Supplementary Materials:

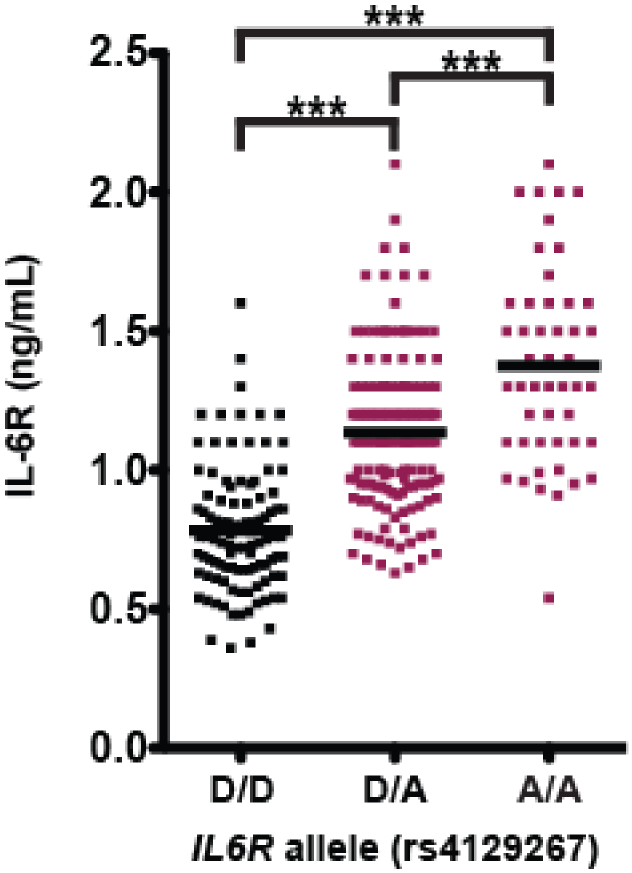

Fig. S1. **sIL6R levels in CSF by genotype at D358A.** Soluble IL-6R concentration is higher in CSF of *IL6R* A358 carriers compared to those with *IL6R* D358 genotype in ADNI samples. Line = median, D/D n= 102, D/A n= 146, A/A n= 48. Comparisons between all combinations of groups *** $p<0.001$ (two-sample t-test $\leq 5.31 \times 10^{-5}$). Magenta : A358 allele carriers.

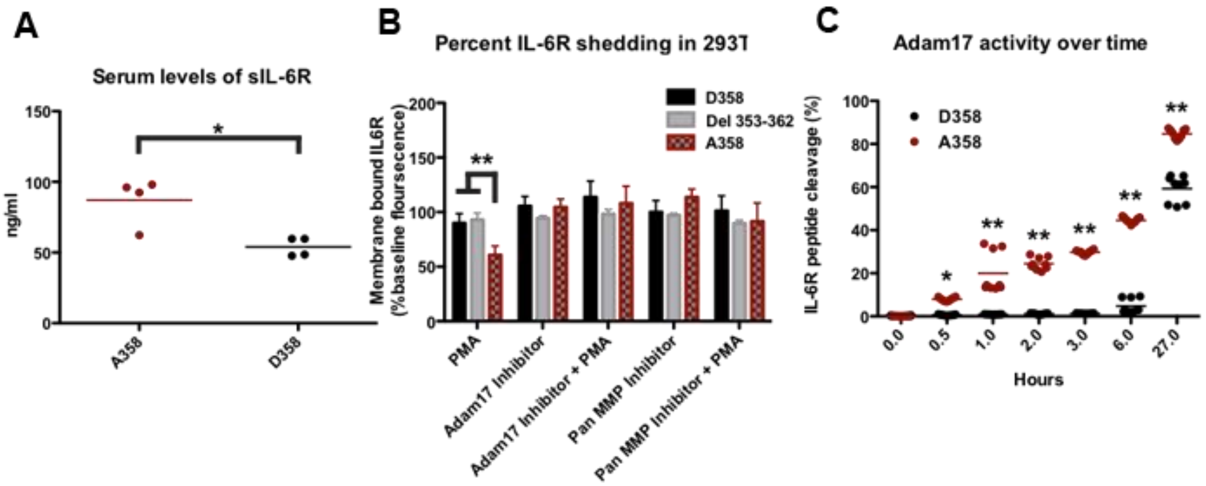

Fig. S2. **Increased shedding of A358 IL-6R.** (A) A358 is associated with increased circulating levels of sIL-6R in healthy donors. Blood from four healthy genotyped donors was collected. Circulating levels (ng/ml) of sIL-6R in serum was measured by ELISA. (B) A358 enhances ADAM17 mediated shedding. Membrane bound IL-6R was analyzed by FACS. 293T cells were transfected with D358, A358 and ADAM17 inactive del353-362 constructs of IL-6R. After 48 hours of transfection, cells were treated with/without 20uM of TAPI-2 (ADAM 17 Inhibitor) or with/without 100nM of GM 6001 (a pan-MMP inhibitor) for 60 minutes prior to treatment with/without 100nM PMA for 60 minutes. The mean fluorescence intensity relative to untreated cells (where untreated cells are given a value of 100%) of four individual experiments is shown. Error bars are standard deviation. (C) Adam 17 at 2.5ug/ml and D358 or A358 IL-6R peptides at 10 uM concentration were added in an assay buffer (25mM Tris, 2.5 uM $ZnCl_2$, 0.005 Brij-35 (v/v) pH 9.0) and incubated at 37° C for indicated time. Data represents the activity of Adam 17 over the time on the IL-6R peptides. We quantitated cleaved and uncleaved product by checking area under the curve at expected Masses by Mass-spectrometry.

Results shows percent cleaved product (area under the curve) considering total (cleaved + uncleaved area under the curve) as 100%. p value <0.05= *, <0.005=**, <0.0005=***.

