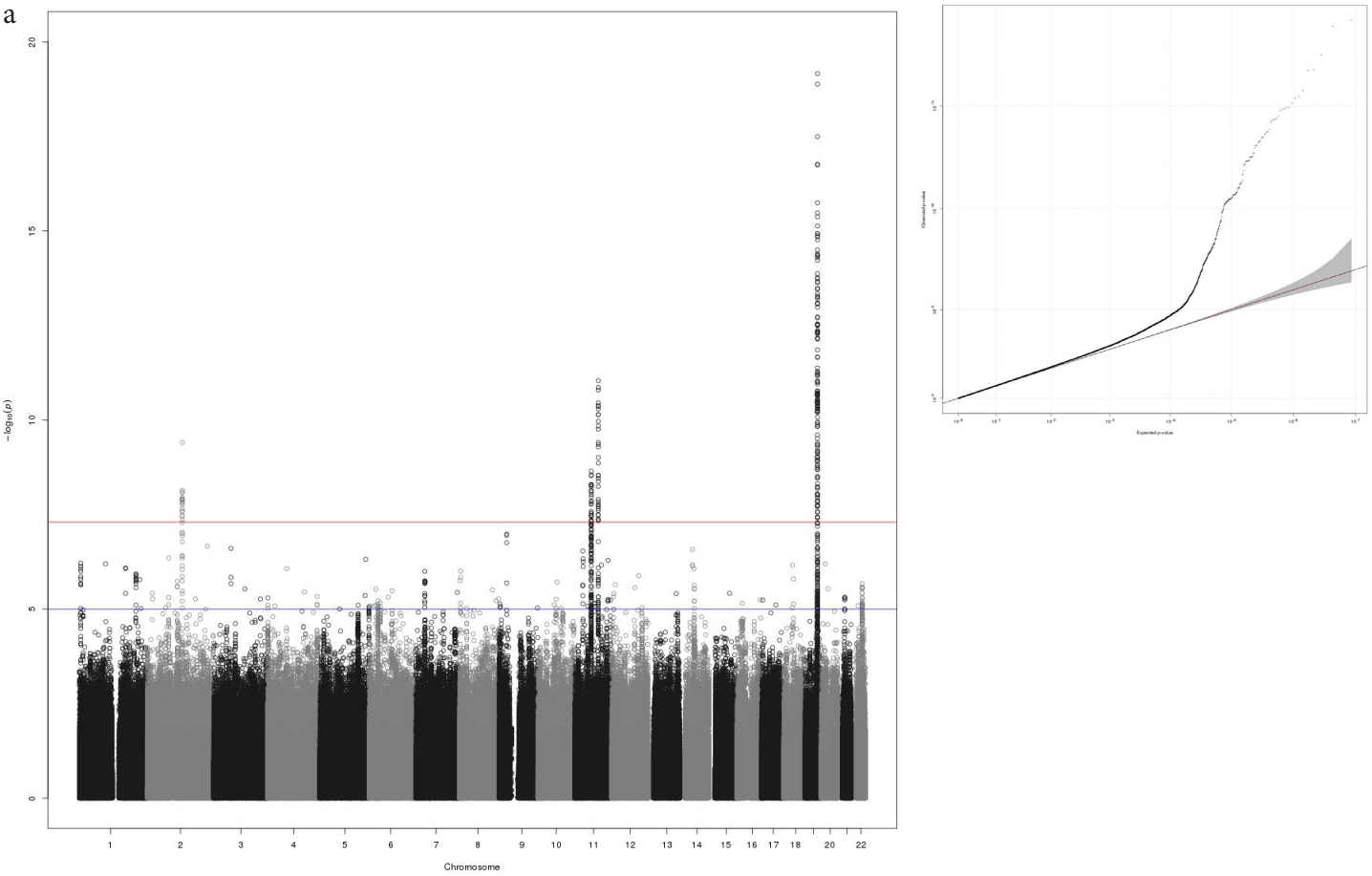
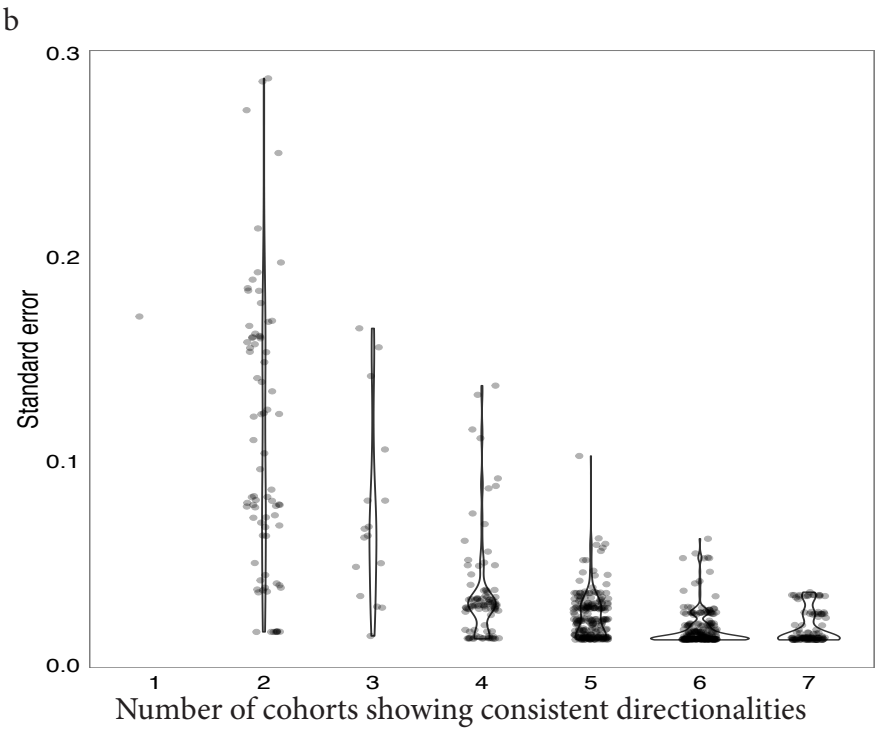
