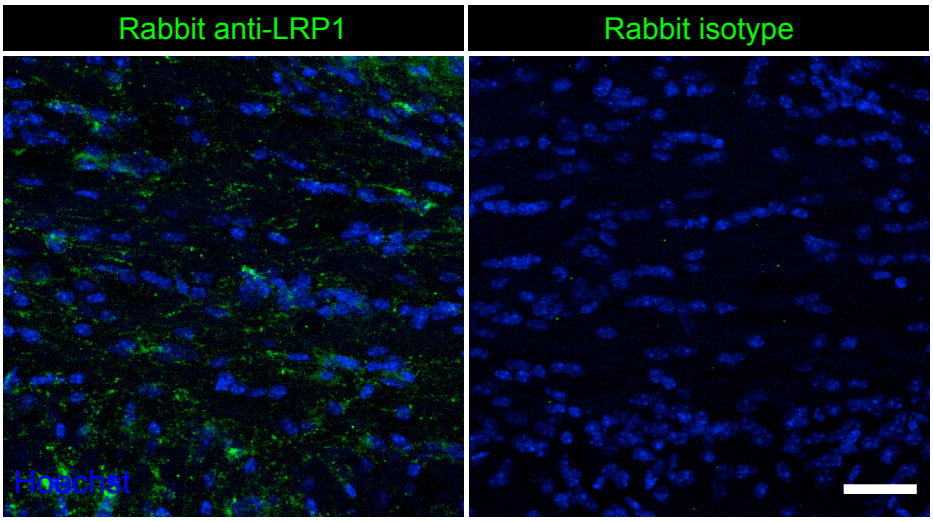
a



b

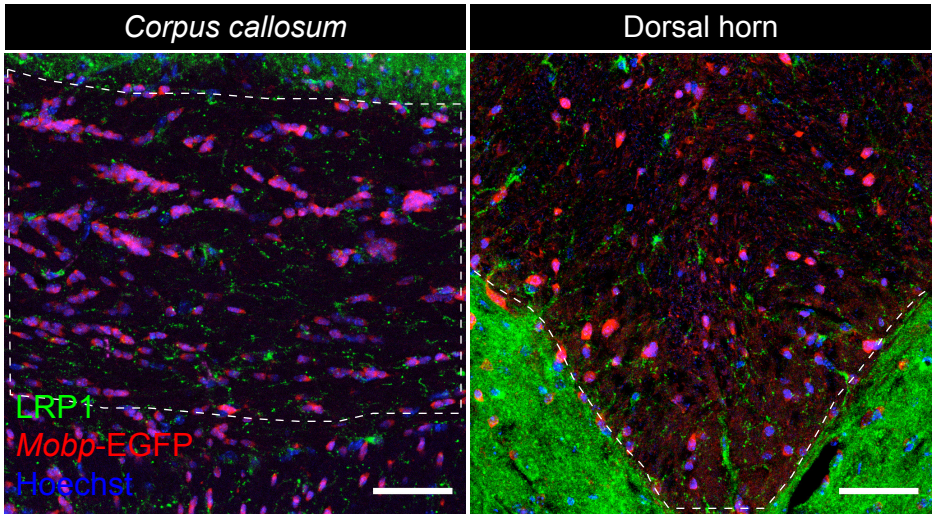


Fig. S1 LRP1 expression in mature oligodendrocytes (**a**) *Corpus callosum* staining with rabbit anti-LRP1 antibody and rabbit isotype control. Scale bar 30µm. (**b**) Brain (*corpus callosum*) and spinal cord (dorsal horn) slices from *Mobp*-EGFP reporter mice stained for LRP1. Dashed lines demarcate white matter borders. Scale bars 50µm.