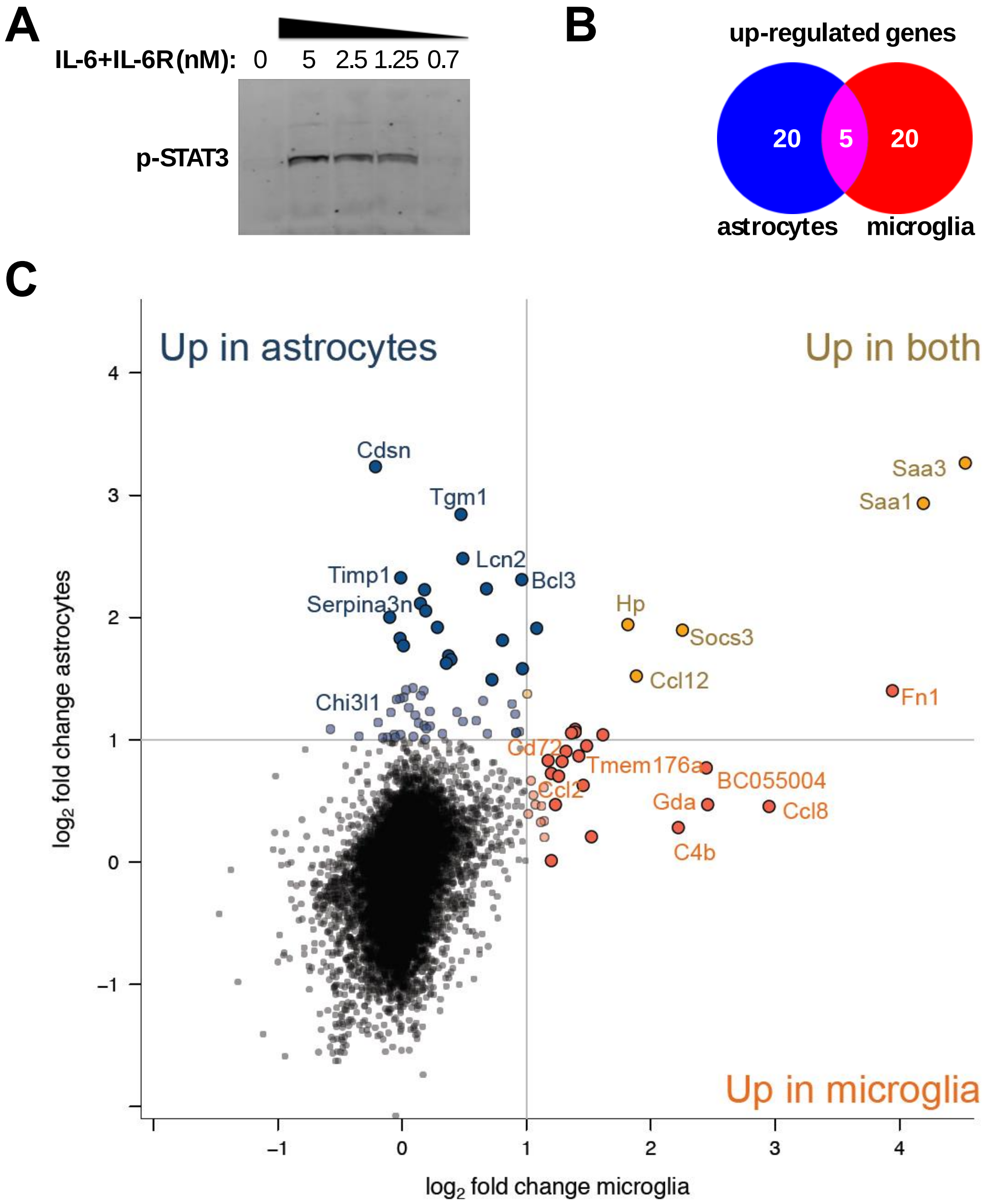

Fig. S3. **IL-6 responsive genes in astrocyte and microglia co-culture.** (A) Immunoblot of p-STAT3 of mouse astrocyte and microglia co-cultures 15 minutes after treatment with a range of IL-6 and sIL-6R (0 to 5nM) concentrations. (B) Five genes are in the top 25 differentially expressed gene sets in both astrocyte and microglia enriched cell types. (C) Fold change plot for IL-6 and sIL-6R treated astrocytes and microglia. Average $\log_2$ (fold change) for microglia (x-axis) and astrocyte (y-axis) samples. Genes in color are significantly up-regulated upon treatment of IL-6 and sIL-6R (adjusted p-value < 0.01, |fold change| > 2). Genes in bold are the top 25 genes (for each cell type, by fold change) up-regulated by IL-6 and sIL-6R treatment. Genes in gold are in the top 25 in both cell types.

