-0.194	0.054	0.0004	0.025
14	64692377	-0.090	0.026	0.0004	0.025
14	64712355	-0.096	0.027	0.0004	0.025
14	64811865	-0.183	0.051	0.0004	0.025
14	64577389	-0.170	0.050	0.0007	0.026
14	64689440	-0.087	0.026	0.0007	0.026
14	64691320	-0.103	0.030	0.0007	0.026
14	64696200	-0.107	0.031	0.0008	0.026
14	64698623	-0.103	0.030	0.0007	0.026
14	64701446	-0.104	0.030	0.0007	0.026
14	64739505	-0.114	0.033	0.0006	0.026
14	64756020	-0.165	0.049	0.0007	0.026
14	64704994	-0.093	0.028	0.0009	0.029
14	64694082	-0.103	0.031	0.0010	0.030
14	64753039	-0.168	0.051	0.0010	0.030
14	64576062	-0.116	0.036	0.0011	0.030
14	64665881	-0.156	0.048	0.0013	0.030
14	64689289	-0.084	0.026	0.0012	0.030
14	64716693	-0.170	0.052	0.0011	0.030
14	64745263	-0.165	0.051	0.0012	0.030
14	64751713	-0.156	0.048	0.0013	0.030
14	64701430	-0.099	0.031	0.0013	0.031
14	64701042	0.060	0.019	0.0014	0.031
14	64646290	-0.177	0.056	0.0016	0.032
14	64646396	-0.178	0.056	0.0016	0.032
14	64693385	0.058	0.018	0.0016	0.032
14	64721439	-0.076	0.024	0.0016	0.032
14	64591519	-0.073	0.024	0.0023	0.042
14	64726365	-0.086	0.028	0.0022	0.042
14	64728463	-0.086	0.028	0.0023	0.042
14	64729385	-0.086	0.028	0.0023	0.042
14	64604281	-0.075	0.025	0.0025	0.043
14	64811237	0.097	0.032	0.0025	0.043
14	64709091	0.057	0.019	0.0030	0.050

eTable 3. SNPs associated with microinfarcts in women.

Pathology Index	<i>ER gene</i>	Chr.	Position	Estimate	SE	Raw P-value	FDR q-value
Microinfarcts	<i>GPER1</i>	7	1133678	-0.456	0.137	0.0009	0.021
		7	1133731	-0.456	0.137	0.0009	0.021
		7	1135263	-0.457	0.137	0.0009	0.021
		7	1135883	-0.452	0.137	0.0010	0.021
		7	1137889	-0.453	0.137	0.0010	0.021
		7	1138640	-0.45	0.137	0.0011	0.021
		7	1139892	-0.439	0.137	0.0013	0.021
		7	1140515	-0.44	0.137	0.0013	0.021
		7	1140919	-0.44	0.137	0.0013	0.021
		7	1141129	-0.451	0.146	0.0020	0.028
		7	1122851	-0.425	0.143	0.0029	0.037

eTable 4. CpG sites associated with the level of global cognition in women.

<i>ER gene</i>	CpG	Chr.	Position	Estimate	SE	Raw P-value	FDR q-value
<i>ER1</i>	cg00655307*	6	152128743	-14.066	3.231	<0.0001	<0.001
	cg22389949*	6	152003038	-3.891	0.891	<0.0001	<0.001
	cg22839866*	6	152128584	-18.205	4.286	<0.0001	<0.001
	cg03037684*	6	152421333	-6.440	1.561	<0.0001	<0.001
	cg24900983*	6	152128528	-13.031	3.254	<0.0001	0.001
	cg23165623*	6	152128411	-8.654	2.200	<0.0001	0.001
	cg01066157*	6	152451023	-7.094	1.854	0.0001	0.002
	cg12106976*	6	152002859	-4.070	1.091	0.0001	0.002
	cg07746998*	6	152126785	-7.783	2.108	0.0002	0.002
	cg02720618*	6	152129791	-20.115	5.715	0.0002	0.004
	cg21950534*	6	152128483	-9.206	2.677	0.0003	0.004
	cg13612689*	6	152128634	-11.793	3.470	0.0005	0.005
	cg07455133	6	152379044	-4.760	1.510	0.0006	0.009
	cg23467008	6	152128537	-20.569	6.479	0.0007	0.009
	cg25565730	6	152085565	-7.065	2.249	0.0017	0.009
	cg05171584	6	152128535	-9.680	3.241	0.0016	0.014
	cg23009221	6	152128588	-10.151	3.569	0.0018	0.021
	cg22157087	6	152012887	-4.589	1.676	0.0030	0.027
	cg17264271	6	152126938	-7.815	2.912	0.0047	0.030
ch.6.2949012F*	6	152044517	-2.496	0.954	0.0065	0.035	
<i>ER2</i>	cg23494957*	14	64761548	-8.818	1.594	<0.0001	<0.001
	cg01845091*	14	64761519	-8.599	1.958	<0.0001	<0.001
	cg22778790*	14	64761409	-12.285	3.201	<0.0001	0.002
	cg13037437*	14	64562705	-7.441	2.221	0.0009	0.009
	cg18852633*	14	64727509	-4.944	1.457	0.0008	0.009
<i>GPER1</i>	cg13435834*	7	1123508	-6.402	1.076	<0.0001	<0.001
	cg03595161*	7	1127767	-7.956	1.462	<0.0001	<0.001
	cg04498913*	7	1135747	-5.013	1.011	<0.0001	<0.001
	cg20934096*	7	1117418	-4.890	0.976	<0.0001	<0.001
	cg11697111*	7	1126903	-7.640	1.558	<0.0001	<0.001
	cg03214053*	7	1132134	-7.047	1.475	<0.0001	<0.001
	cg15028507*	7	1121929	-4.623	0.978	<0.0001	<0.001
	cg02955354*	7	1135879	-5.825	1.346	<0.0001	<0.001
	cg03791074*	7	1117852	-6.371	1.463	<0.0001	<0.001
	cg00745693*	7	1136023	-5.490	1.283	<0.0001	<0.001
	cg18378883*	7	1126406	-10.703	2.516	<0.0001	<0.001
	cg12633817*	7	1117479	-4.876	1.161	<0.0001	<0.001
	cg04606995*	7	1116361	-5.273	1.289	0.0001	<0.001
	cg08137085*	7	1117540	-4.141	1.012	0.0001	<0.001
	cg05171693*	7	1117775	-5.339	1.313	0.0001	<0.001
	cg11461808*	7	1126579	-5.437	1.382	0.0001	<0.001
cg03348196*	7	1132345	-5.894	1.540	0.0002	<0.001	

