Table 1. Summary of the consortium data sets used for stages 1, 2 and stage 3. Data are from the Genetic and Environmental Risk for Alzheimer's Disease (GERAD)/Defining Genetic, Polygenic and Environmental Risk for Alzheimer's Disease (PERADES) Consortium, the Alzheimer's Disease Genetic Consortium (ADGC), the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) and the European Alzheimer's disease Initiative (EADI)(Supplement).

	Consortium	N Controls	N Cases	N Total
Stage 1	GERAD/PERADES	2974	6000	8974
	ADGC	7002	8706	15708
	CHARGE	8101	1391	9492
Total		18077	16097	**34174**
Stage 2	GERAD/PERADES genotype	5049	4049	9098
	CHARGE-genotype	1839	1434	3273
	CHARGE-*in silico*	3246	722	3968
	EADI-genotype	11787	7836	19623
Total		21921	14041	**35962**
Stage 3	ADGC-*in silico*	8345	6652	**14997**
Stage 1 + 2 + 3 Total		**48402**	**37022**	**85133**

Table 2. Summary of stage 1, 2, 3 and combined meta-analysis results for SNVs at $P<5x10^{-8}$.

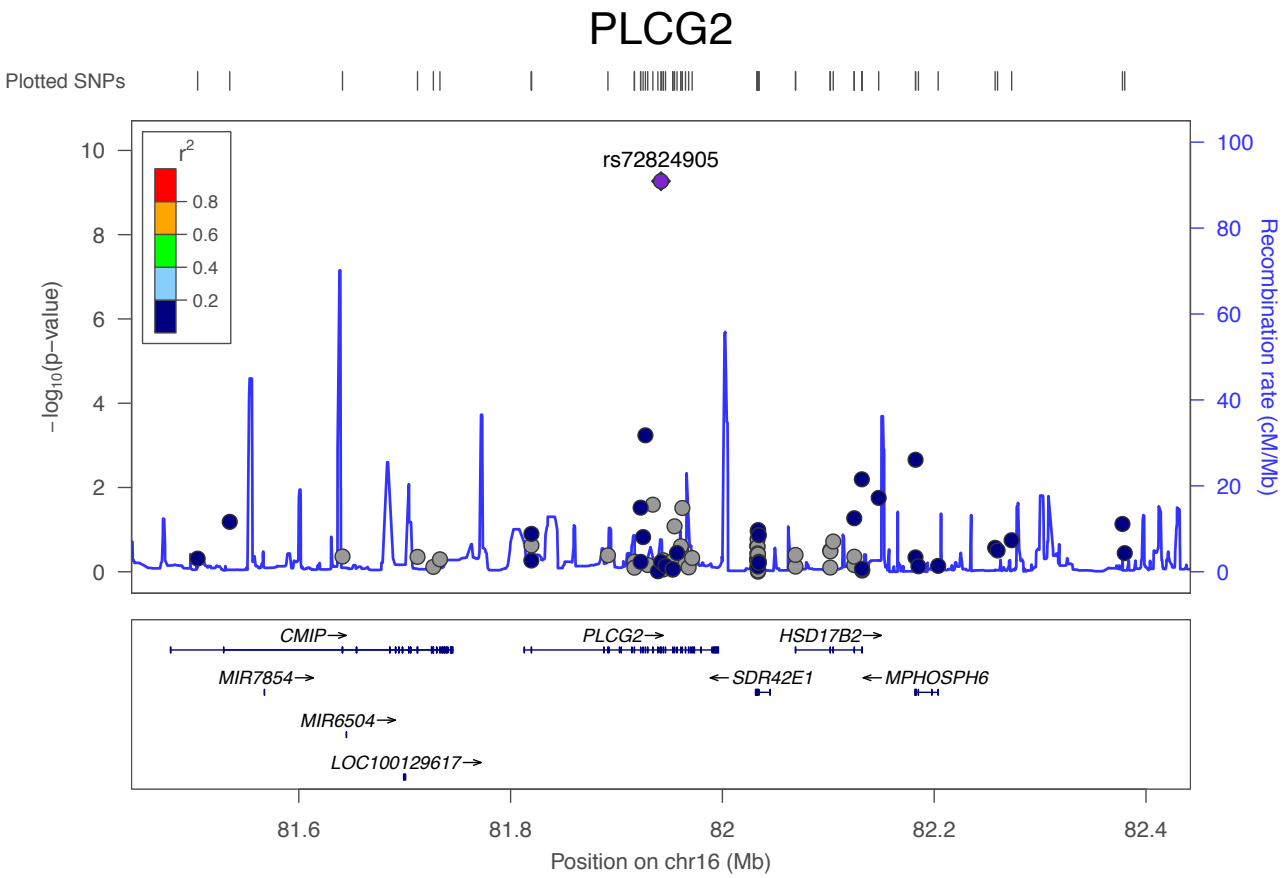
SNV	Chr	Position	Gene	Effect Allele	Stage 1					Stage 2				
					P	OR	MAF Cases	MAF Controls	N	*P*	OR	MAF Cases	MAF Controls	N
rs75932628	6	41129252	*TREM2*	T	3.02E-12	2.46	0.003	0.001	30018	4.38E-08	2.37	0.004	0.002	35831
rs143332484	6	41129207	*TREM2*	T	3.48E-09	1.58	0.015	0.010	33786	3.66E-07	3.97	0.014	0.006	3968
rs72824905	16	81942028	*PLCG2*	G	1.19E-05	0.65	0.006	0.011	33786	1.35E-04	0.70	0.006	0.008	35831
rs616338	17	47297297	*ABI3*	T	2.16E-05	1.42	0.013	0.010	33786	8.37E-05	1.41	0.010	0.008	35831