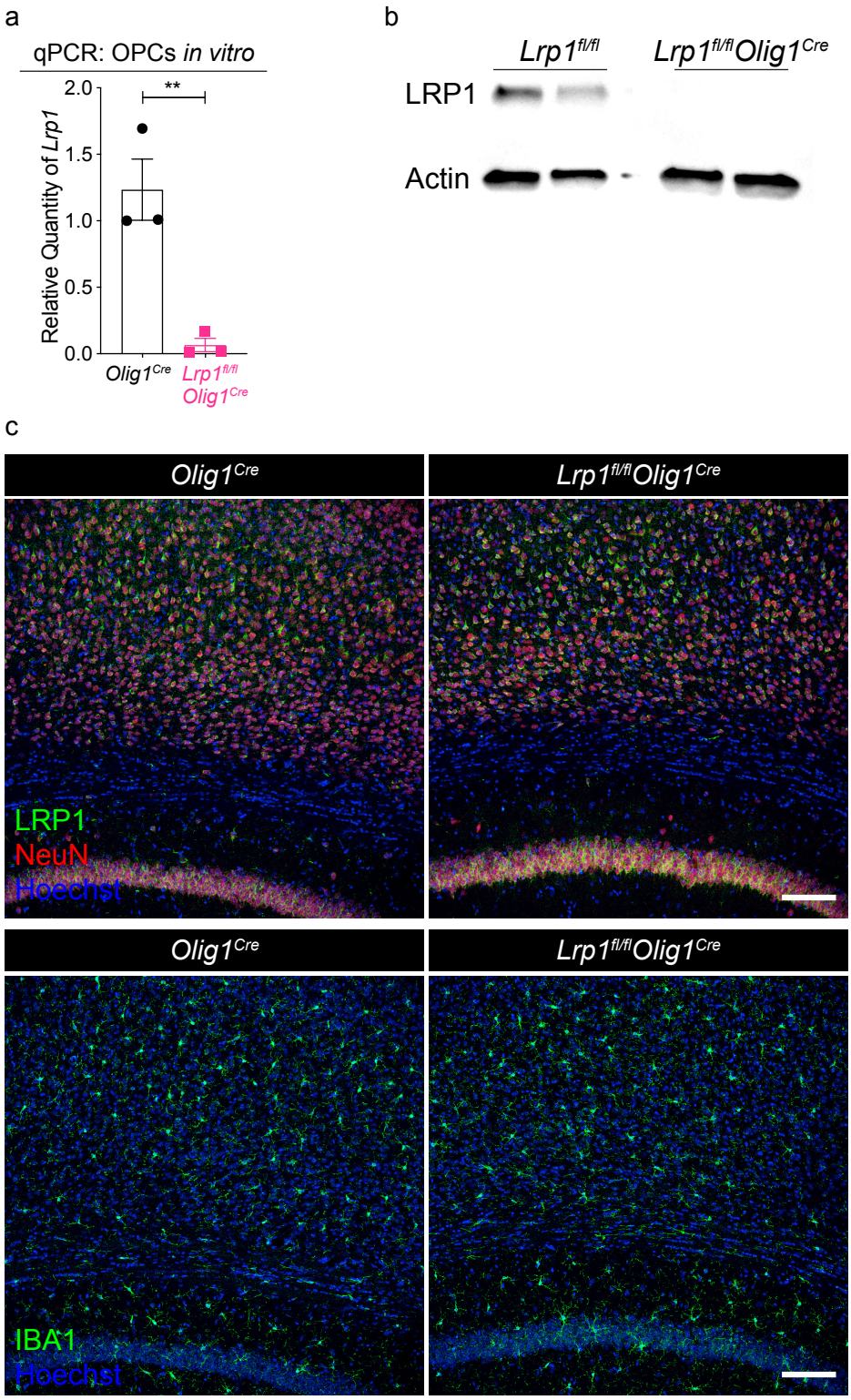


Fig. S2 Silencing of LRP1 in OPCs does not affect neuronal and myeloid compartments (**a**) qPCR for *Lrp1* from cultured OPCs (unpaired t-test, **p=0.0077; n=3 mice per genotype; error bars represent +/- SEM). (**b**) Western blot for LRP1 and actin from cultured OPCs (2 mice per genotype). (**c**) Cortical slices stained for LRP1 and NeuN from *Olig1*^{Cre} and *Lrp1*$^{fl/fl}$*Olig1*^{Cre} mice (upper panels). IBA1 staining in cortical slices from *Olig1*^{Cre} and *Lrp1*$^{fl/fl}$*Olig1*^{Cre} mice (lower panels). Scale bar 100µm.