cg26532930*	7	1137659	-13.475	3.519	0.0001	<0.001
cg04693046*	7	1132853	-5.755	1.558	0.0003	0.001
cg02910650*	7	1131628	-5.477	1.497	0.0003	0.001
cg01504489*	7	1131626	-5.029	1.451	0.0006	0.002
cg09510128*	7	1132036	-4.268	1.275	0.0009	0.003
cg03980715*	7	1130187	-5.781	1.778	0.0013	0.005
cg09672200*	7	1117916	-7.412	2.314	0.0015	0.005
cg07805999*	7	1123920	-3.853	1.213	0.0016	0.005
cg07012460*	7	1127709	-2.493	0.799	0.0019	0.006
cg07202610*	7	1142643	-4.492	1.442	0.0020	0.006
cg20293725*	7	1121899	-3.107	1.006	0.0022	0.006
cg19033943*	7	1140782	-4.424	1.443	0.0023	0.007
cg20028661*	7	1113854	-3.845	1.274	0.0027	0.008
cg08472276*	7	1133186	-4.721	1.570	0.0028	0.008
cg06720190*	7	1133882	-5.948	2.012	0.0033	0.009
cg21255128*	7	1140094	-6.687	2.279	0.0035	0.009
cg04206484*	7	1121657	-1.938	0.681	0.0046	0.011
cg26620655	7	1113029	-3.087	1.081	0.0045	0.011
cg27457078*	7	1126761	-9.210	3.217	0.0044	0.011
cg21235678	7	1130967	-3.374	1.265	0.0080	0.018
cg18565130	7	1120637	-4.765	1.798	0.0084	0.019
cg02666955*	7	1133979	-6.680	2.558	0.0094	0.02
cg22630939*	7	1135958	-3.808	1.453	0.0091	0.02
cg25826644*	7	1137374	-5.777	2.218	0.0095	0.02
cg23519637*	7	1121738	-2.115	0.832	0.0114	0.023
cg03317820*	7	1141533	-2.255	0.916	0.0143	0.027
cg10055222*	7	1125111	-4.971	2.015	0.0141	0.027
cg27010136*	7	1131122	-3.008	1.227	0.0147	0.027
cg00364696*	7	1142433	-4.027	1.657	0.0155	0.028
cg07904865*	7	1127420	-3.095	1.353	0.0227	0.04
cg16127845*	7	1126423	-3.652	1.603	0.0233	0.04
cg18297960	7	1142765	-3.019	1.325	0.0233	0.04
cg08719095	7	1135190	-3.059	1.370	0.0262	0.042
cg09597710	7	1121124	-2.909	1.306	0.0264	0.042
cg19947463	7	1113237	-2.549	1.140	0.0260	0.042
cg21126453	7	1120247	-3.129	1.391	0.0250	0.042
cg24005260*	7	1138185	-3.054	1.383	0.0278	0.043

*DNA methylation sites that are also associated with rate of cognitive decline.

eTable 5. CpG sites associated with the rate of cognitive decline in women.

<i>ER gene</i>	CpG	Chr.	Position	Estimate	SE	Raw P-value	FDR q-value
<i>ER1</i>	cg22389949*	6	152003038	-0.434	0.101	<0.0001	0.001
	cg01066157*	6	152451023	-0.767	0.210	0.0003	0.007
	cg12106976*	6	152002859	-0.451	0.123	0.0003	0.007
	cg00655307*	6	152128743	-1.293	0.367	0.0004	0.007
	cg21157690	6	152126895	-0.726	0.208	0.0005	0.007
	ch.6.2949012F*	6	152044517	-0.374	0.108	0.0005	0.007
	cg03037684*	6	152421333	-0.595	0.175	0.0007	0.007
	cg02720618*	6	152129791	-2.153	0.650	0.0009	0.008
	cg23165623*	6	152128411	-0.828	0.250	0.0009	0.008
	cg24900983*	6	152128528	-1.206	0.367	0.0010	0.008
	cg07746998*	6	152126785	-0.776	0.239	0.0012	0.008
	cg22839866*	6	152128584	-1.483	0.487	0.0023	0.015
	cg21950534*	6	152128483	-0.876	0.305	0.0041	0.024
	cg00601836	6	152130332	-0.355	0.127	0.0052	0.028
cg13612689*	6	152128634	-1.021	0.392	0.0092	0.047	
<i>ER2</i>	cg23494957*	14	64761548	-0.856	0.181	<0.0001	<0.001
	cg01845091*	14	64761519	-0.923	0.223	<0.0001	<0.001
	cg22778790*	14	64761409	-1.340	0.358	0.0002	0.003
	cg18852633*	14	64727509	-0.507	0.167	0.0024	0.030
	cg13037437*	14	64562705	-0.747	0.255	0.0034	0.034
<i>GPER1</i>	cg13435834*	7	1123508	-0.697	0.121	<0.0001	<0.001
	cg18378883*	7	1126406	-1.516	0.275	<0.0001	<0.001
	cg03595161*	7	1127767	-0.864	0.164	<0.0001	<0.001
	cg04498913*	7	1135747	-0.579	0.114	<0.0001	<0.001
	cg03214053*	7	1132134	-0.759	0.168	<0.0001	<0.001
	cg15028507*	7	1121929	-0.495	0.110	<0.0001	<0.001
	cg11461808*	7	1126579	-0.680	0.155	<0.0001	<0.001
	cg02910650*	7	1131628	-0.699	0.171	<0.0001	<0.001
	cg03348196*	7	1132345	-0.721	0.176	<0.0001	<0.001
	cg04606995*	7	1116361	-0.597	0.146	<0.0001	<0.001
	cg01504489*	7	1131626	-0.656	0.166	<0.0001	<0.001
	cg02955354*	7	1135879	-0.600	0.153	<0.0001	<0.001
	cg05171693*	7	1117775	-0.576	0.146	<0.0001	<0.001
	cg09510128*	7	1132036	-0.572	0.145	<0.0001	<0.001
	cg19033943*	7	1140782	-0.648	0.164	<0.0001	<0.001
	cg20934096*	7	1117418	-0.443	0.112	<0.0001	<0.001
	cg00745693*	7	1136023	-0.565	0.145	0.0001	<0.001
	cg03791074*	7	1117852	-0.632	0.167	0.0002	<0.001
	cg21255128*	7	1140094	-0.947	0.261	0.0003	0.001
	cg11697111*	7	1126903	-0.632	0.176	0.0003	0.001
cg08137085*	7	1117540	-0.405	0.115	0.0005	0.002	
cg12633817*	7	1117479	-0.467	0.135	0.0005	0.002	

cg07805999*	7	1123920	-0.472	0.138	0.0006	0.002
cg04693046*	7	1132853	-0.606	0.179	0.0007	0.002
cg26532930*	7	1137659	-1.372	0.410	0.0008	0.003
cg03980715*	7	1130187	-0.649	0.203	0.0014	0.005
cg20293725*	7	1121899	-0.363	0.114	0.0015	0.005
cg07012460*	7	1127709	-0.294	0.094	0.0017	0.005
cg16127845*	7	1126423	-0.573	0.182	0.0017	0.005
cg22630939*	7	1135958	-0.520	0.166	0.0017	0.005
cg07904865*	7	1127420	-0.472	0.152	0.0019	0.005
cg06720190*	7	1133882	-0.679	0.229	0.0031	0.008
cg09672200*	7	1117916	-0.776	0.262	0.0031	0.008
cg07202610*	7	1142643	-0.480	0.163	0.0032	0.008
cg04206484*	7	1121657	-0.228	0.078	0.0034	0.008
cg02666955*	7	1133979	-0.840	0.290	0.0038	0.009
cg08472276*	7	1133186	-0.509	0.179	0.0044	0.010
cg10055222*	7	1125111	-0.650	0.229	0.0046	0.010
cg03317820*	7	1141533	-0.286	0.105	0.0063	0.014
cg20028661*	7	1113854	-0.382	0.143	0.0075	0.016
cg27010136*	7	1131122	-0.371	0.140	0.0080	0.016
cg23519637*	7	1121738	-0.249	0.095	0.0086	0.017
cg27457078*	7	1126761	-0.957	0.365	0.0087	0.017
cg25826644*	7	1137374	-0.650	0.256	0.0112	0.021
cg00364696*	7	1142433	-0.441	0.188	0.0192	0.036
cg24005260*	7	1138185	-0.350	0.158	0.0271	0.049

*DNA methylation sites that are also associated with the level of cognition.

eTable 6. Summary of the associations of *ER* DNA methylation sites with the level and rate of cognitive decline prior to death in women.