SNV	Chr	Position	Gene	Effect Allele	Stage 3					Stage1, 2 and 3 Meta-Analysis				
					P	OR	MAF Cases	MAF Controls	N	*P*	OR	MAF Cases	MAF Controls	N
rs75932628	6	41129252	*TREM2*	T	1.23E-06	2.58	0.006	0.003	14884	5.38E-24	2.46	0.004	0.002	80733
rs143332484	6	41129207	*TREM2*	T	2.45E-03	1.55	0.012	0.008	15288	1.55E-14	1.67	0.014	0.009	53042
rs72824905	16	81942028	*PLCG2*	G	2.48E-02	0.69	0.006	0.007	15288	5.38E-10	0.68	0.006	0.009	84905
rs616338	17	47297297	*ABI3*	T	1.75E-02	1.58	0.010	0.008	14876	4.56E-10	1.43	0.011	0.008	84493

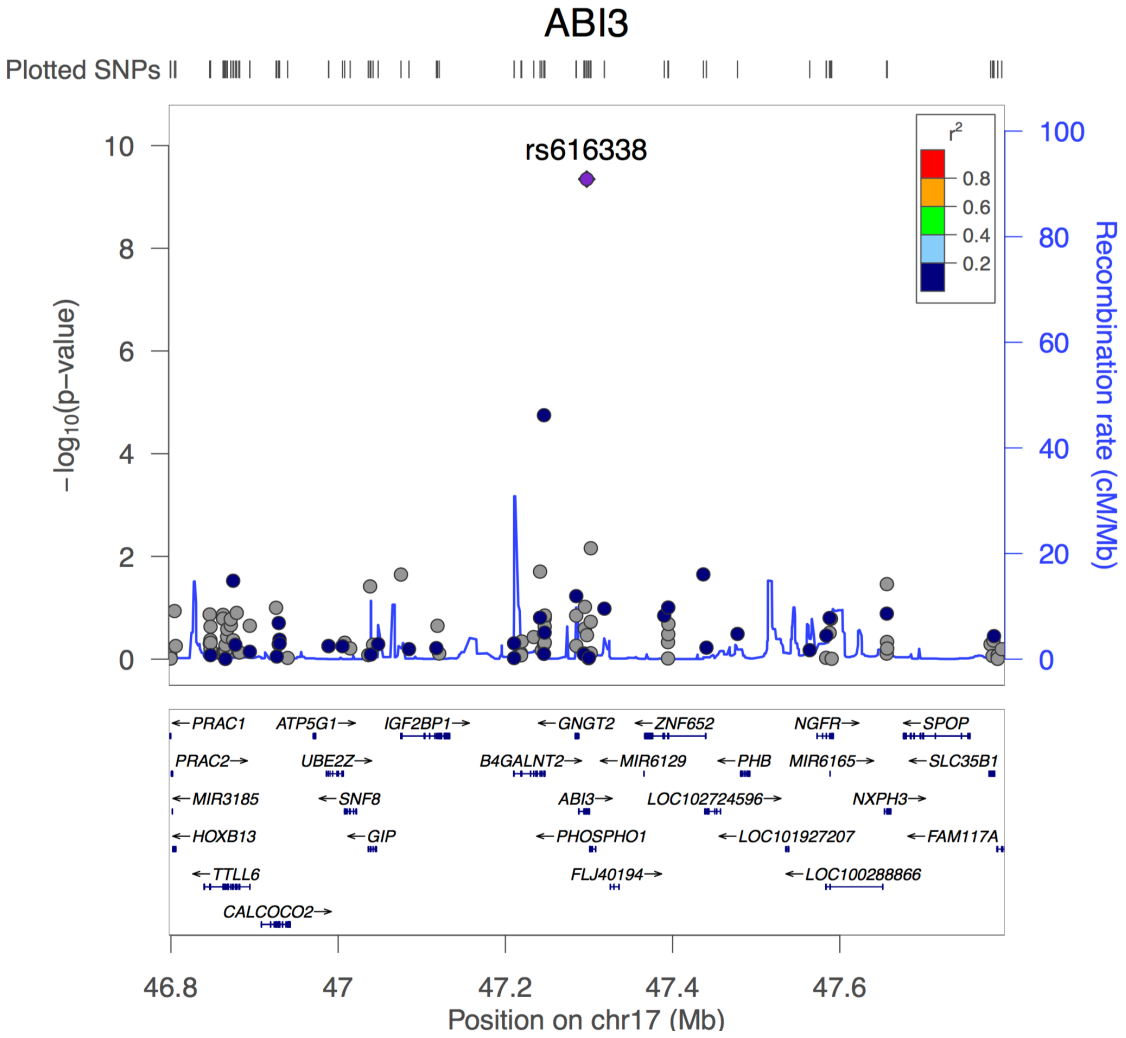
*Concordance for alternate allele carrier genotypes between imputed versus called SNPs in Stage 3 was 75.2% for rs75932628, 91.1% for rs143332484, 95.7% for rs72824905, and 81.9% for rs616338 (concordance for all genotypes was >99% for all 4 variants).