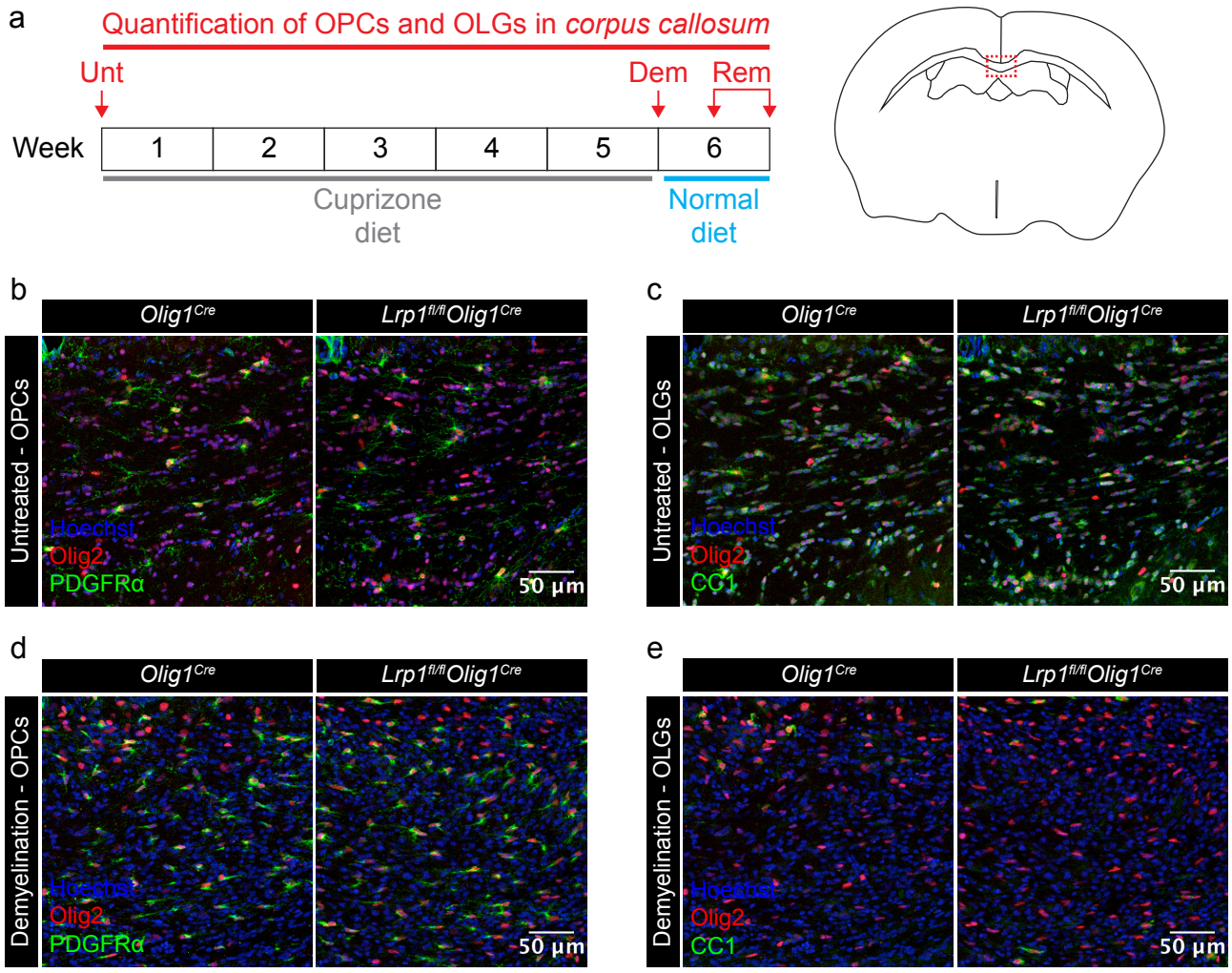


Fig. S3 OPCs and oligodendrocytes in the naïve and demyelinating *corpus callosum* (**a**) Schematic illustrating the cuprizone diet timeline and the timepoints at which the *corpus callosum* was imaged in *Olig1*^{Cre} and *Lrp1*$^{fl/fl}$*Olig1*^{Cre} mice. (**b**) Representative images of OPCs and (**c**) mature oligodendrocytes in the untreated *corpus callosum*. (**d**) Representative images of OPCs and (**e**) mature oligodendrocytes in the demyelinating *corpus callosum*.

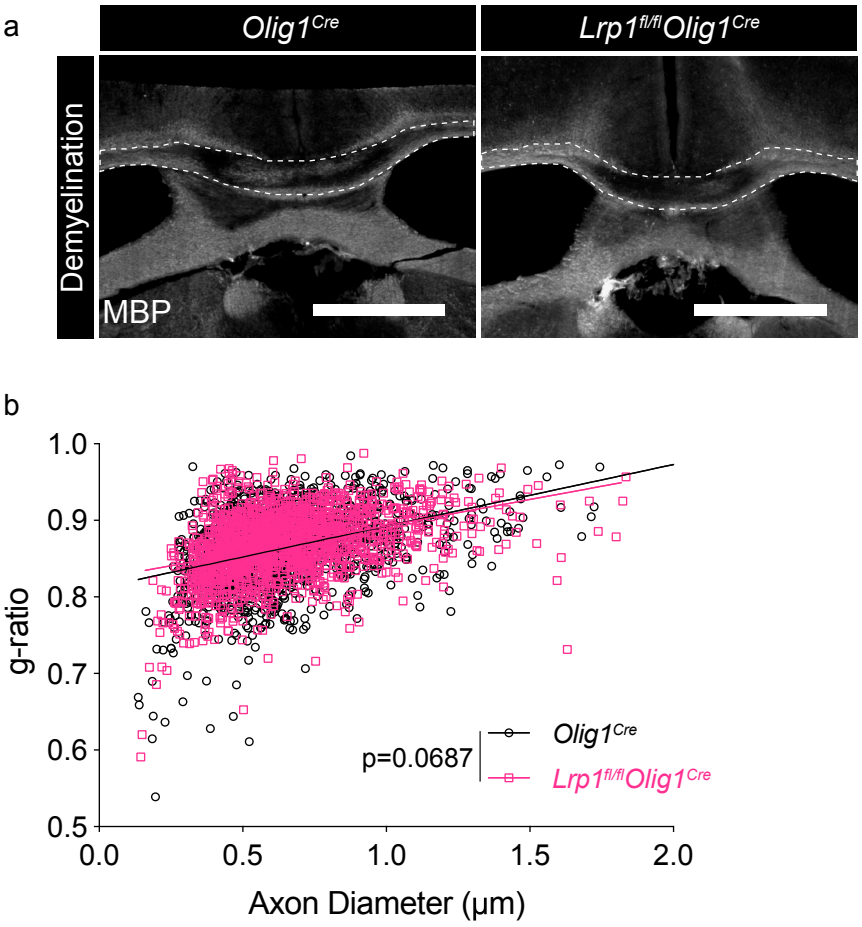


Fig. S4 MBP staining during demyelination and G-ratio analysis in the remyelinating *corpus callosum* (**a**) MBP immunofluorescence staining at 4 weeks of cuprizone treatment in the *corpus callosum* of *Olig1*^{Cre} and *Lrp1*$^{fl/fl}$*Olig1*^{Cre} mice. Scale bars 1000μm. (**b**) Calculated g-ratios from axons in the remyelinating (0.5 Wk Rem) *corpus callosum* of *Olig1*^{Cre} and *Lrp1*$^{fl/fl}$*Olig1*^{Cre} mice (linear regression analysis with slopes comparison).