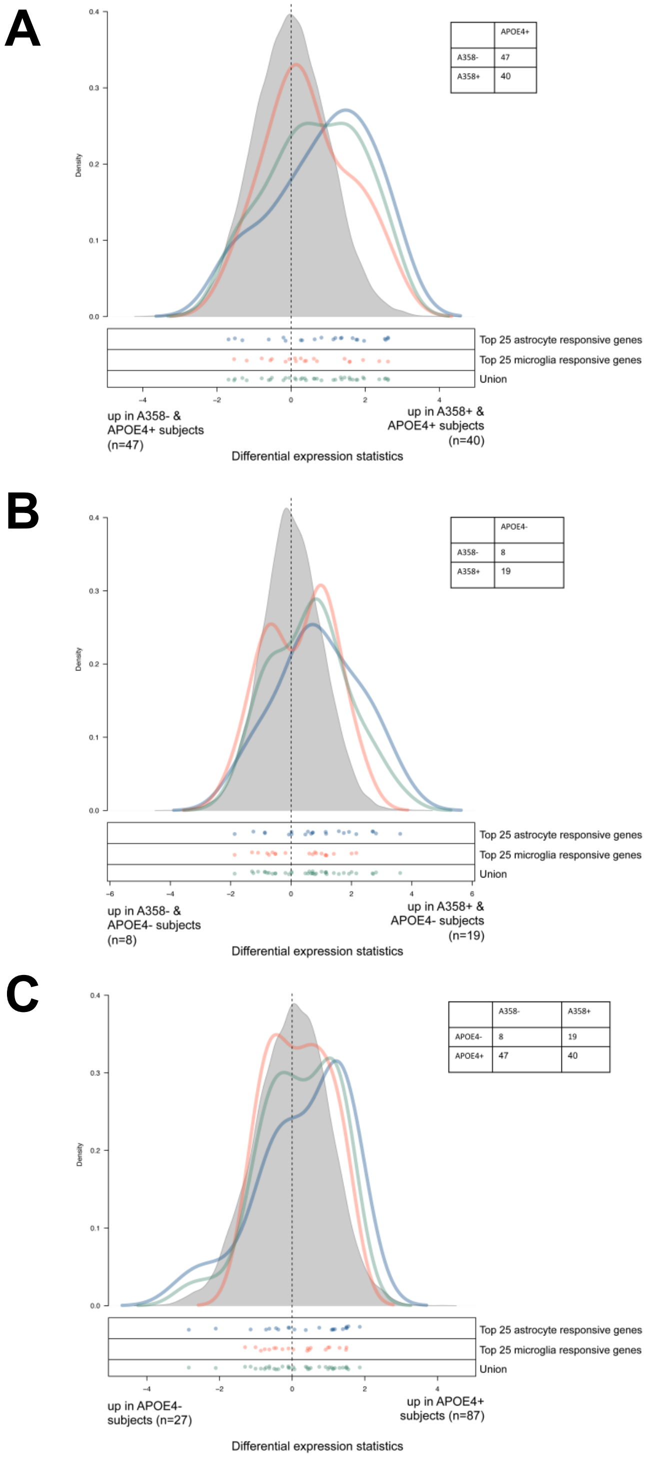

Fig. S4. **Density plots for three comparisons in the AD microarray samples.** Density of the t-statistics for all genes in human AD patients is shown in grey. The t-statistic densities of the astrocyte (blue) and microglia (orange) gene sets are also plotted. Individual gene statistics are plotted below the density plots. (A) IL-6 set enriched in patients with AD, APOE4, and *IL6R* risk variant. Each t-statistic is measuring the relative difference between the average expression in patients who carry A358 and APOE4 and patients who carry APOE4 but not A358 (after adjusting for sex and batch). Note that the IL-6 responsive gene set densities are shifted toward the right of the plot, indicating that the expression of these genes is higher in the A358 carriers. The astrocyte set has the highest level of enrichment among A358 carriers with APOE4 and disease with 34.8% of genes up-regulated in this set (ROAST p-value = 0.019). The microglia (p-value = 0.107) gene set is not enriched among A358 carriers. (B) IL-6 set enriched in patients with AD, APOE3, and *IL6R* risk variant. Each t-statistic is measuring the relative difference between the average expression in patients who carry A358 and are APOE4- and patients who lack both risk alleles (after adjusting for sex and batch). Note that the IL-6 responsive gene set densities are slightly shifted toward the right of the plot, indicating that the expression of these genes is slightly higher in the A358 carriers. The astrocyte set has the highest level of enrichment among A358 carriers with APOE3 and disease with 34.8% of genes up-regulated in this set (ROAST p-value = 0.040). The microglia gene set is not enriched (p-value = 0.065). (C) IL-6 set not enriched in AD patients who carry A358 and APOE4 versus AD patients who carry A358 and APOE2/3. Each t-statistic is measuring the relative difference between the average expression in patients who carry A358 and APOE4 and patients who carry A358 and APOE2/3 (after adjusting for sex and batch). Note that the IL-6 responsive gene set densities are not shifted toward the right of the plot, indicating that the expression of these genes is not different in the APOE4 carriers (p-value ≥ 0.135).

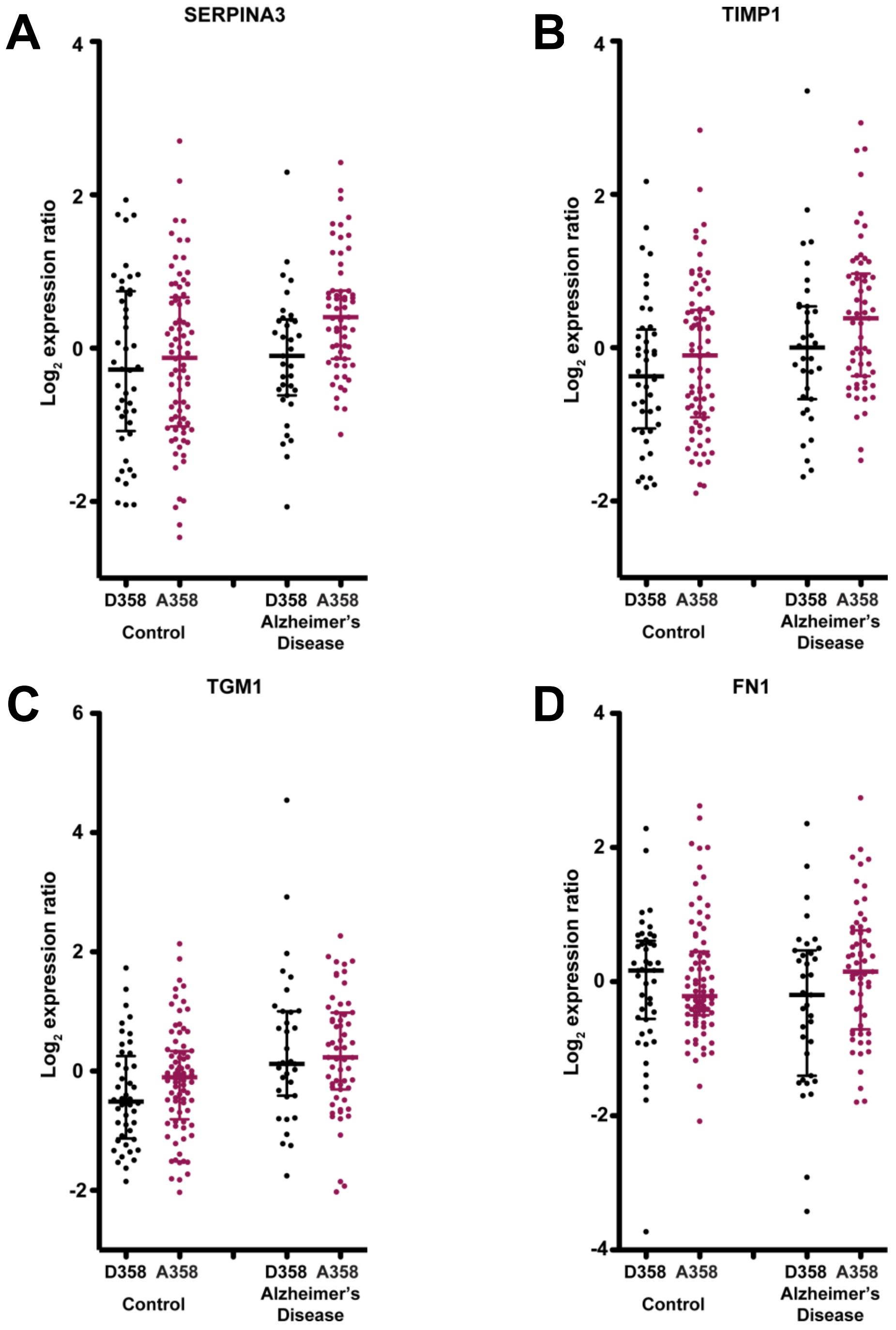

Fig. S5. **Gene expression of individual genes of the IL-6 responsive score.** (A-D) Gene expression for the four genes that constitute the IL-6 responsive score stratified by disease status and *IL6R* genotype. Error bars represent ± 1 standard deviation from the mean.