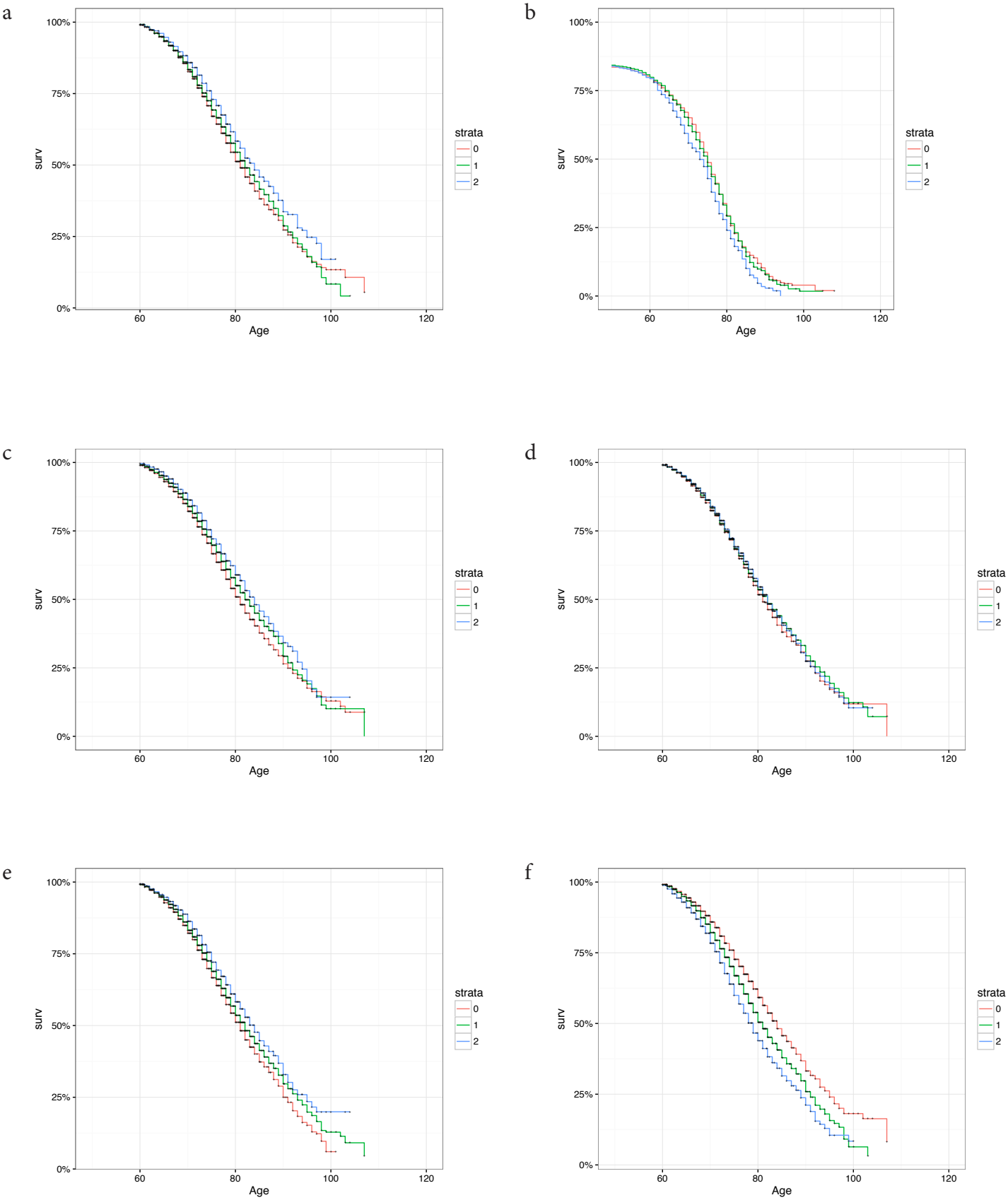