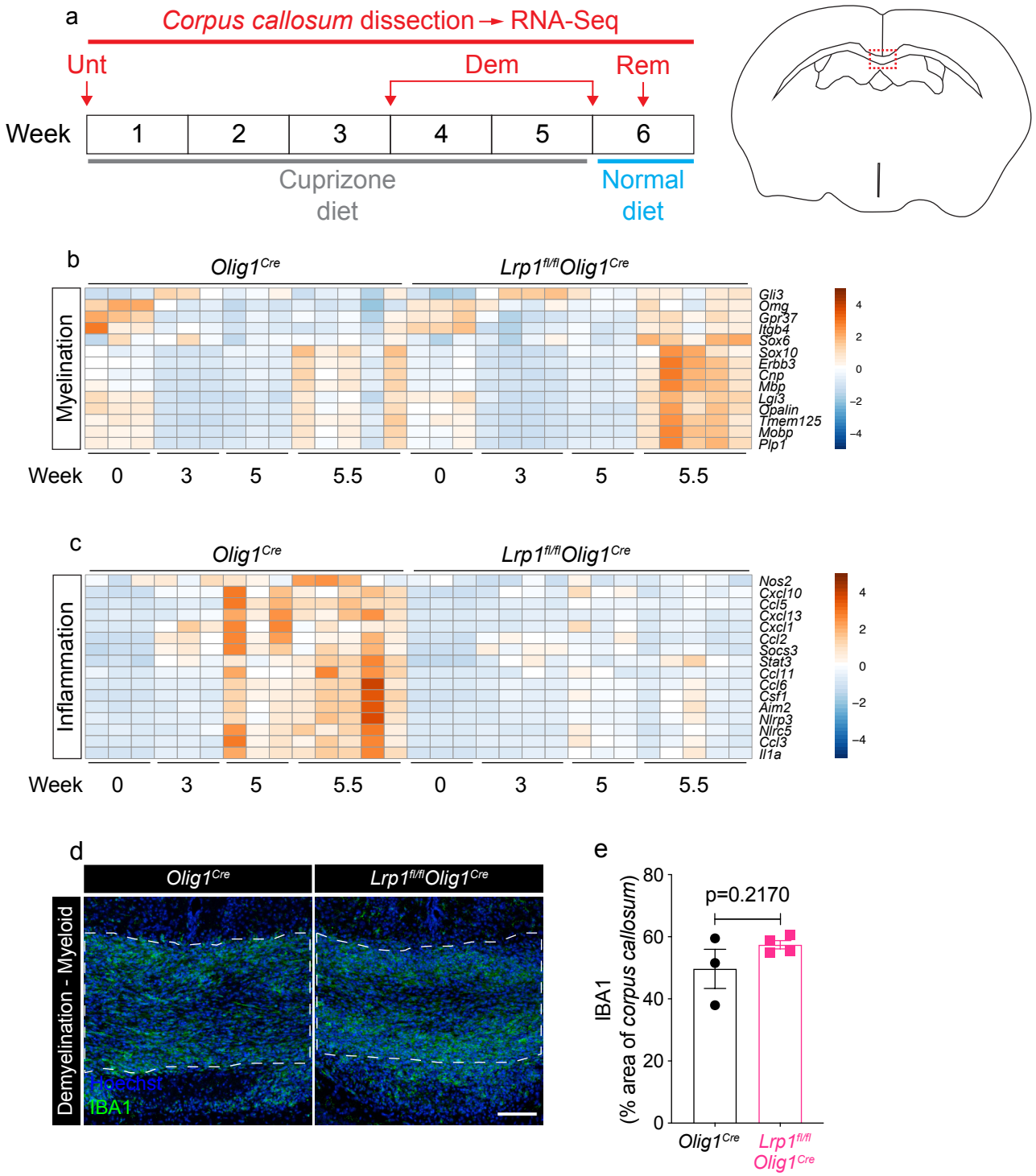


Fig. S5 RNA-seq analysis of the *corpus callosum* over the course of cuprizone treatment (**a**) Schematic illustrating the cuprizone diet timeline and timepoints at which the *corpus callosum* was dissected and analyzed by RNA-seq. (**b**) Heat map of myelination- and (**c**) inflammation-related genes in *Olig1*^{Cre} and *Lrp1*$^{fl/fl}$*Olig1*^{Cre} mice. Heat maps have a normalized count scale with z-score normalization. (**d**) Staining and (**e**) quantification of IBA1 in the *corpus callosum* of *Olig1*^{Cre} and *Lrp1*$^{fl/fl}$*Olig1*^{Cre} mice after 5 weeks of cuprizone treatment (unpaired t-test; n=3-4 mice per genotype; error bars represent +/- SEM). Scale bar 50μm.