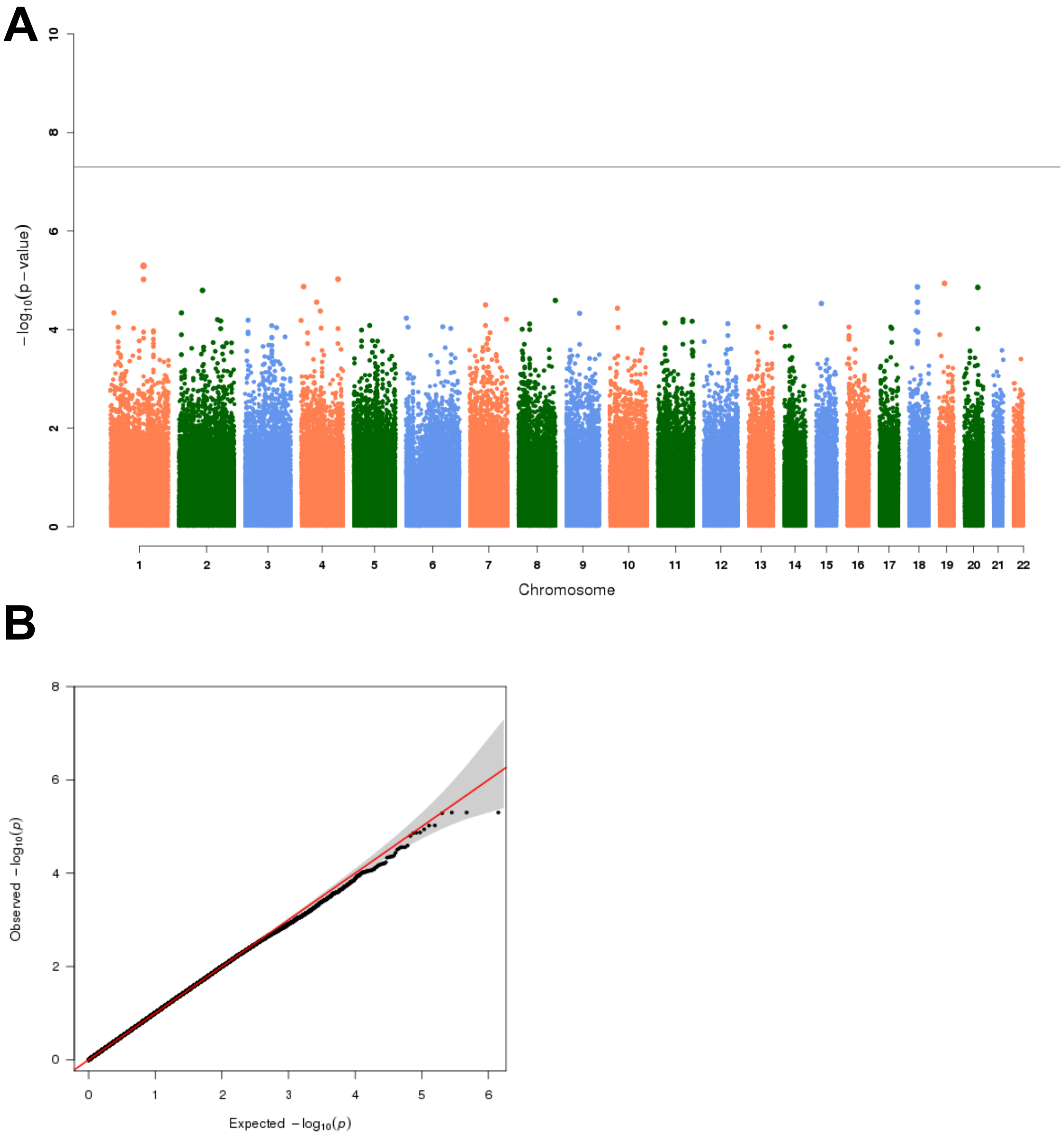

Fig. S6. **Manhattan plot of genome-wide p-values of primary study.** (A) Manhattan plot of the genome-wide association results for the primary study. (B) QQ plot comparing observed genome-wide association p-values with the expectation under the null hypothesis of no association. No evidence of inflation of the test statistic was seen (genomic inflation factor, $\lambda = 1.01$)