Supplementary Figure 1. Result and quality control analysis of the IGAP AD-survival meta-analysis. (a) Manhattan plot and QQ-plot of the GWAS. The final meta-analysis showed little evidence of genomic inflation ($\lambda = 1.026$). (b) The average standard error versus the number of cohorts with consistent directionalities of effect sizes.

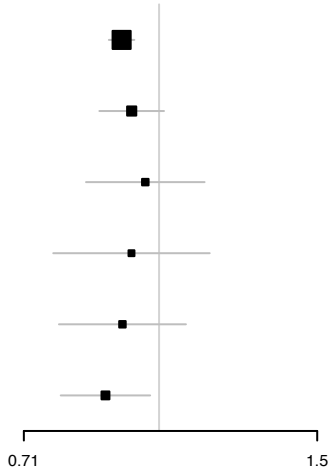


Supplementary Figure 2. Forest plots of survival analysis associations in the ADGC cohort of (a) rs1057233, (b) rs10919252, (c) rs567075, (d) rs7867518, (e) rs7930318, (f) rs4803758.

a

rs1057233

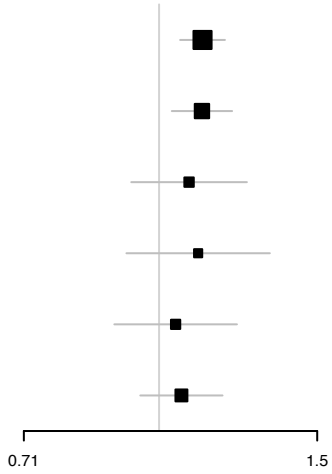
Cohort	Hazard Ratio (95% CI)	P value
ADGC	0.91 (0.88–0.94)	8.5e−09
EADI case−control	0.93 (0.86–1.01)	0.097
EADI longitudinal	0.97 (0.83–1.12)	0.649
CHARGE FHS	0.93 (0.76–1.14)	0.489
CHARGE CHS	0.91 (0.77–1.07)	0.258
CHARGE Rotterdam	0.87 (0.78–0.98)	0.019



b

rs10919252

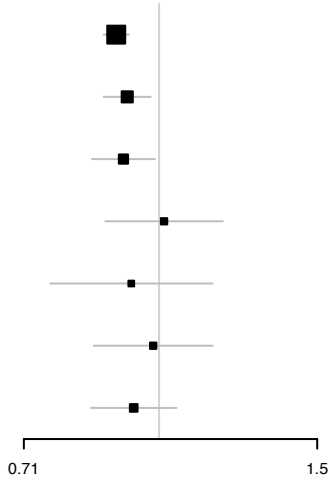
Cohort	Hazard Ratio (95% CI)	P value
GERAD	1.12 (1.06–1.18)	0.00014
EADI case−control	1.12 (1.03–1.21)	0.00532
EADI longitudinal	1.08 (0.93–1.25)	0.30926
CHARGE FHS	1.11 (0.92–1.33)	0.28585
CHARGE CHS	1.04 (0.89–1.22)	0.59691
CHARGE Rotterdam	1.06 (0.95–1.18)	0.28705



c

rs567075

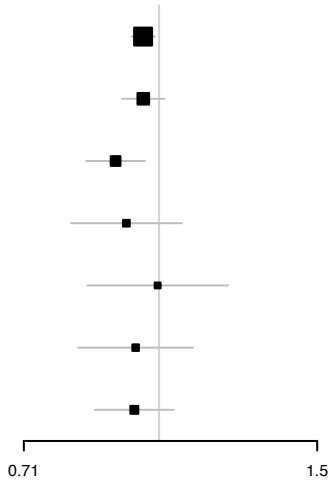
Cohort	Hazard Ratio (95% CI)	P value
ADGC	0.9 (0.87–0.93)	4e−11
GERAD	0.92 (0.87–0.98)	0.0079
EADI case−control	0.91 (0.84–0.99)	0.0266
EADI longitudinal	1.01 (0.87–1.18)	0.8677
CHARGE FHS	0.93 (0.76–1.15)	0.5022
CHARGE CHS	0.99 (0.85–1.15)	0.8462
CHARGE Rotterdam	0.94 (0.84–1.05)	0.2453



d

rs7867518

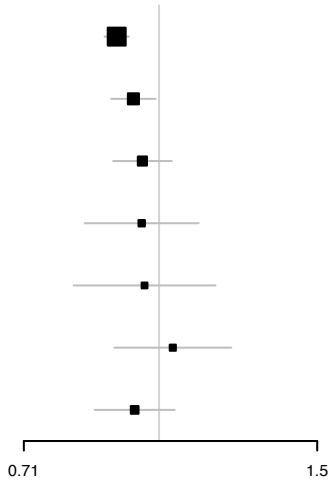
Cohort	Hazard Ratio (95% CI)	P value
ADGC	0.96 (0.93–0.99)	0.0079
GERAD	0.96 (0.91–1.01)	0.1426
EADI case–control	0.89 (0.83–0.96)	0.0037
EADI longitudinal	0.92 (0.8–1.06)	0.2473
CHARGE FHS	1 (0.83–1.19)	0.9684
CHARGE CHS	0.94 (0.81–1.09)	0.4249
CHARGE Rotterdam	0.94 (0.85–1.04)	0.2195