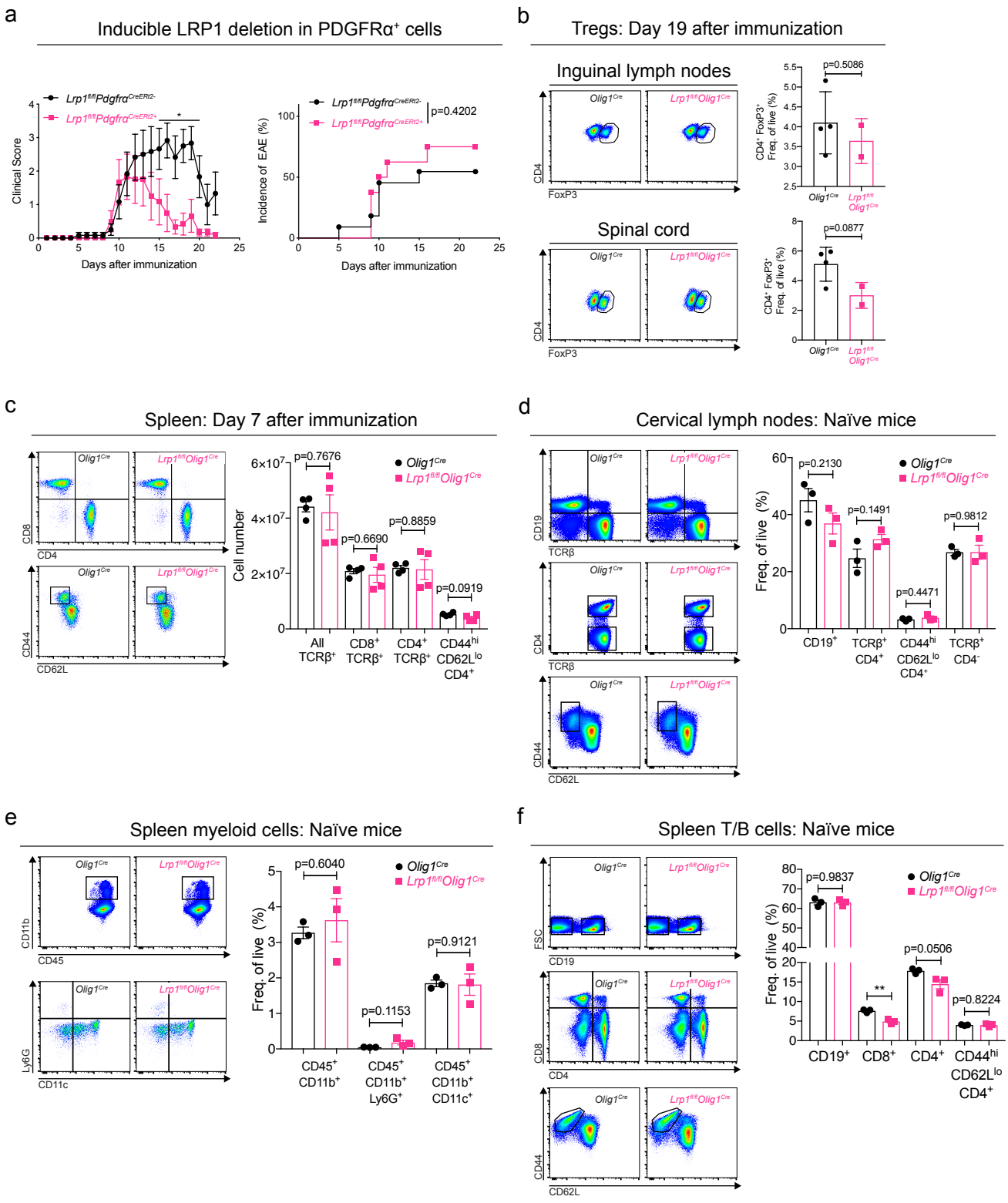


Fig. S6 Inflammatory phenotype in LRP1-deficient mice is not mediated by peripheral immune defects (**a**) EAE clinical scores and incidence from *Lrp1*$^{fl/fl}$*Pdgfra*^{CreERt2} mice (EAE scores: Mann-Whitney U test, *p<0.05; n=6 mice with disease per genotype; incidence: Log-rank test; n=8-11 total mice per genotype). (**b**) Flow cytometric analysis of Tregs (TCRβ⁺ CD4⁺ FoxP3⁺) in the draining lymph nodes (inguinal) and spinal cord during EAE in *Olig1*^{Cre} and *Lrp1*$^{fl/fl}$*Olig1*^{Cre} mice (unpaired t-test; n=2-4 mice per genotype). (**c**) Representative flow plots and quantification of T cell subsets in the spleen 7 days after EAE immunization. (**d**) T and B cell populations in the cervical lymph nodes of naïve mice. (**e**) Myeloid cells and (**f**) T and B cell populations in the spleen of naïve mice (FSC: forward scatter height). Error bars represent +/- SEM.