ProbeId	Mouse Entrez Id	Human Entrez Id	Mouse Symbol	Gene Name	log2 FC in Astrocytes	Adjusted p-value in Astrocytes	log2 FC in Astrocytes (qPCR)	log2 FC in Microglia	Adjusted p-value in Microglia	log2 FC in Microglia (qPCR)
A_55_P1953169	20210	NA	Saa3	serum amyloid A 3	**3.26358**	**2.92E-14**	**3.942**	**4.529**	**2.21E-17**	**4.067**
A_52_P318673	20208	6288	Saa1	serum amyloid A 1	**2.9329**	**2.66E-15**	**-0.4773**	**4.19**	**6.46E-19**	**1.527**
A_52_P627816	21816	7051	Tgm1	transglutaminase 1, K polypeptide	**2.83847**	**1.02E-21**	**2.867**	**0.4723**	**0.004356**	**1.897**
A_55_P2048607	15439	3240	Hp	haptoglobin	**1.93923**	**2.03E-16**	**2.229**	**1.814**	**1.15E-14**	**3.625**
A_51_P474459	12702	9021	Socs3	suppressor of cytokine signaling 3	**1.89115**	**2.04E-17**	**NA**	**2.252**	**7.11E-19**	**NA**
A_51_P110301	12266	718	C3	complement component 3	**1.81132**	**2.69E-15**	**1.06**	**0.8055**	**7.60E-06**	**0.267**
A_55_P1984556	20293	6347	Ccl12	chemokine (C-C motif) ligand 12	**1.51534**	**4.13E-12**	**NA**	**1.882**	**1.32E-13**	**NA**
A_55_P2130178	14268	2335	Fn1	fibronectin 1	**1.4**	**2.64E-08**	**0.8182**	**3.941**	**4.16E-19**	**2.561**
A_51_P212782	16176	3553	Il1b	interleukin 1 beta	**0.8276**	**0.00413**	**0.6914**	**1.172**	**0.001575**	**0.6835**
A_52_P638459	20304	6352	Ccl5	chemokine (C-C motif) ligand 5	**0.5707**	**0.008417**	**0.6579**	**1.929**	**1.29E-09**	**2.155**
A_51_P464703	20307	6355	Ccl8	chemokine (C-C motif) ligand 8	**0.4508**	**3.21E-05**	**2.204**	**2.949**	**1.53E-24**	**3.731**
A_51_P283499	13491	1815	Drd4	dopamine receptor D4	**0.4464**	**0.005563**	**-1.228**	**0.6853**	**0.0009103**	**-0.2283**
A_55_P2186027	14433	NA	Gapdh	glyceraldehyde-3-phosphate dehydrogenase	**0.4036**	**0.0003672**	**-0.2006**	**0.4141**	**0.003306**	**0.04353**
A_51_P375146	12491	948	Cd36	CD36 antigen	**-0.4241**	**0.003393**	**-1.644**	**-1.471**	**4.25E-11**	**-2.114**
A_55_P2158990	16476	3725	Jun	Jun oncogene	**-0.9505**	**0.0001527**	**-0.05985**	**-0.7092**	**0.02663**	**-0.173**
A_55_P2025153	15289	3146	Hmgb1	high mobility group box 1	**-1.286**	**7.79E-08**	**0.0857**	**-0.6917**	**0.006691**	**-0.1057**
A_55_P2020472	70432	55680	Rufy2	RUN and FYVE domain-containing 2	**-1.293**	**1.32E-10**	**0.1174**	**-0.733**	**0.0001447**	**-0.01272**
A_55_P2183172	19684	5962	Rdx	radixin	**-1.487**	**3.37E-09**	**-0.02185**	**-0.6208**	**0.01613**	**-0.2222**
A_55_P2190994	386463	1041	Cdsn	corneodesmosin	**3.23403**	**8.53E-21**	**3.778**	-0.2146	0.461	-1.091
A_55_P2070869	16819	3934	Lcn2	lipocalin 2	**2.48001**	**1.27E-19**	**NA**	0.4878	0.004142	NA
A_55_P1985850	21857	7076	Timp1	tissue inhibitor of metalloproteinase 1	**2.32311**	**5.48E-23**	**2.956**	-0.01194	0.9691	2.421
A_55_P2066116	12051	602	Bcl3	B cell leukemia/lymphoma 3	**2.30501**	**2.11E-12**	**NA**	0.9602	0.0007113	NA
A_51_P444447	12609	1052	Cebpd	CCAAT/enhancer binding protein (C/EBP), delta	**2.23287**	**5.89E-17**	**NA**	0.6761	0.00034	NA
A_51_P159453	20716	12	Serpina3n	serine (or cysteine) peptidase inhibitor, clade A, member 3N	**2.22307**	**1.55E-22**	**3.861**	0.1787	0.2262	0.09047
A_55_P2039284	15507	3315	Hspb1	heat shock protein 1	**2.11388**	**2.88E-19**	**NA**	0.1457	0.5145	NA
A_55_P1953341	67701	10406	Wfdc2	WAP four-disulfide core domain 2	**2.05118**	**1.10E-14**	**NA**	0.1892	0.5568	NA
A_52_P338956	104816	374569	Aspg	asparaginase homolog (S. cerevisiae)	**2.00063**	**2.58E-11**	**NA**	-0.1007	0.8688	NA
A_51_P338443	57875	51129	Angptl4	angiopoietin-like 4	**1.91434**	**1.99E-11**	**NA**	0.2831	0.4443	NA
A_51_P212754	21810	7045	Tgfbi	transforming growth factor, beta induced	**1.90746**	**1.33E-16**	**NA**	1.081	4.23E-09	NA
A_51_P374726	19288	5806	Ptx3	pentraxin related gene	**1.82445**	**1.58E-15**	**NA**	-0.01836	0.9675	NA
A_51_P312336	108052	6563	Slc14a1	solute carrier family 14 (urea transporter), member 1	**1.76706**	**1.27E-19**	**NA**	0.009055	0.9784	NA
A_55_P2050390	104010	64405	Cdh22	cadherin 22	**1.68127**	**1.98E-12**	**NA**	0.3732	0.1099	NA
A_51_P501248	20698	8877	Sphk1	sphingosine kinase 1	**1.65491**	**9.68E-11**	**NA**	0.3918	0.167	NA
A_52_P220879	21817	7052	Tgm2	transglutaminase 2, C polypeptide	**1.62389**	**2.23E-13**	**0.798**	0.354	0.08341	0.1812
A_55_P2017789	16190	3566	Il4ra	interleukin 4 receptor, alpha	**1.57945**	**1.80E-11**	**NA**	0.9672	9.71E-06	NA
A_55_P2097279	18733	NA	Lilrb3	leukocyte immunoglobulin-like receptor, subfamily B (with TM and ITIM domains), member 3	**1.49114**	**2.04E-12**	**NA**	0.7208	0.0001032	NA
A_51_P144264	16598	10365	Klf2	Kruppel-like factor 2 (lung)	**1.367**	**2.37E-06**	**0.4709**	0.5379	0.1615	0.5824
A_55_P2041828	22152	10381	Tubb3	tubulin, beta 3 class III	**1.324**	**4.21E-07**	**0.9723**	-0.5905	0.05518	-0.2726
A_51_P268234	76527	146433	Il34	interleukin 34	**1.016**	**5.87E-09**	**0.8387**	-0.1567	0.5678	-0.2283
A_55_P1997756	16193	3569	Il6	interleukin 6	**0.9761**	**6.24E-10**	**2.162**	-0.09943	0.7206	-1.473