<i>ER</i> gene	Total Number of CpGs	Number of CpGs associated with		
		Only level of cognition, n (%)	Only rate of cognitive decline, n (%)	Both level and rate of cognitive decline, n (%)
<i>GPER1</i>	84	8 (10)	0	46 (55)
<i>ER2</i>	50	0	0	5 (10%)
<i>ER1</i>	76	7 (9)	2 (3)	13 (17%)

eTable 7. CpG sites associated with the AD pathology indices in women.

Index	ER gene	CpG	Chr.	Position	Estimate	SE	Raw P-value	FDR q-value	
Tau	ER1	cg02720618	6	152129791	20.425	5.539	0.0003	0.023	
	ER2	cg23494957	14	64761548	5.998	1.582	0.0002	0.010	
	GPER1		cg03595161	7	1127767	5.248	1.452	0.0003	0.013
			cg04498913	7	1135747	3.754	0.998	0.0002	0.013
			cg03214053	7	1132134	4.728	1.453	0.0012	0.025
			cg20934096	7	1117418	3.218	0.964	0.0009	0.025
			cg15028507	7	1121929	3.078	0.968	0.0016	0.027
			cg13435834	7	1123508	3.236	1.079	0.0029	0.035
			cg18378883	7	1126406	7.535	2.497	0.0027	0.035
			cg00745693	7	1136023	3.683	1.267	0.0039	0.036
			cg20028661	7	1113854	3.653	1.244	0.0035	0.036
			cg11461808	7	1126579	3.814	1.354	0.0051	0.043
Global AD Pathology Score	GPER1		7	1117418	1.292	0.333	0.0001	0.008	
			7	1132134	1.712	0.505	0.0008	0.015	
			7	1135747	1.212	0.346	0.0005	0.015	
			7	1117775	1.497	0.447	0.0009	0.015	
			7	1117540	1.153	0.344	0.0009	0.015	
			7	1127767	1.596	0.507	0.0018	0.025	
			7	1138903	1.668	0.549	0.0026	0.027	
			7	1121929	1.015	0.335	0.0026	0.027	
			7	1117916	2.328	0.781	0.0031	0.029	
			7	1135879	1.350	0.460	0.0035	0.029	
			7	1136023	1.242	0.439	0.0049	0.034	
			7	1137659	3.408	1.194	0.0045	0.034	
			7	1117852	1.361	0.499	0.0066	0.043	
			7	1142643	1.311	0.488	0.0075	0.045	

eTable 8. A linear mixed effects model examining association of RNA expression of *GPER1* in DLPFC with cognitive decline.

Models' terms	Estimate (SE), p-value
Intercept	1.714 (0.631), 0.007
Age at death	-0.032 (0.006), <0.001
Education	0.044 (0.013), <0.001
GPER1 RNA expression level	-0.181 (0.045), <0.001
Time	0.096 (0.058), 0.010
Age at death×Time	-0.000 (0.001), 0.614
Education×Time	0.002 (0.001), 0.073
GPER1 RNA expression level ×Time	-0.014 (0.004), <0.001

eTable 9. A linear regression model examining association of RNA expression of *GPER1* in DLPFC with tau tangles density.

Models' terms	Estimate (SE), p-value
Intercept	-0.281 (0.713), 0.694
Age at death	0.030 (0.007), <0.001
Education	-0.023 (0.015), 0.111
GPER1 RNA expression level	0.140 (0.051), 0.006

eTable 10. Associations of *GPER1* RNA expressions with AD phenotypes in women stratified by AD pathological diagnosis.

Outcome	AD Pathological Diagnosis	
	Yes	No
	Estimate, (SE), P-value	
Level of cognition proximate to death	-0.221 (0.058), <0.001	-0.052 (0.061), 0.395
Rate of cognitive decline	-0.015 (0.005), 0.004	-0.010 (0.006), 0.107

Estimates of associations of *GPER1* RNA expression with cognitive decline are derived from mixed effects models controlled for age at death, education, and their interaction with time.

eTable 11. Associations of RNA expressions in DLPFC of genes of JNK, ERK, and Akt signaling pathways with cognitive decline in women.

Model	Gene	Level of cognition	Rate of cognitive decline
		Estimate, (SE), q-value	
1	<i>JNK1</i>	-0.260 (0.205), 0.330	-0.028 (0.019), 0.216
	<i>JNK2</i>	0.882 (0.271), 0.005	0.092 (0.025), 0.002
	<i>JNK3</i>	-0.127 (0.190), 0.504	-0.008 (0.017), 0.749
2	<i>ERK1</i>	-0.448 (0.264), 0.230	-0.046 (0.024), 0.139
	<i>ERK2</i>	0.948 (0.268), 0.003	0.083 (0.025), 0.003
3	<i>Akt1</i>	-0.487 (0.308), 0.230	-0.051 (0.028), 0.139
	<i>Akt2</i>	-0.046 (0.242), 0.935	-0.004 (0.022), 0.859
	<i>Akt3</i>	0.018 (0.226), 0.935	-0.012 (0.021), 0.735

Estimates are derived from 3 separate mixed effects models, each examined one of the signaling pathways (JNK, ERK, Akt) mediating activated estrogen receptors. Models' terms were RNA expressions of genes identified in the second column, time, and interaction of the RNA expressions with time. All models were controlled for age at death and education and interaction of age at death and education with time. The q-values are FDR corrected p-values.

eTable 12. Associations of RNA expressions in DLPFC of genes of JNK, ERK, and Akt signaling pathways with AD pathological indices in women.

Model	Gene	AD pathologic indices		
		A β	Tau	Global AD Pathology Score
		Estimate, (SE), q-value		
1	<i>JNK1</i>	0.384 (0.206), 0.166	0.186 (0.232), 0.483	0.152 (0.069), 0.074
	<i>JNK2</i>	-0.921 (0.271), 0.006	-0.979 (0.305), 0.013	-0.316 (0.091), 0.004
	<i>JNK3</i>	-0.052 (0.191), 0.896	0.437 (0.215), 0.084	0.036 (0.064), 0.660
2	<i>ERK1</i>	0.215 (0.266), 0.559	0.284 (0.299), 0.457	0.008 (0.089), 0.925
	<i>ERK2</i>	-0.796 (0.268), 0.012	-0.866 (0.302), 0.017	-0.219 (0.090), 0.062
3	<i>Akt1</i>	0.411 (0.308), 0.292	0.712 (0.347), 0.084	0.107 (0.103), 0.483
	<i>Akt2</i>	0.388 (0.241), 0.217	0.362 (0.270), 0.289	0.143 (0.081), 0.155
	<i>Akt3</i>	0.013 (0.226), 0.955	-0.003 (0.254), 0.992	-0.050 (0.076), 0.660

Estimates are derived from 3 series of linear regressions each examined one of the signaling pathways (JNK, ERK, Akt) of activated estrogen receptors. Each series constituted of 3 separate linear regressions with models' terms being RNA expressions of genes identified in the second column and the outcomes being AD pathologic indices. All models were controlled for age at death and education. The q-values are FDR corrected p-values.

eTable 13. Associations of RNA expressions in DLPFC of 100 randomly selected genes with cognitive decline in women.