Figure 1. Association plots of *PLCG2*, *ABI3*, and *TREM2*. **(a)** Regional plot of identified association at the *PLCG2* locus. Top hit rs72824905 indicated in purple. Data presented for rs72824905 includes stage 1, stage 2 and stage 3 (N=84,905). **(b)** Regional plot of identified association at the *ABI3* locus. Top hit rs616338 indicated in purple. Data presented for rs616338 includes stage 1, stage 2 and stage 3 (N=84,493). **(c)** Regional plot of identified association at the *TREM2* locus. Top hit rs75932628 indicated in purple. Data presented for rs75932628 and rs143332484 includes stage 1, stage 2 and stage 3 (N=80,733 and 53,042, respectively).

a


PLCG2
Plotted SNPs
rs72824905
r2
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
CMIP
PLCG2
HSD17B2
MIR7854
SDR42E1
MPHOSPH6
MIR6504
LOC100129617
Position on chr16 (Mb)

b


ABI3
Plotted SNPs
rs616338
r²
0.8
0.6
0.4
0.2
10
8
6
4
2
0
−log10(p−value)
100
80
60
40
20
0
Recombination rate (cM/Mb)
PRAC1
ATP5G1
IGF2BP1
GNGT2
ZNF652
NGFR
SPOP
PRAC2
UBE2Z
B4GALNT2
MIR6129
PHB
MIR6165
SLC35B1
MIR3185
SNF8
ABI3
LOC102724596
NXPH3
HOXB13
GIP
PHOSPHO1
LOC101927207
FAM117A
TTLL6
FLJ40194
LOC100288866
CALCOCO2
46.8
47
47.2
47.4
47.6
Position on chr17 (Mb)