e

rs7930318

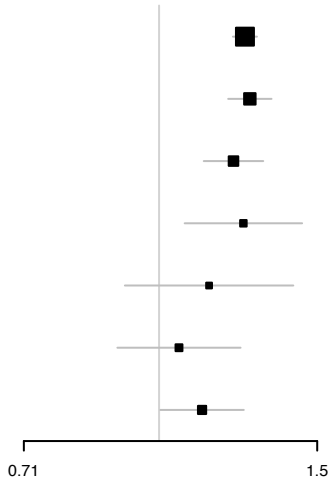
Cohort	Hazard Ratio (95% CI)	P value
ADGC	0.9 (0.87–0.93)	8.1e−12
GERAD	0.94 (0.88–0.99)	0.023
EADI case–control	0.96 (0.89–1.03)	0.263
EADI longitudinal	0.96 (0.83–1.11)	0.550
CHARGE FHS	0.96 (0.8–1.16)	0.688
CHARGE CHS	1.04 (0.89–1.2)	0.646
CHARGE Rotterdam	0.94 (0.85–1.04)	0.232



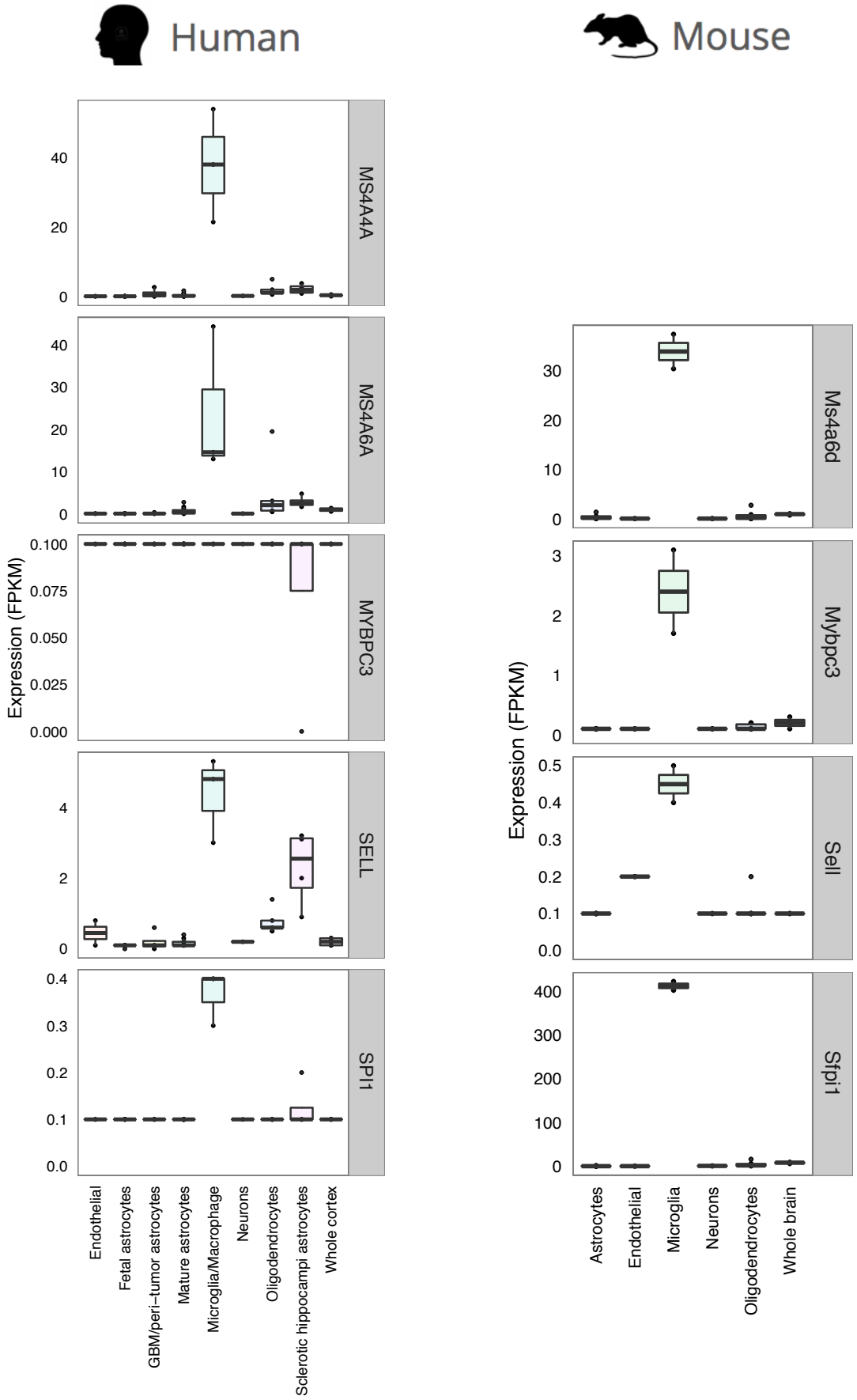
f

rs4803758

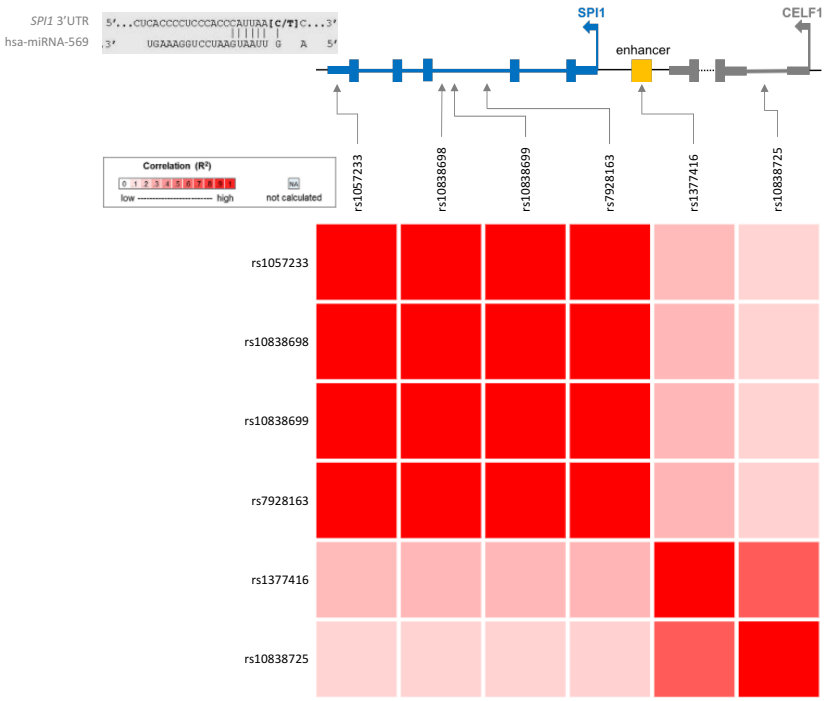
Cohort	Hazard Ratio (95% CI)	P value
ADGC	1.25 (1.21–1.29)	< 2e−16
GERAD	1.26 (1.19–1.33)	< 2e−16
EADI case–control	1.21 (1.12–1.31)	9.5e−07