Gene#	Gene	Gene description	Level of cognition	Rate of cognitive decline
			Estimate, (SE), q-value	
1	ENSG00000011638	Lipid Droplet Assembly Factor 1	-0.21 (0.086), 0.062	-0.017 (0.008), 0.100
2	ENSG00000055211	Glycosylated Integral Membrane Protein 1	-0.242 (0.147), 0.233	-0.030 (0.013), 0.094
3	ENSG00000058673	Zinc Finger CCCH-Type Containing 11A	-0.905 (0.173), <0.001	-0.077 (0.016), <0.001
4	ENSG00000074755	Zinc Finger ZZ-Type And EF-Hand Domain Containing 1	-0.226 (0.268), 0.579	-0.012 (0.025), 0.747
5	ENSG00000075429	Calcium Voltage-Gated Channel Auxiliary Subunit Gamma 5	-0.057 (0.056), 0.53	-0.008 (0.005), 0.269
6	ENSG00000082014	SWI/SNF Related, Matrix Associated, Actin Dependent Regulator Of Chromatin, Subfamily D, Member 3	-0.866 (0.201), <0.001	-0.076 (0.019), 0.001
7	ENSG00000083290	Unc-51 Like Autophagy Activating Kinase 2	0.028 (0.221), 0.903	-0.002 (0.02), 0.956
8	ENSG00000085276	MDS1 And EVI1 Complex Locus	-0.067 (0.071), 0.564	-0.009 (0.006), 0.348
9	ENSG00000085999	RAD54 Like	0.092 (0.062), 0.293	0.011 (0.006), 0.134
10	ENSG00000088340	Fer-1 Like Family Member 4 (Pseudogene)	0.243 (0.08), 0.018	0.022 (0.007), 0.015
11	ENSG00000099992	TBC1 Domain Family Member 10A	-0.028 (0.108), 0.833	-0.007 (0.01), 0.617
12	ENSG00000101181	Mitochondrial Ribosome Associated GTPase 2	0.164 (0.177), 0.564	-0.002 (0.016), 0.922
13	ENSG00000101421	Charged Multivesicular Body Protein 4B	0.803 (0.316), 0.051	0.075 (0.029), 0.04
14	ENSG00000102119	Emerin	0.569 (0.122), <0.001	0.050 (0.011), <0.001
15	ENSG00000104450	Sperm Associated Antigen 1	-0.229 (0.15), 0.283	-0.027 (0.014), 0.134
16	ENSG00000105393	BRISCA And BRCA1 A Complex Member 1	0.421 (0.219), 0.159	0.036 (0.02), 0.184
17	ENSG00000106526	Actin Related Protein 3C	0.074 (0.079), 0.564	0.007 (0.007), 0.538
18	ENSG00000106733	Nicotinamide Riboside Kinase 1	0.092 (0.104), 0.568	0.009 (0.01), 0.538
19	ENSG00000106852	LIM Homeobox 6	0.116 (0.083), 0.338	0.017 (0.008), 0.086
20	ENSG00000108771	DExH-Box Helicase 58	0.338 (0.095), 0.003	0.027 (0.009), 0.014

21	ENSG00000109079	TNF Alpha Induced Protein 1	-0.068 (0.236), 0.823	-0.022 (0.022), 0.514
22	ENSG00000110917	Malectin	-0.341 (0.183), 0.165	-0.034 (0.017), 0.134
23	ENSG00000111674	Enolase 2	0.308 (0.083), 0.003	0.030 (0.008), 0.001
24	ENSG00000111877	Minichromosome Maintenance 9 Homologous Recombination Repair Factor	-0.268 (0.182), 0.297	-0.030 (0.017), 0.189
25	ENSG00000114767	Ribosomal RNA Processing 9, U3 Small Nucleolar RNA Binding Protein	0.365 (0.178), 0.128	0.036 (0.016), 0.094
26	ENSG00000116752	BCAS2 Pre-mRNA Processing Factor	0.531 (0.178), 0.018	0.045 (0.016), 0.030
27	ENSG00000119523	ALG2 Alpha-1,3/1,6-Mannosyltransferase	0.469 (0.173), 0.033	0.050 (0.016), 0.010
28	ENSG00000120800	UTP20 Small Subunit Processome Component	0.345 (0.188), 0.167	0.023 (0.017), 0.369
29	ENSG00000120896	Sorbin And SH3 Domain Containing 3	-0.085 (0.124), 0.651	-0.012 (0.011), 0.514
30	ENSG00000122203	KIAA1191	0.509 (0.304), 0.225	0.041 (0.028), 0.294
31	ENSG00000123104	Inositol 1,4,5-Trisphosphate Receptor Type 2	-0.068 (0.114), 0.679	-0.007 (0.01), 0.641
32	ENSG00000128789	Proteasome Assembly Chaperone 2	0.175 (0.164), 0.518	0.015 (0.015), 0.538
33	ENSG00000132670	Protein Tyrosine Phosphatase Receptor Type A	-0.166 (0.285), 0.679	-0.005 (0.026), 0.896
34	ENSG00000132842	Adaptor Related Protein Complex 3 Subunit Beta 1	-0.117 (0.135), 0.568	-0.016 (0.012), 0.373
35	ENSG00000133028	Synthesis Of Cytochrome C Oxidase 1	-0.327 (0.195), 0.225	-0.019 (0.018), 0.514
36	ENSG00000133302	SMC5-SMC6 Complex Localization Factor 1	0.267 (0.135), 0.144	0.025 (0.012), 0.134
37	ENSG00000135625	Early Growth Response 4	0.023 (0.038), 0.679	0.003 (0.003), 0.558
38	ENSG00000135709	KIAA0513	0.222 (0.149), 0.293	0.015 (0.014), 0.502
39	ENSG00000135750	Potassium Two Pore Domain Channel Subfamily K Member 1	0.06 (0.09), 0.651	0.002 (0.008), 0.860
40	ENSG00000135966	Transforming Growth Factor Beta Receptor Associated Protein 1	-0.322 (0.25), 0.389	-0.018 (0.023), 0.580
41	ENSG00000136866	ZFP37 Zinc Finger Protein	-0.03 (0.09), 0.807	-0.007 (0.008), 0.580
42	ENSG00000136875	Pre-mRNA Processing Factor 4	0.889 (0.245), 0.003	0.067 (0.023), 0.017