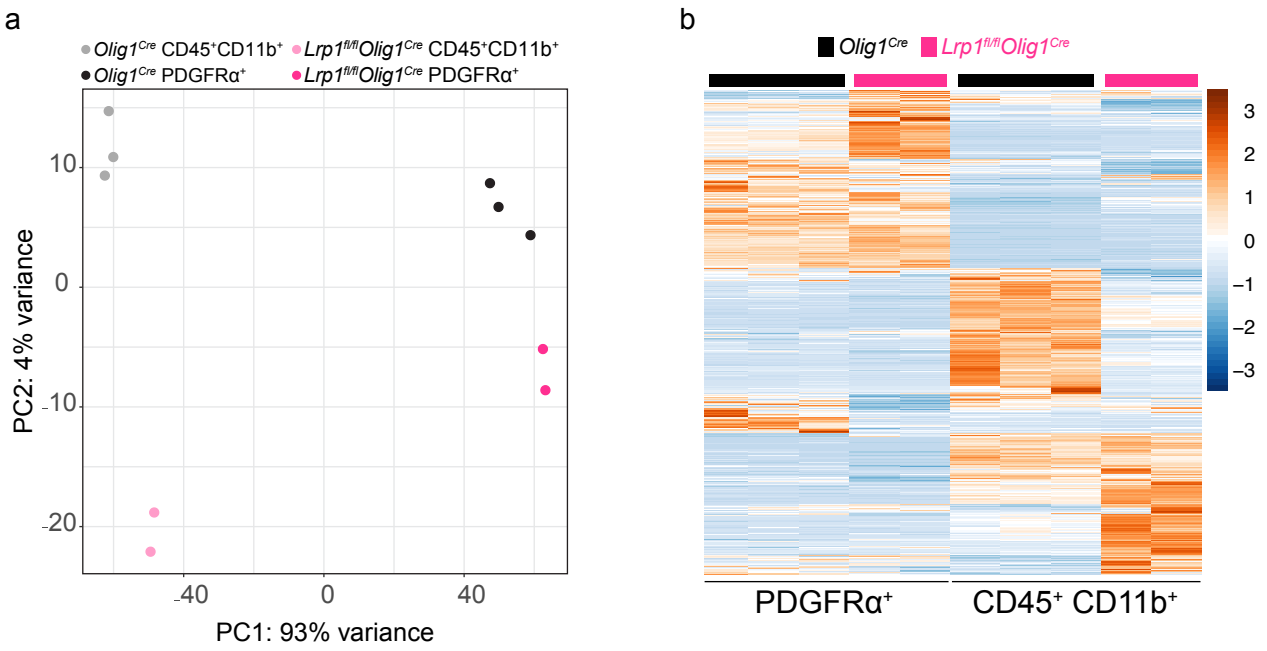


Fig. S7 Transcriptional profiling of the EAE spinal cord (**a**) Principal component analysis (PCA) plot and (**b**) heat map of the transcriptomes of sorted cells from EAE spinal cords of *Olig1*^{Cre} and *Lrp1*$^{fl/fl}$*Olig1*^{Cre} mice. Heat maps have a normalized count scale with z-score normalization.

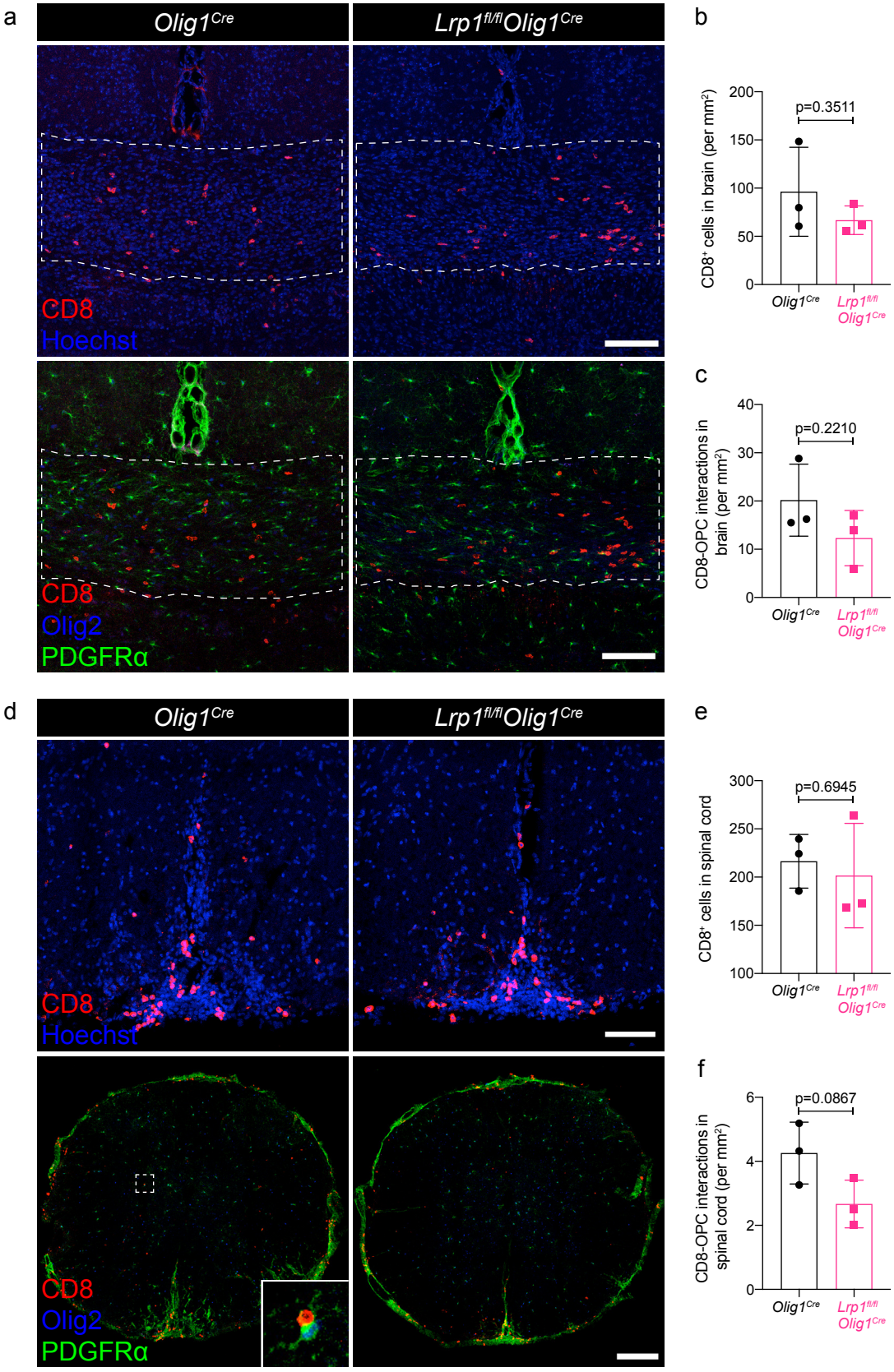


Fig. S8 CD8 cells in the cuprizone brain and EAE spinal cord. (**a**) Staining for CD8 (top panels), Olig2 and PDGFRα (lower panels) in the remyelinating brain (1 Wk Rem) of *Olig1*^{Cre} and *Lrp1*$^{fl/fl}$*Olig1*^{Cre} mice (dashed line outlines the *corpus callosum*). Scale bars 100μm. (**b**) Quantification of CD8 cells and (**c**) CD8-OPC interactions in remyelinating brains (unpaired t-test; n=3 mice per genotype). (**d**) Staining for CD8 (top panels), Olig2 and PDGFRα (lower panels) in EAE spinal cords (genotypes have similar disease scores; scale bars 75μm and 200μm, respectively.). (**e**) Quantification of CD8 cells and (**f**) CD8-OPC interactions in chronic EAE spinal cords (unpaired t-test; n=3 mice per genotype). Error bars represent +/- SEM.