A_55_P1968068	22059	7157	Trp53	transformation related protein 53	**0.7519**	**2.92E-07**	**-0.1406**	0.2153	0.2884	-0.4502
A_55_P2093286	11815	347	Apod	apolipoprotein D	**0.7444**	**0.0008963**	**0.7066**	-0.1981	0.6857	1.42
A_52_P52303	14580	2670	Gfap	glial fibrillary acidic protein	**0.7319**	**0.002787**	**0.3145**	-0.3612	0.4026	-0.5467
A_55_P1986188	23854	54849	Def8	differentially expressed in FDCP 8	**0.6798**	**0.000135**	**-0.02472**	-0.002325	0.9964	0.1394
A_51_P255699	17392	4314	Mmp3	matrix metallopeptidase 3	**0.6359**	**1.11E-06**	**2.75**	0.02065	0.9542	-0.172
A_51_P279100	19224	5742	Ptgs1	prostaglandin-endoperoxide synthase 1	**0.609**	**6.01E-06**	**-0.2276**	0.3193	0.05643	-0.006356
A_55_P2002557	20787	6720	Srebf1	sterol regulatory element binding transcription factor 1	**0.599**	**0.0005014**	**0.009386**	-0.005159	0.9938	0.2883
A_55_P2130090	71994	1266	Cnn3	calponin 3, acidic	**0.472**	**0.001974**	**0.09737**	0.02934	0.9506	-0.381
A_55_P1955906	20846	6772	Stat1	signal transducer and activator of transcription 1	**-0.2332**	**0.009964**	**-0.187**	-0.1928	0.1574	-0.2986
A_51_P167971	23821	23621	Bace1	beta-site APP cleaving enzyme 1	**-0.2392**	**0.04303**	**0.4867**	-0.0312	0.9317	0.3311
A_51_P239673	15452	3251	Hprt	hypoxanthine guanine phosphoribosyl transferase	**-0.3619**	**0.003794**	**0.5307**	-0.008682	0.9844	-0.08503
A_65_P04961	18212	4915	Ntrk2	neurotrophic tyrosine kinase, receptor, type 2	**-0.6124**	**2.41E-05**	**-0.1595**	-0.09559	0.7702	-0.4127
A_55_P1967216	11487	102	Adam10	a disintegrin and metallopeptidase domain 10	**-0.6486**	**0.001072**	**-0.01704**	0.03393	0.9565	-0.2172
A_55_P2016462	15945	3627	Cxcl10	chemokine (C-X-C motif) ligand 10	**-0.6488**	**0.01341**	**-0.5447**	0.152	0.8275	-0.1848
A_55_P1981415	56637	2932	Gsk3b	glycogen synthase kinase 3 beta	**-0.7354**	**0.0001824**	**-0.02413**	-0.2574	0.4585	-0.3139
A_55_P2052892	11798	112401	Xiap	X-linked inhibitor of apoptosis	**-1.081**	**1.55E-06**	**-0.1925**	-0.01024	0.9879	-0.217
A_66_P108267	116810	121643	Foxn4	forkhead box N4	**-1.13**	**1.07E-05**	**-0.8682**	-0.01521	0.9852	-0.2283
A_55_P2054628	18189	9378	Nrxn1	neurexin I	**-1.54**	**1.52E-06**	**-0.1601**	-0.02342	0.9809	0.1198
A_55_P2158227	11600	284	Angpt1	angiopoietin 1	**-1.55**	**6.71E-06**	**0.1321**	-0.1348	0.8808	-0.2283
A_52_P306305	11641	NA	Akap2	A kinase (PRKA) anchor protein 2	**-1.572**	**3.43E-07**	**0.346**	-0.156	0.819	-1.94
A_55_P2085974	16000	3479	Igf1	insulin-like growth factor 1	**-1.691**	**1.49E-05**	**-0.6025**	-0.0309	0.9805	-0.4024
A_55_P2017826	17863	4602	Myb	myeloblastosis oncogene	**-1.74**	**1.10E-14**	**-1.228**	0.1681	0.53	-0.1646
A_55_P2001238	67684	51747	Luc7l3	LUC7-like 3 (S. cerevisiae)	**-1.886**	**1.18E-07**	**0.2857**	-0.7362	0.08011	-0.001676
A_51_P279038	19017	10891	Ppargc1a	peroxisome proliferative activated receptor, gamma, coactivator 1 alpha	**-1.903**	**3.78E-13**	**-0.2134**	-0.0568	0.912	-2.05
A_55_P2097478	14544	9615	Gda	guanine deaminase	0.4641	0.02333	NA	**2.45624**	**5.76E-13**	**NA**
A_55_P2026139	381680	NA	BC055004	cDNA sequence BC055004	0.7669	5.061E-08	NA	**2.44527**	**4.10E-20**	**NA**
A_55_P2078633	12268	721	C4b	complement component 4B (Chido blood group)	0.2818	0.01119	NA	**2.22009**	**2.50E-19**	**NA**
A_51_P341108	20732	6692	Spint1	serine protease inhibitor, Kunitz type 1	1.039	3.396E-09	NA	**1.61425**	**7.88E-13**	**NA**
A_52_P363216	14538	2651	Gcnt2	glucosaminyl (N-acetyl) transferase 2, I-branching enzyme	0.2039	0.05255	NA	**1.5205**	**2.35E-15**	**NA**
A_52_P422494	246746	146722	Cd300lf	CD300 antigen like family member F	0.9488	3.76E-11	NA	**1.48161**	**3.02E-15**	**NA**
A_55_P1972605	11542	140	Adora3	adenosine A3 receptor	0.6266	0.0004212	NA	**1.45518**	**4.05E-09**	**NA**
A_51_P181341	117148	54550	Necab2	N-terminal EF-hand calcium binding protein 2	0.862	3.65E-02	NA	**1.42033**	**7.95E-03**	**NA**
A_51_P346938	76905	116844	Lrg1	leucine-rich alpha-2-glycoprotein 1	1.061	4.73E-11	NA	**1.39081**	**5.76E-13**	**NA**
A_51_P488739	80885	338442	Niacr1	niacin receptor 1	1.083	1.006E-09	NA	**1.39005**	**3.45E-11**	**NA**
A_55_P1961270	12517	971	Cd72	CD72 antigen	1.056	1.90E-08	NA	**1.36002**	**8.77E-10**	**NA**
A_55_P2100645	170458	170589	Gpha2	glycoprotein hormone alpha 2	0.9042	0.01069	NA	**1.31596**	**4.19E-03**	**NA**
A_55_P1963920	327957	388325	A430084P05R	RIKEN cDNA A430084P05 gene	0.8221	2.992E-07	NA	**1.28548**	**2.68E-10**	**NA**
A_51_P145785	11699	259	Ambp	alpha 1 microglobulin/bikunin	0.7032	0.00003485	NA	**1.25662**	**1.36E-08**	**NA**
A_55_P2085142	20750	6696	Spp1	secreted phosphoprotein 1	0.4706	0.03912	NA	**1.2324**	**3.50E-05**	**NA**
A_51_P234864	94282	94097	Sfxn5	sideroflexin 5	0.008232	9.57E-01	NA	**1.19957**	**4.05E-12**	**NA**
A_55_P2013143	77411	80004	Esrp2	epithelial splicing regulatory protein 2	0.7225	5.44E-02	NA	**1.19871**	**1.46E-02**	**NA**
A_55_P2111355	353156	51162	Egfl7	EGF-like domain 7	0.1588	3.62E-01	-0.0253	**-1.378**	**1.78E-09**	**-1.108**