43	ENSG00000138767	CCR4-NOT Transcription Complex Subunit 6 Like	-0.132 (0.23), 0.679	-0.018 (0.021), 0.558
44	ENSG00000140015	Potassium Voltage-Gated Channel Subfamily H Member 5	0.091 (0.089), 0.53	0.007 (0.008), 0.555
45	ENSG00000140564	Furin, Paired Basic Amino Acid Cleaving Enzyme	-0.875 (0.161), <0.001	-0.083 (0.015), <0.001
46	ENSG00000140798	ATP Binding Cassette Subfamily C Member 12	0.242 (0.062), 0.001	0.021 (0.006), 0.002
47	ENSG00000140939	Nucleolar Protein 3	0.316 (0.139), 0.08	0.024 (0.013), 0.159
48	ENSG00000147889	Cyclin Dependent Kinase Inhibitor 2A	-0.042 (0.061), 0.651	-0.004 (0.006), 0.628
49	ENSG00000148356	Leucine Rich Repeat And Sterile Alpha Motif Containing 1	0.786 (0.185), <0.001	0.071 (0.017), 0.001
50	ENSG00000150779	Translocase Of Inner Mitochondrial Membrane 8 Homolog B	0.393 (0.205), 0.159	0.029 (0.019), 0.269
51	ENSG00000154874	Coiled-Coil Domain Containing 144B, Pseudogene	0.066 (0.057), 0.472	0.005 (0.005), 0.555
52	ENSG00000158483	Family With Sequence Similarity 86 Member C1, Pseudogene	0.076 (0.093), 0.594	0.007 (0.009), 0.601
53	ENSG00000161040	F-Box And Leucine Rich Repeat Protein 13	0.019 (0.075), 0.833	0.003 (0.007), 0.747
54	ENSG00000162688	Amylo-Alpha-1, 6-Glucosidase, 4-Alpha-Glucanotransferase	0.329 (0.139), 0.071	0.021 (0.013), 0.242
55	ENSG00000163377	TAFA Chemokine Like Family Member 4	-0.028 (0.075), 0.796	0.005 (0.007), 0.628
56	ENSG00000163605	Protein Phosphatase 4 Regulatory Subunit 2	-0.895 (0.139), <0.001	-0.078 (0.013), <0.001
57	ENSG00000163625	WD Repeat And FYVE Domain Containing 3	-1.043 (0.278), 0.002	-0.094 (0.025), 0.002
58	ENSG00000165259	Highly Divergent Homeobox	0.275 (0.145), 0.16	0.032 (0.014), 0.074
59	ENSG00000166225	Fibroblast Growth Factor Receptor Substrate 2	-0.516 (0.175), 0.02	-0.048 (0.016), 0.015
60	ENSG00000167664	Transmembrane And Immunoglobulin Domain Containing 2	0.05 (0.052), 0.559	0.005 (0.005), 0.538
61	ENSG00000167874	Transmembrane Protein 88	0.022 (0.051), 0.784	0.004 (0.005), 0.580
62	ENSG00000168116	KIAA1586	-0.02 (0.162), 0.903	-0.001 (0.015), 0.972

63	ENSG00000168496	Flap Structure-Specific Endonuclease 1	0.057 (0.086), 0.651	0.005 (0.008), 0.628
64	ENSG00000171466	Zinc Finger Protein 562	-0.084 (0.21), 0.79	-0.023 (0.019), 0.440
65	ENSG00000172175	MALT1 Paracaspase	-0.598 (0.179), 0.006	-0.054 (0.016), 0.008
66	ENSG00000172466	Zinc Finger Protein 24	-0.641 (0.177), 0.003	-0.061 (0.016), 0.002
67	ENSG00000174132	Family With Sequence Similarity 174 Member A	0.231 (0.122), 0.16	0.026 (0.011), 0.074
68	ENSG00000175130	MARCKS Like 1	0.153 (0.125), 0.427	0.011 (0.011), 0.538
69	ENSG00000175309	5-Phosphohydroxy-L-Lysine Phospho-Lyase	0.074 (0.131), 0.679	0.010 (0.012), 0.558
70	ENSG00000176125	UFM1 Specific Peptidase 1 (Inactive)	-0.022 (0.066), 0.808	-0.002 (0.006), 0.839
71	ENSG00000177076	Alkaline Ceramidase 2	-0.14 (0.057), 0.059	-0.012 (0.005), 0.086
72	ENSG00000177108	Zinc Finger DHHC-Type Palmitoyltransferase 22	-0.149 (0.114), 0.381	-0.013 (0.011), 0.416
73	ENSG00000177640	Cancer Susceptibility 2	0.24 (0.113), 0.11	0.022 (0.011), 0.130
74	ENSG00000179134	Sterile Alpha Motif Domain Containing 4B	0.5 (0.174), 0.023	0.029 (0.016), 0.170
75	ENSG00000180667	YOD1 Deubiquitinase	-0.338 (0.146), 0.076	-0.020 (0.013), 0.294
76	ENSG00000182185	RAD51 Paralog B	-0.183 (0.099), 0.165	-0.013 (0.009), 0.294
77	ENSG00000187664	Hyaluronan And Proteoglycan Link Protein 4	0.057 (0.078), 0.646	0.005 (0.007), 0.611
78	ENSG00000198538	Zinc Finger Protein 28	-0.317 (0.128), 0.059	-0.025 (0.012), 0.121
79	ENSG00000198712	Mitochondrially Encoded Cytochrome C Oxidase II	-0.147 (0.132), 0.489	-0.011 (0.012), 0.555
80	ENSG00000198865	Coiled-Coil Domain Containing 152	0.08 (0.091), 0.568	0.002 (0.008), 0.860
81	ENSG00000205572	Small EDRK-Rich Factor 1B	0.354 (0.1), 0.003	0.031 (0.009), 0.008
82	ENSG00000215126	Zn Regulated GTPase Metalloprotein Activator 1F	0.028 (0.08), 0.803	0.002 (0.007), 0.833
83	ENSG00000223963	THAP Domain Containing 12 Pseudogene 8	-0.033 (0.057), 0.679	0.002 (0.005), 0.833
84	ENSG00000228376	Growth Arrest Specific 2 Like 1 Pseudogene 2	-0.043 (0.049), 0.568	0.000 (0.004), 0.977
85	ENSG00000231672	Disrupted In Renal Carcinoma 3	0.015 (0.076), 0.874	-0.004 (0.007), 0.646
86	ENSG00000232433	GXYLT1 Pseudogene 3	-0.009 (0.073), 0.903	-0.002 (0.007), 0.860

87	ENSG00000239665	Unidentified gene	-0.174 (0.061), 0.024	-0.010 (0.006), 0.204
88	ENSG00000247679	Novel Transcript	-0.107 (0.048), 0.089	-0.015 (0.004), 0.007
89	ENSG00000260261	Programmed Cell Death 6 (PDCD6) Pseudogene	-0.028 (0.074), 0.796	-0.003 (0.007), 0.770
90	ENSG00000260280	SLX1B-SULT1A4 Readthrough (NMD Candidate)	0.047 (0.07), 0.651	0.009 (0.006), 0.294
91	ENSG00000269834	ZNF528 Antisense RNA 1	0.04 (0.053), 0.629	0.003 (0.005), 0.628
92	ENSG00000270276	H4 Clustered Histone 15	0.01 (0.033), 0.823	0.001 (0.003), 0.828
93	ENSG00000271936	Novel Transcript, Antisense To ADCY3	-0.169 (0.062), 0.033	-0.017 (0.006), 0.021
94	ENSG00000272899	ATP6V1F Neighbor	-0.035 (0.035), 0.53	-0.006 (0.003), 0.168
95	ENSG00000273064	Novel Transcript	-0.04 (0.081), 0.733	-0.005 (0.007), 0.628
96	ENSG00000273151	Novel Transcript, Antisense To GET4	-0.057 (0.063), 0.564	-0.005 (0.006), 0.555
97	ENSG00000276529	Novel Transcript	-0.068 (0.064), 0.518	-0.004 (0.006), 0.641
98	ENSG00000279811	Uncategorized gene	0.067 (0.041), 0.234	0.007 (0.004), 0.175
99	ENSG00000280422	Uncategorized gene	-0.066 (0.093), 0.648	-0.001 (0.008), 0.956
100	ENSG00000284737	Unidentified gene	-0.099 (0.043), 0.076	-0.010 (0.004), 0.040

Estimates are derived from 100 separate mixed effects models, each examined one of the 100 randomly selected RNA expression level. Models' terms were RNA expressions of genes identified in the second column, time, and interaction of the RNA expressions with time. All models were controlled for age at death and education and interaction of age at death and education with time. The q-values are FDR corrected p-values.

eTable 14. Associations of RNA expressions in DLPFC of 100 randomly selected genes with AD pathological indices in women.