Table S1 Ages of mice at experimental endpoints

Figure Panel	Age (weeks)
Fig. 1a,b	8
Fig. 1d	16
Fig. 1e	16
Fig. 2a	35-42
Fig. 2b-d	22
Fig. 2e,f	8
Fig. 3b-e cohort 1	35-42
Fig. 3b-e cohort 2	34
Fig. 3b-e cohort 3	22-25
Fig. 3f-h cohort 1	34
Fig. 3f-h cohort 2	22-25
Fig. 4a,b cohort 1	34
Fig. 4a,b cohort 2	22-25
Fig. 4c,d	17
Fig. 5b-g	16-25
Fig. 6a,b cohort 1	17-22
Fig. 6a,b cohort 2	12-16
Fig. 6c-i	17-24
Fig. 6j,k	26
Fig. 7a-f cohort 1	17-24
Fig. 7a-f cohort 2	27
Fig. 7g-j	14-17

Table S2 Differentially expressed genes in the *corpus callosum* of *Olig1*^{Cre} and *Lrp1*$^{fl/fl}$ *Olig1*^{Cre} mice at week 0

ENSEMBL	baseMean	log2FoldChange	lfcSE	stat	pvalue	padj	SYMBOL	Up/Down in *Lrp1*$^{fl/fl}$ *Olig1*^{Cre}
ENSMUSG00000068396	421.2400213	9.530674878	1.736238796	5.489265013	4.04E-08	8.46E-05	Rpl34-ps1	Up
ENSMUSG00000028736	37.47535702	9.02157036	2.270849669	3.972773047	7.10E-05	0.027931427	Pax7	Up
ENSMUSG00000001504	48.48650706	7.970635908	1.863623722	4.276955596	1.89E-05	0.01291707	Irx2	Up
ENSMUSG00000053747	12.55659766	7.471338108	1.751783964	4.264988298	2.00E-05	0.013003975	Sox14	Up
ENSMUSG00000097623	11.18597684	6.551515034	1.516299073	4.320727455	1.56E-05	0.011283259	B230323A14Rik	Up
ENSMUSG00000034384	10.36146052	6.517949801	1.425595754	4.572088393	4.83E-06	0.004470185	Barhl2	Up
ENSMUSG00000015619	35.09825765	6.456802394	1.194455419	5.405645359	6.46E-08	0.000121815	Gata3	Up
ENSMUSG00000034917	20.06535515	6.210961029	1.588280445	3.910493925	9.21E-05	0.033413795	Tjp3	Up
ENSMUSG00000026805	19.56004358	6.043340257	1.597548017	3.782884892	0.000155021	0.046417751	Barhl1	Up
ENSMUSG00000039217	39.14688581	6.012681851	1.386571577	4.336366007	1.45E-05	0.01093038	Il18	Up
ENSMUSG00000059246	18.50645027	5.967154128	1.501081423	3.975236811	7.03E-05	0.027931427	Foxb1	Up
ENSMUSG00000048349	100.4290744	5.619795882	1.467248871	3.8301586	0.000128061	0.040863014	Pou4f1	Up
ENSMUSG00000027833	68.25695807	5.582516376	1.283151106	4.350630529	1.36E-05	0.01093038	Shox2	Up
ENSMUSG00000028280	5.940707506	5.171579938	1.351310943	3.827083593	0.00012967	0.040863014	Gabrr1	Up
ENSMUSG00000000263	17.49708288	4.149583683	1.031500597	4.022861154	5.75E-05	0.026452626	Glra1	Up
ENSMUSG00000018486	8.831628702	4.131912452	1.100040539	3.756145621	0.00017255	0.04993454	Wnt9b	Up
ENSMUSG00000031734	23.81825338	3.924533766	1.014238242	3.869439746	0.000109086	0.037414424	Irx3	Up
ENSMUSG00000073555	40.180958	3.639119902	0.932770798	3.901408482	9.56E-05	0.034038706	Gm4951	Up
ENSMUSG00000010476	94.56881644	3.173719797	0.827496831	3.835325622	0.000125398	0.040863014	Ebf3	Up
ENSMUSG00000011658	86.48116341	3.074140031	0.773822705	3.97266714	7.11E-05	0.027931427	Fuz	Up
ENSMUSG00000015652	69.46564362	3.020226594	0.696081089	4.338900515	1.43E-05	0.01093038	Steap1	Up
ENSMUSG00000028717	155.9155353	2.845562154	0.590197912	4.821369401	1.43E-06	0.001582091	Tal1	Up
ENSMUSG00000020264	12.72961554	2.730695834	0.721681133	3.783798286	0.000154453	0.046417751	Slc36a2	Up
ENSMUSG00000031111	220.6344737	2.251598642	0.493146305	4.565782244	4.98E-06	0.004470185	Igsf1	Up
ENSMUSG00000030111	3015.893843	2.171765339	0.421805924	5.148731247	2.62E-07	0.000412264	A2m	Up
ENSMUSG00000058174	44.60359428	1.406446466	0.302718681	4.646051109	3.38E-06	0.003359273	Gm5148	Up
ENSMUSG00000026042	147.9687002	1.371897225	0.322869909	4.249071186	2.15E-05	0.013497739	Col5a2	Up
ENSMUSG00000047181	694.7309031	1.136422284	0.230525264	4.929708199	8.24E-07	0.000970936	Samd14	Up
ENSMUSG00000041741	148.6116826	1.126290706	0.222945187	5.051872701	4.37E-07	0.000589499	Pde3a	Up
ENSMUSG00000001665	114.8214899	0.906853974	0.222096184	4.083158733	4.44E-05	0.02290317	Gstt3	Up