C

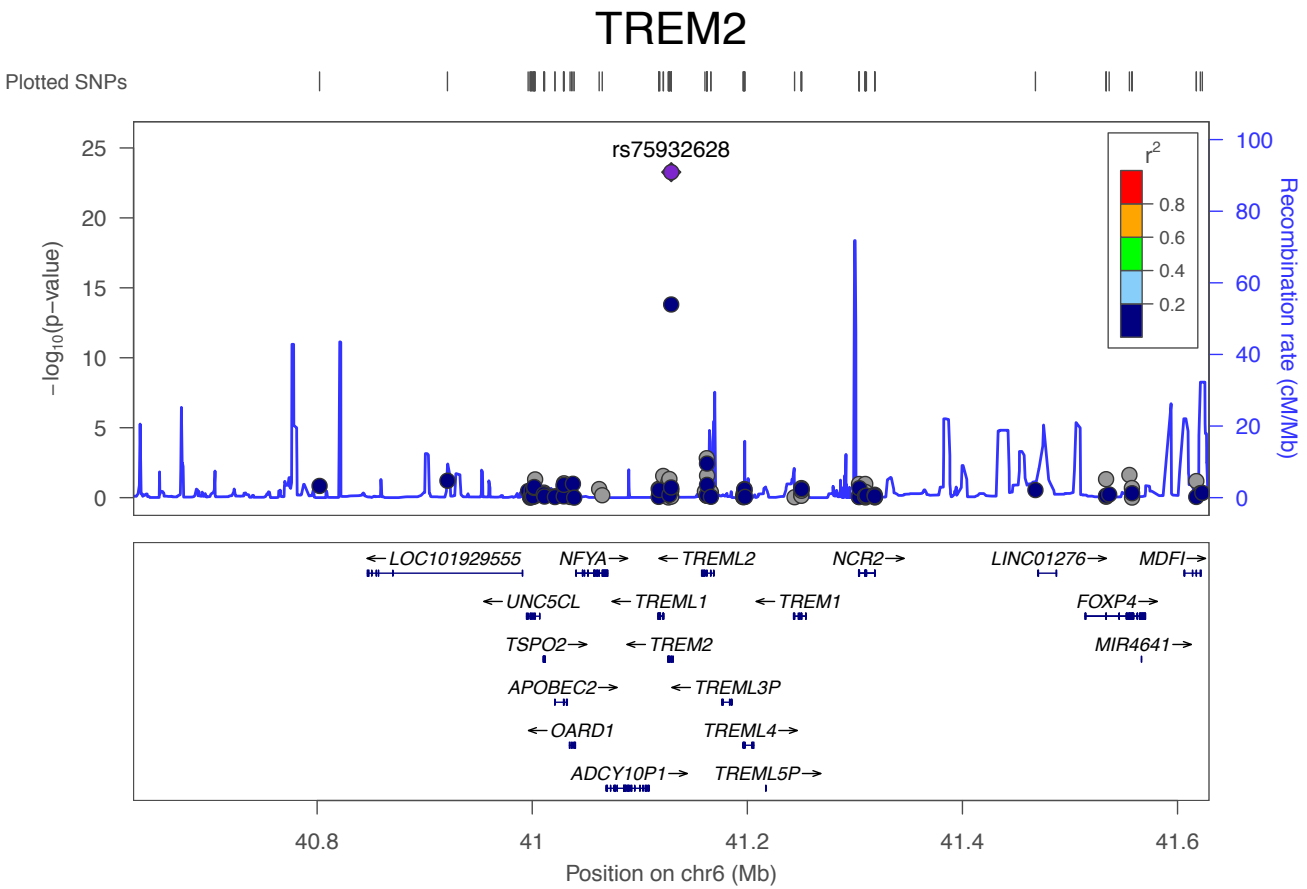
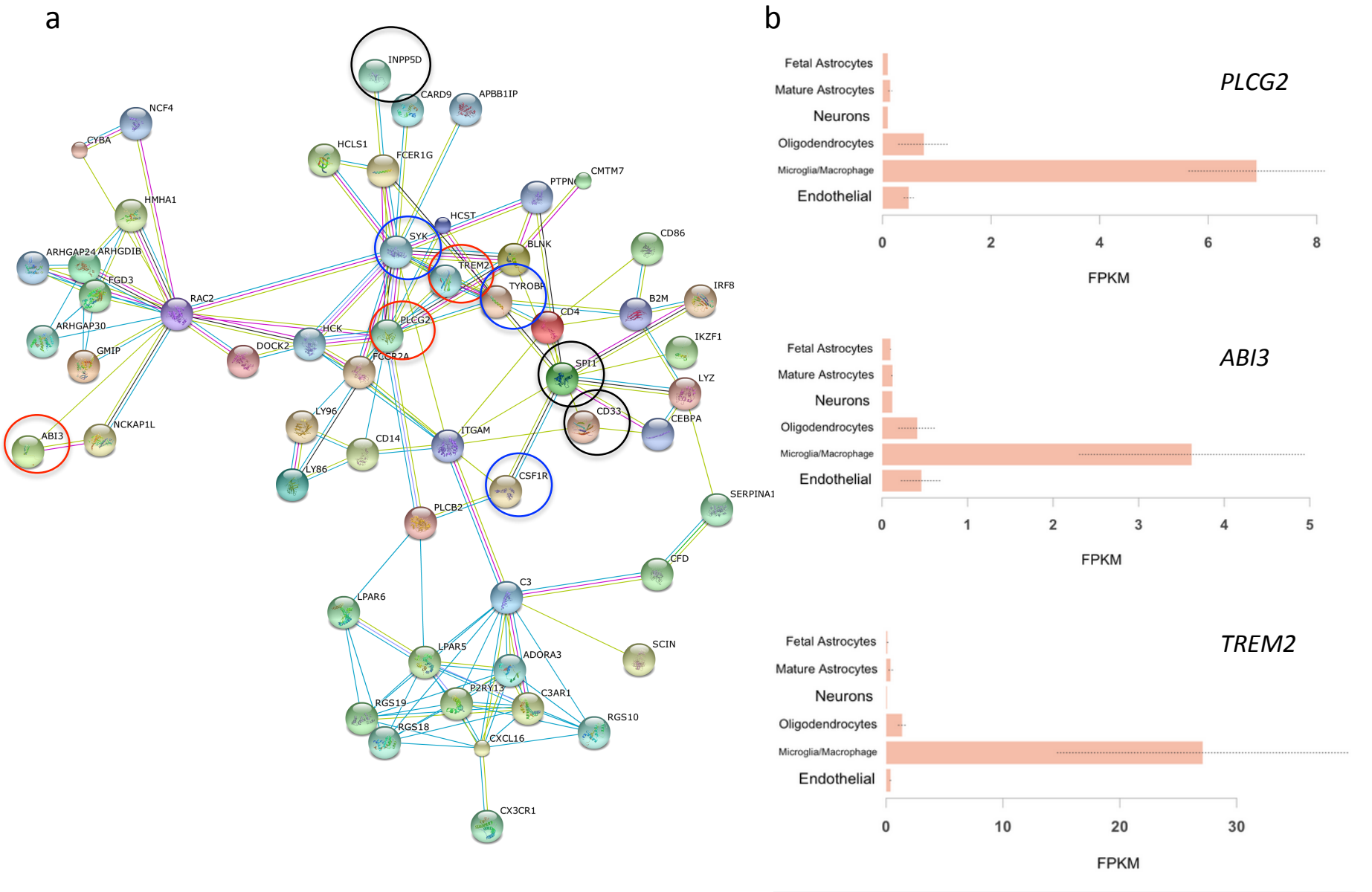