Table S1. Significantly different genes in astrocyte and/or microglia enriched culture samples.

GO analysis in IL-6+sIL-6R treated astrocytes

Gene Ontology	GO Term	P-value	Odds Ratio	Ontology Size	Overlap	Gene Symbols in Category
GO:0006954	inflammatory response	5.72E-08	26.9	343	7	Hp,Il4ra,Saa1,Saa3,Ccl12,Sphk1,Serpina3n
GO:0006953	acute-phase response	1.37E-07	111	40	4	Hp,Saa1,Saa3,Serpina3n
GO:0006950	response to stress	4.99E-06	11.7	1079	8	C3,Il4ra,Saa1,Saa3,Ccl12,Sphk1,Serpina3n,Tgm2
GO:0007275	multicellular organismal development	1.49E-05	6.06	3668	14	Bcl3,C3,Cebpd,Socs3,Hp,Hspb1,Il4ra,Pirb,Ccl12,Sphk1,Tgm1,Tgm2,Timp1,Cdsn
GO:0016265	death	3.10E-05	7.44	1488	9	Bcl3,Hp,Hspb1,Lcn2,Ccl12,Sphk1,Tgm2,Timp1,Angptl4
GO:0007243	intracellular protein kinase cascade	3.74E-05	9.54	831	7	Bcl3,C3,Socs3,Hspb1,Ccl12,Sphk1,Tgm2
GO:0043086	negative regulation of catalytic activity	3.92E-05	11.7	559	6	Hp,Hspb1,Serpina3n,Timp1,Angptl4,Wfdc2
GO:0002250	adaptive immune response	6.58E-05	21.7	187	4	Bcl3,C3,Il4ra,Pirb
GO:0001819	positive regulation of cytokine production	8.05E-05	20.6	197	4	Bcl3,C3,Hspb1,Il4ra
GO:0002376	immune system process	0.000131	6.75	1379	8	Bcl3,C3,Il4ra,Lcn2,Pirb,Ptx3,Ccl12,Timp1
GO:1900407	regulation of cellular response to oxidative stress	0.000141	141	15	2	Hp,Hspb1
GO:0045766	positive regulation of angiogenesis	0.000157	33.2	89	3	C3,Hspb1,Sphk1
GO:0043067	regulation of programmed cell death	0.000169	7.41	1056	7	Bcl3,Hspb1,Ccl12,Sphk1,Tgm2,Timp1,Angptl4
GO:0019724	B cell mediated immunity	0.00019	31	95	3	Bcl3,C3,Pirb
GO:0042832	defense response to protozoan	0.000367	83.1	24	2	Bcl3,Il4ra
GO:0018149	peptide cross-linking	0.000432	76.1	26	2	Tgm1,Tgm2
GO:0042092	type 2 immune response	0.000466	73.1	27	2	Bcl3,Il4ra
GO:0060548	negative regulation of cell death	0.000561	8.76	589	5	Bcl3,Ccl12,Sphk1,Timp1,Angptl4
GO:0032651	regulation of interleukin-1 beta production	0.000616	63	31	2	Hspb1,Sphk1
GO:0042093	T-helper cell differentiation	0.000698	58.9	33	2	Bcl3,Il4ra
GO:0051707	response to other organism	0.000705	19.8	167	3	Il4ra,Lcn2,Ptx3
GO:0042088	T-helper 1 type immune response	0.000741	57.1	34	2	Bcl3,Il4ra
GO:0034097	response to cytokine stimulus	0.00075	11.3	354	4	Pirb,Ccl12,Sphk1,Serpina3n
GO:0002293	alpha-beta T cell differentiation involved in immune response	0.000786	55.3	35	2	Bcl3,Il4ra
GO:0043122	regulation of I-kappaB kinase/NF-kappaB cascade	0.000859	18.3	159	3	Hspb1,Sphk1,Tgm2

GO analysis in IL-6+sIL-6R treated microglia

Gene Ontology	GO Term	P-value	Odds Ratio	Ontology Size	Overlap	Gene Symbols in Category
GO:0006953	acute-phase response	6.25E-10	167	40	5	Fn1,Hp,Il1b,Saa1,Saa3
GO:0006954	inflammatory response	8.02E-07	24.5	343	6	Fn1,Hp,Saa1,Saa3,Ccl12,Ccl8
GO:0050995	negative regulation of lipid catabolic process	0.000173	125	18	2	Il1b,Niacr1
GO:0001944	vasculature development	0.000221	10.9	526	5	Socs3,Fn1,Il1b,Ccl12,Spint1
GO:0060669	embryonic placenta morphogenesis	0.00026	100	22	2	Socs3,Spint1
GO:0009605	response to external stimulus	0.000351	7.83	914	6	Adora3,Fn1,Il1b,Ccl12,Ccl8,Spp1
GO:0046627	negative regulation of insulin receptor signaling pathway	0.000365	83.4	26	2	Socs3,Il1b
GO:0060674	placenta blood vessel development	0.00052	69	31	2	Socs3,Spint1
GO:0044060	regulation of endocrine process	0.000555	66.7	32	2	Il1b,Niacr1
GO:0060986	endocrine hormone secretion	0.000664	60.6	35	2	Il1b,Niacr1
GO:0040011	locomotion	0.000742	6.75	1052	6	Adora3,Fn1,Il1b,Ccl12,Ccl8,Spp1
GO:0006955	immune response	0.000776	8.23	692	5	Adora3,C4b,Il1b,Ccl12,Ccl8
GO:0031663	lipopolysaccharide-mediated signaling pathway	0.000783	55.6	38	2	Il1b,Ccl12
GO:0042063	gliogenesis	0.00084	18.5	172	3	Fn1,Il1b,Ccl12
GO:1900076	regulation of cellular response to insulin stimulus	0.0012	44.4	47	2	Socs3,Il1b
GO:1901701	cellular response to oxygen-containing compound	0.00121	9.95	440	4	Socs3,Hp,Il1b,Ccl12
GO:0060711	labyrinthine layer development	0.00125	43.5	48	2	Socs3,Spint1
GO:0072359	circulatory system development	0.00127	7.34	772	5	Socs3,Fn1,Il1b,Ccl12,Spint1
GO:0030593	neutrophil chemotaxis	0.00141	40.8	51	2	Il1b,Spp1
GO:0051341	regulation of oxidoreductase activity	0.00146	40	52	2	Hp,Il1b
GO:0001763	morphogenesis of a branching structure	0.00147	15.2	209	3	Socs3,Il1b,Spint1
GO:0006950	response to stress	0.00152	4.64	2178	8	Adora3,Fn1,Hp,Il1b,Saa1,Saa3,Ccl12,Ccl8
GO:0016477	cell migration	0.00154	7.01	807	5	Adora3,Fn1,Il1b,Ccl12,Spp1
GO:0009914	hormone transport	0.00171	14.4	220	3	Adora3,Il1b,Niacr1
GO:0051952	regulation of amine transport	0.00207	33.3	62	2	Adora3,Il1b

Table S2. GO analysis in IL-6+sIL-6R treated astrocytes and microglia.

GSEA results in IL-6+sIL-6R treated astrocytes

Gene Set	Prop of genes in set up-regulated	ROAST p-value
Top 25 IL-6+sIL-6R up-regulated genes in astrocytes	1	0.0001
Top 25 IL-6+sIL-6R up-regulated genes in microglia	0.96	0.0001
IL-6-mediated signaling events (Pathway Interaction Database)	0.415	0.0001
Genes involved in Interleukin-6 signaling (Reactome)	0.5	0.0001
IL-6 signaling pathway (Biocarta)	0.474	0.0001
Genes up-regulated in normal fibroblasts in response to IL-6 (Dasu)	0.569	0.0001

GSEA results in IL-6+sIL-6R treated microglia

Gene Set	Prop of genes in set up-regulated	ROAST p-value
Top 25 IL-6+sIL-6R up-regulated genes in astrocytes	0.76	0.0001
Top 25 IL-6+sIL-6R up-regulated genes in microglia	1	0.0001
IL-6-mediated signaling events (Pathway Interaction Database)	0.293	0.0001
Genes involved in Interleukin-6 signaling (Reactome)	0.5	0.0001
IL-6 signaling pathway (Biocarta)	0.368	0.0005
Genes up-regulated in normal fibroblasts in response to IL-6 (Dasu)	0.314	0.0006

Table S3. GSEA results in IL-6+sIL-6R treated astrocytes and microglia.