Gene#	Gene	Gene description	AD pathological indices		
			A β	Tau	Global AD Pathology Score
			Estimate, (SE), q-value		
1	ENSG00000011638	Lipid Droplet Assembly Factor 1	0.209 (0.086), 0.136	0.233 (0.097), 0.100	0.067 (0.029), 0.242
2	ENSG00000055211	Glycosylated Integral Membrane Protein 1	0.283 (0.147), 0.247	0.174 (0.165), 0.516	0.065 (0.049), 0.494
3	ENSG00000058673	Zinc Finger CCCH-Type Containing 11A	0.476 (0.175), 0.127	0.663 (0.196), 0.013	0.103 (0.059), 0.331
4	ENSG00000074755	Zinc Finger ZZ-Type And EF-Hand Domain Containing 1	0.142 (0.269), 0.806	0.087 (0.302), 0.945	0.059 (0.09), 0.715
5	ENSG00000075429	Calcium Voltage-Gated Channel Auxiliary Subunit Gamma 5	-0.001 (0.057), 0.998	-0.079 (0.064), 0.407	-0.037 (0.019), 0.278
6	ENSG00000082014	SWI/SNF Related, Matrix Associated, Actin Dependent Regulator Of Chromatin, Subfamily D, Member 3	0.523 (0.203), 0.127	0.897 (0.227), 0.004	0.143 (0.068), 0.278
7	ENSG00000083290	Unc-51 Like Autophagy Activating Kinase 2	0.119 (0.221), 0.806	-0.442 (0.248), 0.208	-0.062 (0.074), 0.660
8	ENSG00000085276	MDS1 And EVI1 Complex Locus	0.088 (0.071), 0.599	0.012 (0.08), 0.947	-0.001 (0.024), 0.976
9	ENSG00000085999	RAD54 Like	-0.042 (0.061), 0.768	-0.016 (0.069), 0.945	-0.019 (0.021), 0.639
10	ENSG00000088340	Fer-1 Like Family Member 4 (Pseudogene)	-0.138 (0.081), 0.345	-0.182 (0.09), 0.164	-0.066 (0.027), 0.242
11	ENSG00000099992	TBC1 Domain Family Member 10A	0 (0.108), 0.998	-0.066 (0.121), 0.838	0.015 (0.036), 0.867
12	ENSG00000101181	Mitochondrial Ribosome Associated GTPase 2	-0.145 (0.178), 0.702	-0.269 (0.2), 0.363	-0.004 (0.06), 0.976
13	ENSG00000101421	Charged Multivesicular Body Protein 4B	-0.105 (0.319), 0.866	-0.417 (0.358), 0.445	-0.081 (0.107), 0.704
14	ENSG00000102119	Emerin	-0.239 (0.124), 0.247	-0.42 (0.139), 0.033	-0.101 (0.041), 0.242
15	ENSG00000104450	Sperm Associated Antigen 1	-0.067 (0.15), 0.82	0.275 (0.168), 0.262	0.032 (0.05), 0.715

16	ENSG00000105393	BRISC And BRCA1 A Complex Member 1	-0.111 (0.22), 0.806	-0.067 (0.247), 0.945	0.004 (0.074), 0.976
17	ENSG00000106526	Actin Related Protein 3C	-0.115 (0.079), 0.456	-0.053 (0.089), 0.822	-0.048 (0.026), 0.331
18	ENSG00000106733	Nicotinamide Riboside Kinase 1	0.122 (0.104), 0.615	-0.042 (0.117), 0.945	0.025 (0.035), 0.708
19	ENSG00000106852	LIM Homeobox 6	-0.221 (0.083), 0.127	-0.15 (0.094), 0.273	-0.043 (0.028), 0.418
20	ENSG00000108771	DExH-Box Helicase 58	-0.018 (0.096), 0.929	-0.286 (0.107), 0.065	-0.021 (0.032), 0.715
21	ENSG00000109079	TNF Alpha Induced Protein 1	0.195 (0.237), 0.702	0.309 (0.266), 0.445	0.055 (0.079), 0.710
22	ENSG00000110917	Malectin	0.16 (0.184), 0.686	0.043 (0.207), 0.945	-0.016 (0.062), 0.932
23	ENSG00000111674	Enolase 2	-0.167 (0.084), 0.233	-0.164 (0.094), 0.224	-0.04 (0.028), 0.466
24	ENSG00000111877	Minichromosome Maintenance 9 Homologous Recombination Repair Factor	0.157 (0.182), 0.686	0.115 (0.205), 0.838	-0.009 (0.061), 0.960
25	ENSG00000114767	Ribosomal RNA Processing 9, U3 Small Nucleolar RNA Binding Protein	-0.088 (0.179), 0.806	-0.253 (0.2), 0.407	-0.058 (0.06), 0.639
26	ENSG00000116752	BCAS2 Pre-mRNA Processing Factor	-0.363 (0.179), 0.233	-0.409 (0.201), 0.164	-0.11 (0.06), 0.331
27	ENSG00000119523	ALG2 Alpha-1,3/1,6-Mannosyltransferase	-0.226 (0.174), 0.573	0.046 (0.196), 0.945	-0.051 (0.058), 0.656
28	ENSG00000120800	UTP20 Small Subunit Processome Component	-0.205 (0.189), 0.645	-0.492 (0.211), 0.114	-0.127 (0.063), 0.278
29	ENSG00000120896	Sorbin And SH3 Domain Containing 3	0.129 (0.125), 0.645	0.003 (0.14), 0.993	0.017 (0.042), 0.867
30	ENSG00000122203	KIAA1191	0.159 (0.307), 0.806	0.061 (0.345), 0.945	-0.015 (0.102), 0.960
31	ENSG00000123104	Inositol 1,4,5-Trisphosphate Receptor Type 2	0.035 (0.114), 0.869	0.024 (0.128), 0.945	-0.027 (0.038), 0.708
32	ENSG00000128789	Proteasome Assembly Chaperone 2	-0.382 (0.163), 0.145	-0.305 (0.184), 0.258	-0.081 (0.055), 0.454
33	ENSG00000132670	Protein Tyrosine Phosphatase Receptor Type A	0.712 (0.284), 0.136	0.119 (0.321), 0.945	0.185 (0.095), 0.295
34	ENSG00000132842	Adaptor Related Protein Complex 3 Subunit Beta 1	0.19 (0.135), 0.485	-0.002 (0.152), 0.993	0.039 (0.045), 0.656
35	ENSG00000133028	Synthesis Of Cytochrome C Oxidase 1	0.175 (0.196), 0.686	0.393 (0.22), 0.208	0.072 (0.065), 0.593