ENSMUSG00000021338	595.167337	0.770960846	0.185698329	4.151684349	3.30E-05	0.018311244	Carmil1	Up
ENSMUSG00000070003	1051.250896	0.743426912	0.197887787	3.756810479	0.000172093	0.04993454	Ssbp4	Up
ENSMUSG00000021010	415.3598054	0.626778105	0.156023944	4.017191767	5.89E-05	0.026452626	Npas3	Up
ENSMUSG00000022842	521.3676328	0.611221364	0.159903453	3.82244005	0.000132138	0.040863014	Ece2	Up
ENSMUSG00000025911	353.7523585	0.590167477	0.153232652	3.85144725	0.000117422	0.03955438	Adhfe1	Up
ENSMUSG00000028648	902.5765363	0.567960494	0.144037475	3.943143911	8.04E-05	0.030340995	Ndufs5	Up
ENSMUSG00000020022	970.6741304	0.547566286	0.102303218	5.352385755	8.68E-08	0.000148858	Ndufa12	Up
ENSMUSG00000032393	3009.22146	-0.284923446	0.066659502	-4.274311078	1.92E-05	0.01291707	Dpp8	Down
ENSMUSG00000040472	645.1176357	-0.321813847	0.080849648	-3.980398851	6.88E-05	0.027931427	Rabggta	Down
ENSMUSG00000020458	10287.49286	-0.33538891	0.089364748	-3.753033698	0.000174707	0.04993454	Rtn4	Down
ENSMUSG00000026678	1109.633241	-0.44228736	0.111271328	-3.974854683	7.04E-05	0.027931427	Rgs5	Down
ENSMUSG00000055447	2634.556336	-0.616731154	0.111794282	-5.516660969	3.46E-08	8.15E-05	Cd47	Down
ENSMUSG00000029822	534.8044443	-0.620285526	0.150414901	-4.123830303	3.73E-05	0.02008334	Osbpl3	Down
ENSMUSG00000030067	926.4256622	-0.655569697	0.171346553	-3.825987079	0.000130249	0.040863014	Foxp1	Down
ENSMUSG00000021113	368.5847104	-0.920066736	0.184733944	-4.980496351	6.34E-07	0.000797588	Snapc1	Down
ENSMUSG00000049044	10111.08226	-0.967815674	0.244361416	-3.960591196	7.48E-05	0.028782781	Rapgef4	Down
ENSMUSG00000054000	58.70720416	-0.979590916	0.242800644	-4.034548255	5.47E-05	0.026452626	Tusc1	Down
ENSMUSG00000078894	209.0884403	-1.461538794	0.377514264	-3.871479656	0.000108177	0.037414424	2210418O10Rik	Down
ENSMUSG00000090622	33.70827551	-1.526679645	0.363176917	-4.203680287	2.63E-05	0.015011731	A930033H14Rik	Down
ENSMUSG00000041460	76.99514516	-1.594431686	0.364521437	-4.374040936	1.22E-05	0.010458158	Cacna2d4	Down
ENSMUSG00000026315	107.0030684	-1.77682184	0.447069186	-3.974377786	7.06E-05	0.027931427	Serpinb8	Down
ENSMUSG00000097325	20.50082525	-1.796406958	0.426051588	-4.216407141	2.48E-05	0.014632889	Gm16897	Down
ENSMUSG00000085956	15.3493593	-1.931422114	0.455358589	-4.241540973	2.22E-05	0.013508471	NA	Down
ENSMUSG00000039985	76.53830595	-2.070667921	0.508970515	-4.068345535	4.73E-05	0.02350461	Sinhcaf	Down
ENSMUSG00000098702	144.6240394	-3.636872761	0.233142296	-15.59936922	7.35E-55	6.93E-51	1500015A07Rik	Down
ENSMUSG00000054618	5.131686195	-3.785431095	0.962105531	-3.934527942	8.34E-05	0.03083353	NA	Down
ENSMUSG00000044211	65.18925315	-4.138946576	0.868951404	-4.763150798	1.91E-06	0.001997418	NA	Down
ENSMUSG00000067017	284.8246694	-4.492358243	0.477648304	-9.405159004	5.20E-21	2.45E-17	NA	Down
ENSMUSG00000082536	450.8296124	-4.618081693	0.349168388	-13.22594441	6.22E-40	3.91E-36	NA	Down
ENSMUSG00000047347	15.4528267	-5.585769586	1.010443997	-5.528034808	3.24E-08	8.15E-05	Tdg-ps	Down
ENSMUSG00000085666	43.78297745	-6.073844302	0.674836738	-9.00046479	2.25E-19	8.48E-16	NA	Down
ENSMUSG00000080893	185.4966096	-6.240963838	0.362462183	-17.2182482	1.94E-66	3.66E-62	NA	Down
ENSMUSG00000049580	32.68772593	-7.006851592	1.37688116	-5.088929818	3.60E-07	0.000522518	Tsku	Down
ENSMUSG00000081824	131.712625	-7.192723894	1.290232257	-5.574751254	2.48E-08	7.79E-05	NA	Down
ENSMUSG00000061062	35.23638137	-7.411780592	1.842261284	-4.023197282	5.74E-05	0.026452626	NA	Down
ENSMUSG00000057335	69.97080255	-15.99524949	3.919842067	-4.08058519	4.49E-05	0.02290317	Cep170	Down