TREM2
Plotted SNPs
rs75932628
r2
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
25
20
15
10
5
0
100
80
60
40
20
0
←LOC101929555
NFYA→
←TREML2
NCR2→
LINC01276→
MDFI→
←UNC5CL
←TREML1
←TREM1
FOXP4→
TSPO2→
←TREM2
MIR4641→
APOBEC2→
←TREML3P
←OARD1
TREML4→
ADCY10P1→
TREML5P→
40.8
41
41.2
41.4
41.6
Position on chr6 (Mb)

Figure 2. (a) Protein-protein interaction network (using high-confidence human interactions from the STRING database) of 56 genes enriched for both common and rare variants associated with AD risk. Colours of edges refer to the type of evidence linking the corresponding proteins: red=gene fusion, dark blue = co-occurrence, black = co-expression, magenta = experiments, cyan=databases, light green = text mining, mauve = homology. *TREM2*, *PLCG2* and *ABI3* highlighted by red circles, *SYK*, *CSF1R* and *TYROBP* highlighted by blue circles, and *INPP5D*, *SPI1* and *CD33* identified as common variant risk loci[2,5–7], highlighted by black circles. **(b)** Gene-expression profiles (RNA-seq) of *PLCG2*, *ABI3* and*TREM2*, from transcriptome data from six cell types of human cerebral cortex, similar results were generated from mouse brain[38] (see Supplementary Figure 12).


a
INPP5D
CARD9
APBB1IP
NCF4
CYBA
HCLS1
FCER1G
CMTM7
PTPN
HMHA1
HCST
SYK
CD86
BLNK
ARHGAP24
ARHGDIB
TREM2
FGD3
TYROBP
IRF8
RAC2
B2M
CD4
PLCG2
ARHGAP30
HCK
IKZF1
DOCK2
GMIP
FCGR2A
SPI1
LYZ
LY96
CD33
CEBPA
NCKAP1L
ABI3
ITGAM
CD14
CSF1R
LY86
SERPINA1
PLCB2
CFD
C3
LPAR6
SCIN
LPAR5
ADORA3
P2RY13
C3AR1
RGS19
RGS10
RGS18
CXCL16
CX3CR1
b
Fetal Astrocytes
Mature Astrocytes
Neurons
Oligodendrocytes
Microglia/Macrophage
Endothelial
PLCG2
0
2
4
6
8
FPKM
Fetal Astrocytes
Mature Astrocytes
Neurons
Oligodendrocytes
Microglia/Macrophage
Endothelial
ABI3
0
1
2
3
4
5
FPKM
Fetal Astrocytes
Mature Astrocytes
Neurons
Oligodendrocytes
Microglia/Macrophage
Endothelial
TREM2
0
10
20
30
FPKM