36	ENSG00000133302	SMC5-SMC6 Complex Localization Factor 1	-0.31 (0.135), 0.145	-0.283 (0.152), 0.190	-0.09 (0.045), 0.278
37	ENSG00000135625	Early Growth Response 4	0.003 (0.038), 0.965	-0.015 (0.043), 0.945	0.004 (0.013), 0.914
38	ENSG00000135709	KIAA0513	-0.105 (0.149), 0.768	-0.058 (0.168), 0.945	-0.009 (0.05), 0.957
39	ENSG00000135750	Potassium Two Pore Domain Channel Subfamily K Member 1	0.004 (0.09), 0.981	0.105 (0.102), 0.525	0.005 (0.03), 0.957
40	ENSG00000135966	Transforming Growth Factor Beta Receptor Associated Protein 1	0.372 (0.251), 0.448	0.598 (0.281), 0.155	0.149 (0.084), 0.331
41	ENSG00000136866	ZFP37 Zinc Finger Protein	-0.035 (0.09), 0.842	-0.025 (0.101), 0.945	-0.018 (0.03), 0.744
42	ENSG00000136875	Pre-mRNA Processing Factor 4	-0.603 (0.246), 0.136	-0.833 (0.276), 0.033	-0.189 (0.082), 0.249
43	ENSG00000138767	CCR4-NOT Transcription Complex Subunit 6 Like	0.116 (0.229), 0.806	0.025 (0.258), 0.982	0.017 (0.077), 0.952
44	ENSG00000140015	Potassium Voltage-Gated Channel Subfamily H Member 5	-0.057 (0.089), 0.794	0.101 (0.1), 0.529	0.026 (0.03), 0.656
45	ENSG00000140564	Furin, Paired Basic Amino Acid Cleaving Enzyme	0.292 (0.163), 0.31	0.683 (0.182), 0.006	0.168 (0.054), 0.071
46	ENSG00000140798	ATP Binding Cassette Subfamily C Member 12	-0.143 (0.062), 0.145	-0.234 (0.069), 0.013	-0.049 (0.021), 0.242
47	ENSG00000140939	Nucleolar Protein 3	-0.079 (0.14), 0.806	-0.284 (0.157), 0.206	-0.066 (0.047), 0.466
48	ENSG00000147889	Cyclin Dependent Kinase Inhibitor 2A	0.032 (0.061), 0.806	0.068 (0.068), 0.53	0.022 (0.02), 0.593
49	ENSG00000148356	Leucine Rich Repeat And Sterile Alpha Motif Containing 1	-0.61 (0.186), 0.048	-0.559 (0.21), 0.065	-0.176 (0.062), 0.122
50	ENSG00000150779	Translocase Of Inner Mitochondrial Membrane 8 Homolog B	-0.35 (0.206), 0.345	-0.509 (0.231), 0.134	-0.138 (0.069), 0.278
51	ENSG00000154874	Coiled-Coil Domain Containing 144B, Pseudogene	-0.009 (0.058), 0.929	0.001 (0.065), 0.993	-0.021 (0.019), 0.593
52	ENSG00000158483	Family With Sequence Similarity 86 Member C1, Pseudogene	-0.051 (0.093), 0.806	-0.019 (0.105), 0.945	-0.014 (0.031), 0.864
53	ENSG00000161040	F-Box And Leucine Rich Repeat Protein 13	-0.073 (0.075), 0.646	-0.006 (0.084), 0.984	-0.027 (0.025), 0.593
54	ENSG00000162688	Amylo-Alpha-1, 6-Glucosidase, 4-Alpha-Glucanotransferase	-0.157 (0.14), 0.636	-0.406 (0.157), 0.075	-0.057 (0.047), 0.514

55	ENSG00000163377	TAFA Chemokine Like Family Member 4	0.012 (0.075), 0.929	-0.065 (0.084), 0.713	0 (0.025), 0.999
56	ENSG00000163605	Protein Phosphatase 4 Regulatory Subunit 2	0.616 (0.141), 0.001	0.864 (0.158), <0.001	0.216 (0.047), 0.001
57	ENSG00000163625	WD Repeat And FYVE Domain Containing 3	0.79 (0.279), 0.119	0.637 (0.314), 0.164	0.117 (0.094), 0.514
58	ENSG00000165259	Highly Divergent Homeobox	-0.154 (0.146), 0.645	-0.126 (0.164), 0.713	-0.066 (0.049), 0.494
59	ENSG00000166225	Fibroblast Growth Factor Receptor Substrate 2	0.384 (0.176), 0.181	0.281 (0.198), 0.339	0.087 (0.059), 0.454
60	ENSG00000167664	Transmembrane And Immunoglobulin Domain Containing 2	-0.052 (0.052), 0.646	-0.16 (0.059), 0.063	-0.035 (0.017), 0.278
61	ENSG00000167874	Transmembrane Protein 88	-0.017 (0.051), 0.866	-0.09 (0.058), 0.281	-0.016 (0.017), 0.639
62	ENSG00000168116	KIAA1586	-0.188 (0.163), 0.623	0.113 (0.183), 0.812	0.004 (0.054), 0.976
63	ENSG00000168496	Flap Structure-Specific Endonuclease 1	-0.069 (0.086), 0.707	-0.062 (0.097), 0.809	-0.004 (0.029), 0.964
64	ENSG00000171466	Zinc Finger Protein 562	-0.102 (0.21), 0.806	-0.341 (0.235), 0.33	-0.073 (0.07), 0.593
65	ENSG00000172175	MALT1 Paracaspase	0.173 (0.181), 0.65	0.38 (0.203), 0.190	0.106 (0.06), 0.331
66	ENSG00000172466	Zinc Finger Protein 24	0.366 (0.179), 0.233	0.302 (0.201), 0.310	0.1 (0.06), 0.361
67	ENSG00000174132	Family With Sequence Similarity 174 Member A	-0.188 (0.123), 0.43	-0.15 (0.138), 0.497	-0.06 (0.041), 0.456
68	ENSG00000175130	MARCKS Like 1	0.02 (0.125), 0.929	-0.36 (0.14), 0.075	-0.069 (0.042), 0.374
69	ENSG00000175309	5-Phosphohydroxy-L-Lysine Phospho-Lyase	-0.021 (0.13), 0.929	-0.206 (0.146), 0.339	-0.013 (0.044), 0.932
70	ENSG00000176125	UFM1 Specific Peptidase 1 (Inactive)	-0.011 (0.067), 0.929	0.033 (0.075), 0.918	-0.015 (0.022), 0.71
71	ENSG00000177076	Alkaline Ceramidase 2	0.104 (0.058), 0.309	0.134 (0.065), 0.159	0.004 (0.019), 0.952
72	ENSG00000177108	Zinc Finger DHHC-Type Palmitoyltransferase 22	0.099 (0.114), 0.686	0.294 (0.128), 0.114	0.079 (0.038), 0.278
73	ENSG00000177640	Cancer Susceptibility 2	-0.17 (0.113), 0.448	-0.207 (0.127), 0.262	-0.033 (0.038), 0.656
74	ENSG00000179134	Sterile Alpha Motif Domain Containing 4B	0.084 (0.175), 0.806	-0.383 (0.196), 0.168	-0.042 (0.059), 0.708
75	ENSG00000180667	YOD1 Deubiquitinase	0.467 (0.146), 0.048	0.607 (0.164), 0.006	0.163 (0.049), 0.045