EADI longitudinal	1.24 (1.07–1.44)	0.0049
CHARGE FHS	1.14 (0.92–1.41)	0.2444
CHARGE CHS	1.05 (0.9–1.23)	0.5266
CHARGE Rotterdam	1.12 (1–1.24)	0.0436



Supplementary Figure 3. Forest plots of survival analysis associations across IGAP cohorts of (a) rs1057233, (b) rs10919252, (c) rs567075, (d) rs7867518, (e) rs7930318, (f) rs4803758.

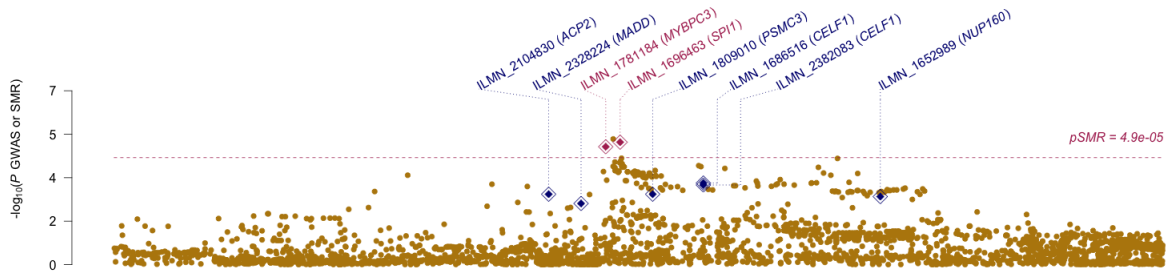


Supplementary Figure 4. Cell-type specific expression of *MS4A4A* (no mouse homolog available), *SPI1, MYBPC3, MS4A6A* and *SELL* in human and mouse brains based on the brain RNA-Seq database.