Clinical GSEA results A358+ vs A358- in all AD cases

Gene Set	Number of Genes in Set	Prop of genes in set up-regulated	ROAST p-value
Top 25 IL-6+sIL-6R up-regulated genes in astrocytes	23	0.435	0.0028
Top 25 IL-6+sIL-6R up-regulated genes in microglia	20	0.3	0.0108
IL-6-mediated signaling events (Pathway Interaction Database)	47	0.17	0.0646
Genes involved in Interleukin-6 signaling (Reactome)	10	0.2	0.3123
IL-6 signaling pathway (Biocarta)	22	0.136	0.1887
Genes up-regulated in normal fibroblasts in response to IL-6 (Dasu)	59	0.241	0.0283

Clinical GSEA results A358+ vs A358- in APOE4+ AD cases

Gene Set	Number of Genes in Set	Prop of genes in set up-regulated	ROAST p-value
Top 25 IL-6+sIL-6R up-regulated genes in astrocytes	23	0.348	0.0194
Top 25 IL-6+sIL-6R up-regulated genes in microglia	20	0.3	0.1072
IL-6-mediated signaling events (Pathway Interaction Database)	47	0.191	0.0777
Genes involved in Interleukin-6 signaling (Reactome)	10	0.3	0.1308
IL-6 signaling pathway (Biocarta)	22	0.227	0.1896
Genes up-regulated in normal fibroblasts in response to IL-6 (Dasu)	59	0.19	0.0816

Clinical GSEA results A358+ vs A358- in APOE4- AD cases

Gene Set	Number of Genes in Set	Prop of genes in set up-regulated	ROAST p-value
Top 25 IL-6+sIL-6R up-regulated genes in astrocytes	23	0.348	0.0398
Top 25 IL-6+sIL-6R up-regulated genes in microglia	20	0.2	0.0649
IL-6-mediated signaling events (Pathway Interaction Database)	47	0.106	0.2591
Genes involved in Interleukin-6 signaling (Reactome)	10	0	0.8431
IL-6 signaling pathway (Biocarta)	22	0.091	0.4701
Genes up-regulated in normal fibroblasts in response to IL-6 (Dasu)	59	0.172	0.2989

Clinical GSEA results A358+ APOE4+ vs APOE- AD cases

Gene Set	Number of Genes in Set	Prop of genes in set up-regulated	ROAST p-value
Top 25 IL-6+sIL-6R up-regulated genes in astrocytes	23	0.13	0.1347
Top 25 IL-6+sIL-6R up-regulated genes in microglia	20	0.05	0.8726
IL-6-mediated signaling events (Pathway Interaction Database)	47	0.085	0.3674
Genes involved in Interleukin-6 signaling (Reactome)	10	0.2	0.2358
IL-6 signaling pathway (Biocarta)	22	0.045	0.7115
Genes up-regulated in normal fibroblasts in response to IL-6 (Dasu)	59	0.086	0.5165

Genotype frequencies

AD cases

	APOE Genotype				
IL6R Genotype	**22**	**23**	**33**	**34**	**44**
D358/D358	0	1	7	20	7
A358/D358	0	0	14	21	10
A358/A358	0	0	5	7	2

NHC cases

	APOE Genotype				
IL6R Genotype	**22**	**23**	**33**	**34**	**44**
D358/D358	3	2	29	9	1
A358/D358	1	3	36	7	3
A358/A358	2	2	19	7	0

Table S4. GSEA results in human temporal cortex LOAD cases.

	A358 *	D358	A358 Homozygotes		Heterozygotes		D358 Homozygotes		Odds Ratio relative to	Odds Ratio relative to
	Frequency	Frequency	Frequency	Individuals	Frequency	Individuals	Frequency	Individuals		
All Controls	0.407	0.593	0.175	522	0.464	1382	0.361	1077		
APOE4+ Controls^	0.392	0.608	0.167	123	0.449	330	0.384	282		
All Cases	0.410	0.590	0.164	675	0.493	2030	0.344	1416	1.01	1.08
APOE4- Cases	0.402	0.598	0.156	258	0.493	818	0.351	582	0.98	NA
APOE34 Cases	0.414	0.586	0.167	311	0.495	923	0.339	632	1.03	1.10
APOE44 Cases	0.420	0.580	0.178	106	0.484	289	0.338	202	1.05	1.12

* A358 = "C" allele of rs2228145; D358 = "A" allele of rs2228145

^ APOE4+ = individuals carryng either the APOE3/4 or APOE4/4 genotype, APOE4- = indviduals not carrying the APOE3/4 or APOE 4.4 genotype

Table S5. Frequency of *IL6R* A358 and D358 by *APOE* status.

	Age	A358 * Frequency	D358 Frequency	A358 Homozygotes		Heterozygotes		D358 Homozygotes		Odds Ratio relative to APOE4+ controls
				Frequency	Individuals	Frequency	Individuals	Frequency	Individuals	
APOE4+ Controls ^	All	0.392	0.608	0.167	123	0.449	330	0.384	282	
APOE4+ Cases	All	0.415	0.585	0.169	417	0.492	1212	0.339	834	1.10
	<=65	0.431	0.569	0.184	115	0.495	310	0.321	201	1.18
	66-74	0.413	0.587	0.163	174	0.499	532	0.338	360	1.09
	>=75	0.406	0.594	0.166	128	0.480	370	0.354	273	1.06

* A358 = "C" allele of rs2228145; D358 = "A" allele of rs2228145

^ APOE4+ = individuals carryng either the APOE3/4 or APOE4/4 genotype, APOE4- = indviduals not carrying the APOE3/4 or APOE 4.4 genotype

Table S6. Frequency of *IL6R* A358 and D358 by different ages of AD cases.

Study	Case e3e4	Case e4e4	Case e2e4	Case total	Ctrl e3e4	Ctrl e4e4	Ctrl e2e4	Ctrl total	Total	Genotyping	SNPs
Primary	68	35		**103**	90	19		109	**212**	HumanOmni1-Quad_v1-0_B	1140419
US replication1	37	21		**58**	255	18	2	275	**333**	HumanOmni2.5-8v1_A	2379855
US replication2	132	74	1	**207**	149	12	18	179	**386**	Human610-Quadv1_B	620901
US replication3	453	249		**702**	232	26		258	**960**	HumanExome-12v1_A	247870
Icelandic	44	31		**75**	37	38		75	**150**	Illumina HiSeq whole genome seq	16,566,811

Table S7. Summary of samples in the genotype datasets used to test for association.