76	ENSG00000182185	RAD51 Paralog B	0.069 (0.099), 0.768	0.021 (0.111), 0.945	0.007 (0.033), 0.954
77	ENSG00000187664	Hyaluronan And Proteoglycan Link Protein 4	-0.033 (0.079), 0.824	0.122 (0.088), 0.345	0.017 (0.026), 0.715
78	ENSG00000198538	Zinc Finger Protein 28	0.259 (0.129), 0.233	0.336 (0.145), 0.114	0.059 (0.043), 0.482
79	ENSG00000198712	Mitochondrially Encoded Cytochrome C Oxidase II	0.14 (0.132), 0.645	0.093 (0.148), 0.812	0.056 (0.044), 0.513
80	ENSG00000198865	Coiled-Coil Domain Containing 152	-0.117 (0.091), 0.574	-0.204 (0.102), 0.168	-0.031 (0.031), 0.612
81	ENSG00000205572	Small EDRK-Rich Factor 1B	-0.122 (0.101), 0.609	-0.221 (0.113), 0.168	-0.027 (0.034), 0.677
82	ENSG00000215126	Zn Regulated GTPase Metalloprotein Activator 1F	-0.074 (0.08), 0.665	-0.038 (0.09), 0.925	-0.007 (0.027), 0.932
83	ENSG00000223963	THAP Domain Containing 12 Pseudogene 8	0.056 (0.057), 0.646	0.133 (0.064), 0.159	0.034 (0.019), 0.331
84	ENSG00000228376	Growth Arrest Specific 2 Like 1 Pseudogene 2	0.031 (0.049), 0.805	0.014 (0.055), 0.945	0.017 (0.016), 0.593
85	ENSG00000231672	Disrupted In Renal Carcinoma 3	0.056 (0.077), 0.766	0.106 (0.086), 0.408	0.027 (0.026), 0.593
86	ENSG00000232433	GXYLT1 Pseudogene 3	0.073 (0.073), 0.646	0.226 (0.081), 0.062	0.039 (0.024), 0.378
87	ENSG00000239665	Unidentified gene	0.073 (0.061), 0.615	0.089 (0.069), 0.392	0.026 (0.021), 0.513
88	ENSG00000247679	Novel Transcript	0.08 (0.048), 0.362	0.079 (0.054), 0.330	0.035 (0.016), 0.278
89	ENSG00000260261	Programmed Cell Death 6 (PDCD6) Pseudogene	0.009 (0.074), 0.939	0.014 (0.083), 0.946	-0.03 (0.025), 0.514
90	ENSG00000260280	SLX1B-SULT1A4 Readthrough (NMD Candidate)	-0.015 (0.07), 0.929	0.024 (0.079), 0.945	-0.022 (0.024), 0.639
91	ENSG00000269834	ZNF528 Antisense RNA 1	0.055 (0.053), 0.645	-0.132 (0.06), 0.134	0.002 (0.018), 0.976
92	ENSG00000270276	H4 Clustered Histone 15	0.012 (0.033), 0.847	-0.008 (0.037), 0.945	-0.003 (0.011), 0.932
93	ENSG00000271936	Novel Transcript, Antisense To ADCY3	0.163 (0.063), 0.127	0.176 (0.07), 0.084	0.037 (0.021), 0.331
94	ENSG00000272899	ATP6V1F Neighbor	-0.016 (0.035), 0.806	0.003 (0.039), 0.984	0.005 (0.012), 0.858
95	ENSG00000273064	Novel Transcript	0.191 (0.081), 0.145	-0.005 (0.092), 0.984	0.021 (0.027), 0.704
96	ENSG00000273151	Novel Transcript, Antisense To GET4	0.065 (0.063), 0.645	0.035 (0.071), 0.882	0.008 (0.021), 0.867
97	ENSG00000276529	Novel Transcript	-0.027 (0.064), 0.824	-0.02 (0.072), 0.945	0.001 (0.022), 0.979
98	ENSG00000279811	Uncategorized gene	0.022 (0.041), 0.806	0.03 (0.046), 0.809	0.018 (0.014), 0.494

99	ENSG00000280422	Uncategorized gene	0.147 (0.093), 0.407	0.057 (0.104), 0.838	0.029 (0.031), 0.639
100	ENSG00000284737	Unidentified gene	0.006 (0.043), 0.929	0.094 (0.048), 0.168	0.009 (0.014), 0.715

Estimates are derived from 3 series of linear regressions, each examined one of the Alzheimer's disease pathology index as the outcome. Each series constituted of 100 separate linear regressions with models' terms being RNA expressions of genes identified in the second column in separate models, and the outcomes were one of the AD pathological indices. All models were controlled for age at death and education. The q-values are FDR corrected p-values.

eTable 15. Summary of associations of the 3 estrogen receptor (*ER*) genes with longitudinal changes of cognition and underlying pathologies in men.

<i>ER</i>	Variant	Cognition		AD pathologic indices			Non-AD pathologies								
		Level	Rate of Decline	A β	Tau	Global AD Score	Lewy Body	TDP-43	HS	Macro-infarct	Micro-infarct	Atherosclerosis	Arteriolo-Sclerosis	CAA	
<i>GPER1</i>	SNPs	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	
	DNA methylation	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	
	RNA	DLP	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
		PCC	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
ACC		NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	
<i>ER2</i>	SNPs	NS	NS	NS	*	NS	NS	NS	NS	NS	NS	NS	NS	NS	
	DNA methylation	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	
	RNA	DLP	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
		PCC	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
ACC		NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	

<i>ERI</i>	SNPs	0.019	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
	DNA methylation	0.043	NS	0.040	0.003	0.033	NS	NS	NS	NS	NS	NS	NS	NS

Cells with single values indicate q-values (FDR-corrected p-values) derived from omnibus tests that combine p-values of the associations of SNPs or CpG sites with the outcomes.

NS: Not significant; HS: Hippocampal sclerosis; CAA: Cerebral amyloid angiopathy; DLP: Dorsolateral prefrontal cortex; ACC: Anterior cingulate cortex; PCC: Posterior cingulate cortex;

eTable 16. *ERI* SNP associated with level of global cognition at baseline in men.

Outcome	Chr.	Position	Estimate	SE	Raw P-value	FDR q-value
Level of global cognition	6	152133351	-0.355	0.077	<0.0001	0.007

eTable 17. *ERI* DNA methylation sites associated with level of global cognition at baseline in men.

Outcome	CpG	Chr.	Position	Estimate	SE	Raw P-value	FDR q-value
Level of global cognition	cg13612689	6	152128634	-13.926	3.972	0.0006	0.029
	cg02285263	6	152129749	-23.194	6.857	0.0009	0.029
	cg17264271	6	152126938	-9.998	3.048	0.0012	0.029
	cg27316393	6	152128675	-15.226	4.739	0.0015	0.029

eTable 18. *ERI* DNA methylation sites associated with AD pathology indices in men.

Index	CpG	Chr.	Position	Estimate	SE	Raw P-value	FDR q-value
Aβ	cg25291603	6	152002969	8.319	2.335	0.0005	0.025
	cg15626350	6	152130207	6.321	1.857	0.0008	0.025
	cg22389949	6	152003038	3.635	1.087	0.001	0.025
	cg02404255	6	152419175	9.398	2.953	0.0017	0.032
	cg00601836	6	152130332	4.846	1.594	0.0027	0.041
Tau	cg15626350	6	152130207	7.607	1.697	<0.0001	0.001
	cg00601836	6	152130332	5.463	1.469	0.0003	0.010
Global AD Pathology Score	cg15626350	6	152130207	2.47	0.663	0.0003	0.016
	cg00601836	6	152130332	2.036	0.568	0.0004	0.016