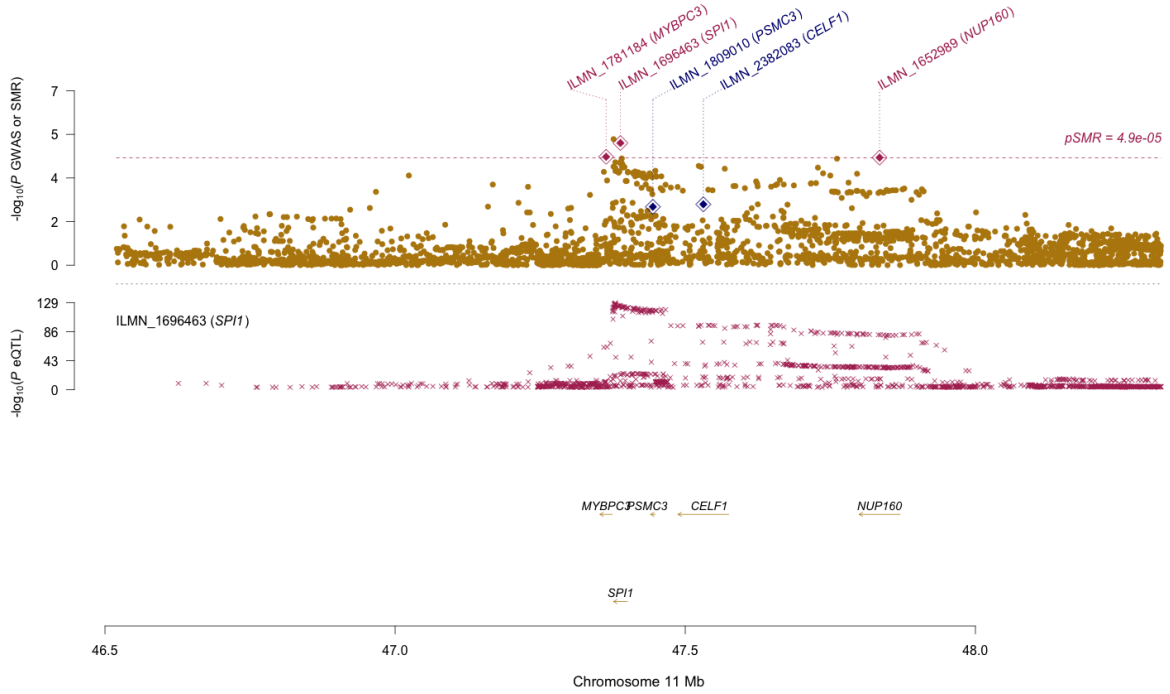


Supplementary Figure 5. Linkage disequilibrium (LD) plot of SNPs of interest in the SPI1/CELF1 locus.

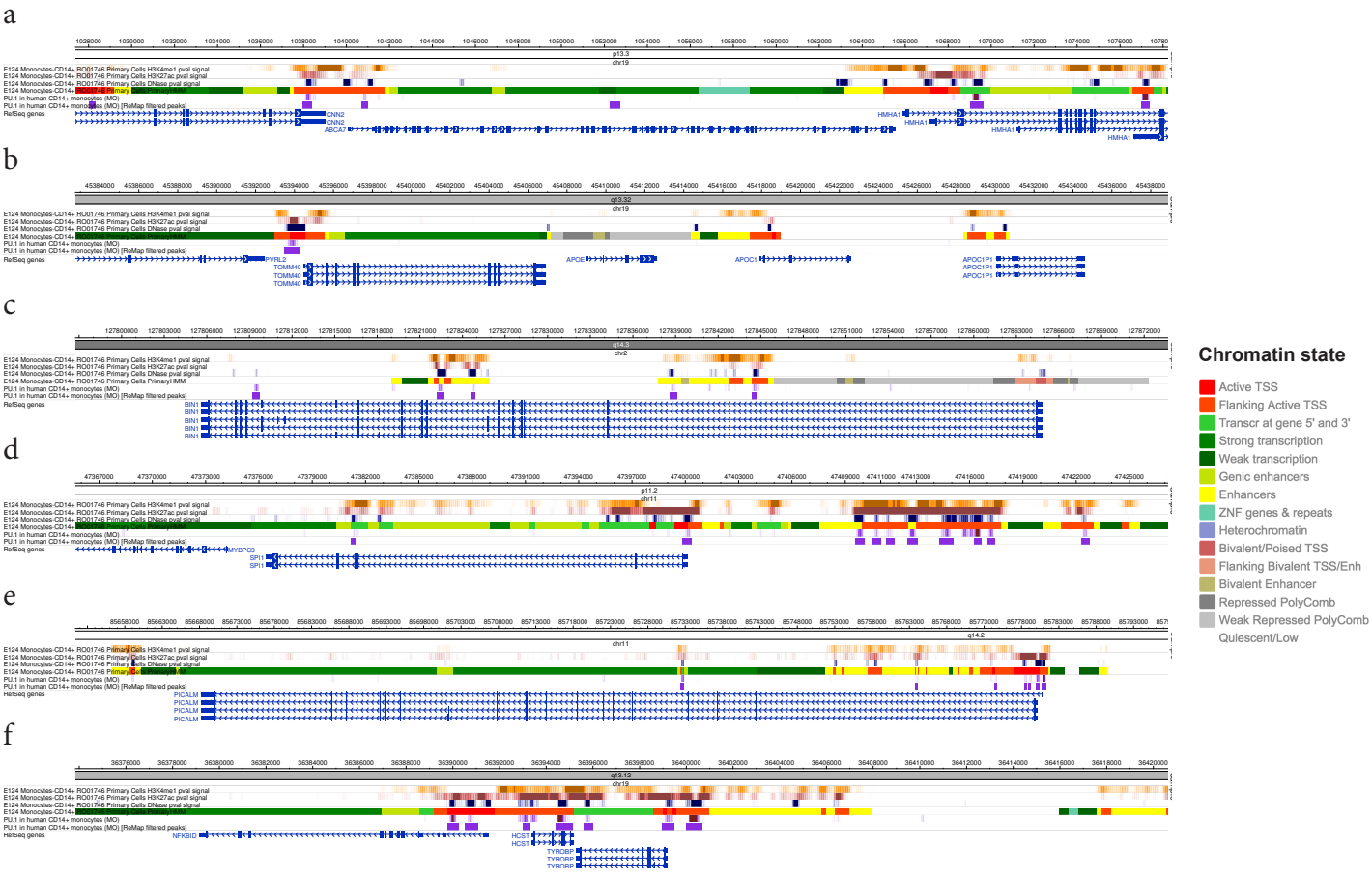
a



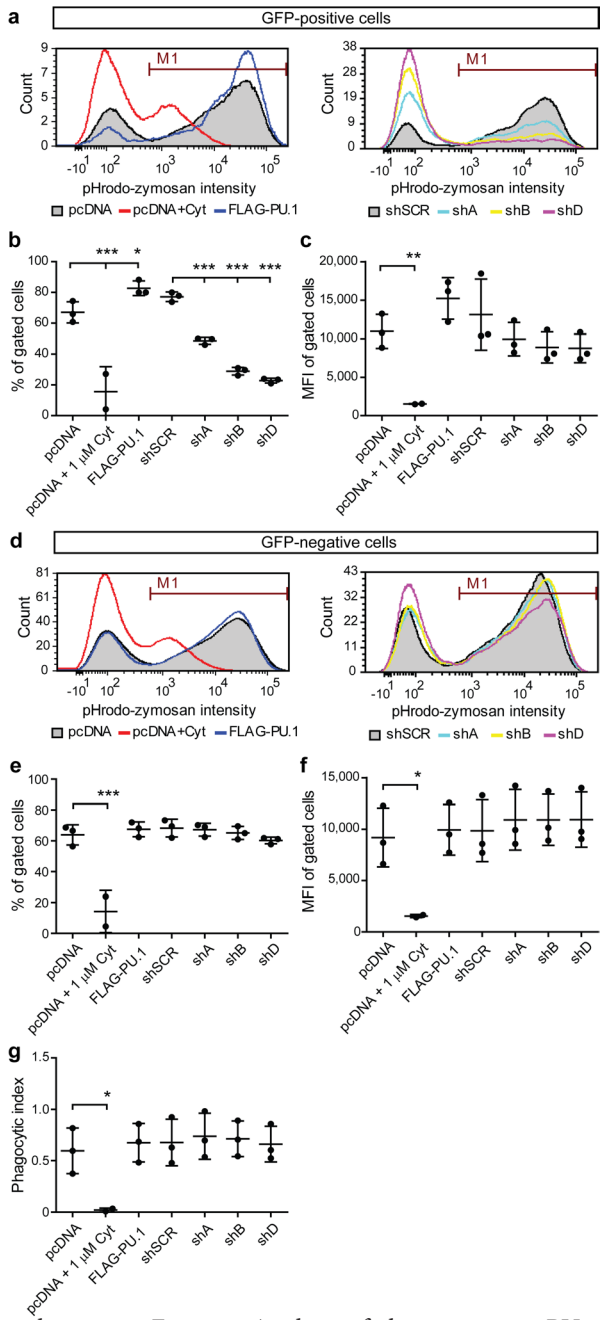
b



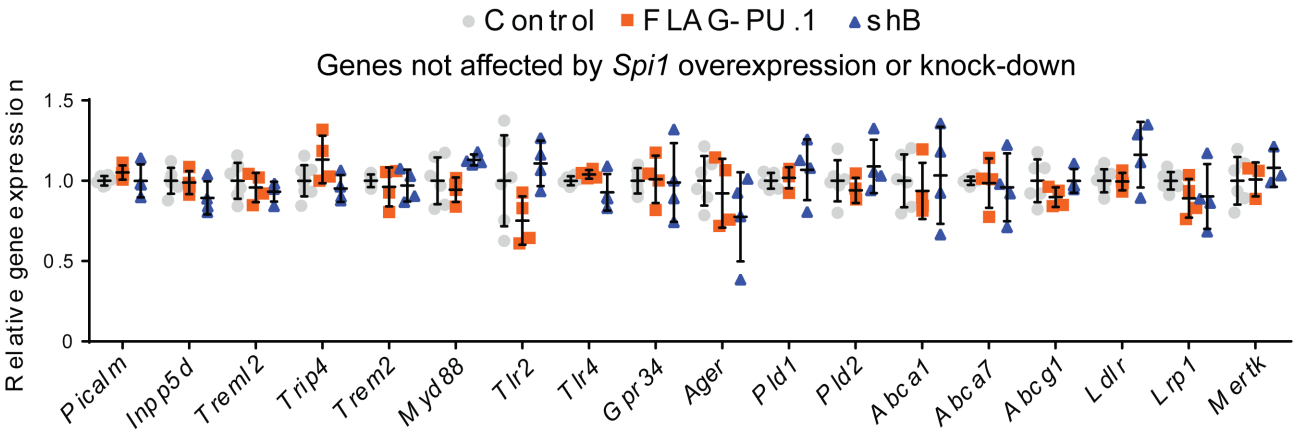
Supplementary Figure 6. SMR plots showing the associations at the SPI1/CELF1 locus from AAOS GWAS and eQTLs in (a) monocytes and (b) macrophages.



Supplementary Figure 7. SPI1 (PU.1) ChIP-Seq binding sites and other epigenetic signatures at AD-associated loci in human CD14+ monocytes. PU.1 binding sites, DNase I hypersensitive sites, histone modifications, and chromatin states at the locus of (a) ABCA7, (b) APOE, (c) BIN1, (d) SPI1, (e) PICALM, and (f) TYROBP.



Supplementary Figure 8. Analysis of phagocytosis in BV2 microglial cells. (a) Flow cytometry histograms of BV2 cells transfected with pcDNA3 (pcDNA) or pcDNA3-FLAG-PU.1 (FLAG-PU.1) with pCMV-GFP for overexpression and scrambled shRNA (shSCR) or PU.1-targeted shRNA (shA, shB and shD) in pGFP-V-RS vector for knock-down of PU.1 after 3 hours of incubation with red pHrodo-labeled zymosan. Cells were gated on GFP+ populations. (b) Flow cytometry analysis of number of gated cells in a presented as mean ± SD, pcDNA 67.03 ± 6.883, pcDNA + 1 μM Cyt 15.64 ± 16.24, FLAG-PU.1 82.71 ± 4.74, shSCR 77.17 ± 3.115, shA 48.63 ± 2.285, shB 28.92 ± 2.495, shD 22.76 ± 1.595. pcDNA vs pcDNA + 1 μM Cyt $P < 0.0001$, pcDNA vs FLAG-PU.1 $P = 0.0306$, shSCR vs shA $P = 0.0002$, shSCR vs shB $P < 0.0001$, shSCR vs shD $P < 0.0001$. $F(6,13) = 58.68$, $n = 3$. (c) Flow cytometry analysis of geometric mean fluorescent pHrodo intensity in a presented as mean ± SD, pcDNA 10952 ± 2206, pcDNA + 1 μM Cyt 1533 ± 47, FLAG-PU.1 15226 ± 2701, shSCR 13129 ± 4617, shA 9937 ± 2168, shB 8872 ± 2019, shD 8754 ± 1856. pcDNA vs pcDNA + 1 μM Cyt $P = 0.0092$. $F(6,13) = 6.228$, $n = 3$. (d) Flow cytometry histograms of BV2 cells transfected as in (a) and gated on GFP- populations. (e) Flow cytometry analysis of number of gated cells in d presented as mean ± SD, pcDNA 63.92 ± 6.575, pcDNA + 1 μM Cyt 14.21 ± 13.66, FLAG-PU.1 67.54 ± 4.826, shSCR 68.31 ± 5.784, shA 67.27 ± 4.144, shB 65.19 ± 4.268, shD 60.3 ± 2.181. pcDNA vs pcDNA + 1 μM Cyt $P < 0.0001$. $F(6,13) = 22.53$, $n = 3$. (f) Flow cytometry analysis of geometric mean fluorescent pHrodo intensity in d presented as mean ± SD, pcDNA 9186 ± 2863, pcDNA + 1 μM Cyt 1545 ± 147, FLAG-PU.1 9931 ± 2458, shSCR 9849 ± 3012, shA 10903 ± 2949, shB 10912 ± 2494, shD 10934 ± 2685. pcDNA vs pcDNA + 1 μM Cyt $P = 0.0367$. $F(6,13) = 3.473$, $n = 3$. (g) Phagocytic index of BV2 GFP- cells analyzed in (e) and (f) presented as mean ± SD, pcDNA 0.5954 ± 0.2223, pcDNA + 1 μM Cyt 0.0209 ± 0.0189, FLAG-PU.1 0.6745 ± 0.188, shSCR 0.6765 ± 0.2274, shA 0.7382 ± 0.2255, shB 0.7131 ± 0.1742, shD 0.6612 ± 0.1748. pcDNA vs pcDNA + 1 μM Cyt $P = 0.0331$. $F(6,13) = 3.53$, $n = 3$. Cytochalasin D treatment in all figures was used as a negative control for phagocytosis. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, repeated measures one-way ANOVA with Sidak's post hoc multiple comparisons test.



Supplementary Figure 9. Expression levels of genes related to phagocytosis that were not affected by altered Spi1 expression. BV2 cells were transiently transfected with pcDNA3-FLAG-PU.1 and pCMV-GFP or pGFP-v-RS-shB against mPU.1. pcDNA3 and pGFP-V-RS-shSCR were used as controls. RNA was extracted from sorted GFP+ cells and used for qPCR validation of expression levels for genes of interest. Values are presented as mean ± SD, n = 4 samples collected independently.