Supplementary Table 1. Differentially expressed genes (DEGs) between *Tmem106b-/-* and *Tmem106b+/+* animals.

Gene_ID	Symbol	Chr	Stepup p-value	Fold-Change
ENSMUSG00000029571	Tmem106b	chr6	2.03E-23	-3.12039
ENSMUSG00000034714	Ttyh2	chr11	2.75E-07	-1.1537
ENSMUSG00000033579	Fa2h	chr8	2.75E-07	-1.30621
ENSMUSG00000037625	Cldn11	chr3	7.92E-07	-1.21051
ENSMUSG00000027375	Mal	chr2	1.31E-05	-1.23669
ENSMUSG00000028412	Slc44a1	chr4	1.74E-05	-1.08721
ENSMUSG00000038668	Lpar1	chr4	4.07E-05	-1.26056
ENSMUSG00000006782	Cnp	chr11	4.90E-05	-1.2202
ENSMUSG00000026830	Ermn	chr2	4.98E-05	-1.24287
ENSMUSG00000006403	Adamts4	chr1	7.42E-05	-1.23671
ENSMUSG00000032854	Ugt8a	chr3	0.000135807	-1.31187
ENSMUSG00000041828	Abca8a	chr11	0.000155299	-1.25286
ENSMUSG00000037280	Galnt6	chr15	0.000231061	-1.21704
ENSMUSG00000036777	Anln	chr9	0.00030604	-1.25418
ENSMUSG00000020023	Tmcc3	chr10	0.000338856	-1.18704
ENSMUSG00000031385	Plxnb3	chrX	0.000338856	-1.18882
ENSMUSG00000039904	Gpr37	chr6	0.000363117	-1.20615
ENSMUSG00000038173	Enpp6	chr8	0.000428456	-1.34278
ENSMUSG00000032625	Thsd7a	chr6	0.000602581	-1.15041
ENSMUSG00000000149	Gna12	chr5	0.000657287	-1.1501
ENSMUSG00000041062	Mslnl	chr17	0.000657287	1.97176
ENSMUSG00000076439	Mog	chr17	0.000657287	-1.15332
ENSMUSG00000005125	Ndrg1	chr15	0.00069827	-1.15117
ENSMUSG00000020758	Itgb4	chr11	0.000724265	-1.19869
ENSMUSG00000022472	Desi1	chr15	0.00109528	-1.08816
ENSMUSG00000033904	Ccp110	chr7	0.00143325	-1.0887
ENSMUSG00000026519	Tmem63a	chr1	0.00151268	-1.19769
ENSMUSG00000049721	Gal3st1	chr11	0.00151268	-1.20775
ENSMUSG00000050121	Opalin	chr19	0.00211334	-1.40524
ENSMUSG00000024812	Tjp2	chr19	0.00211334	-1.15108
ENSMUSG00000033006	Sox10	chr15	0.00217224	-1.2651
ENSMUSG00000022500	Litaf	chr16	0.00217224	-1.21825
ENSMUSG00000001729	Akt1	chr12	0.0023424	-1.03975
ENSMUSG00000032554	Trf	chr9	0.0023424	-1.17954
ENSMUSG00000041895	Wipi1	chr11	0.00265916	-1.12021
ENSMUSG00000028917	Plekhm2	chr4	0.00265916	-1.0802
ENSMUSG00000033949	Trim36	chr18	0.00265916	-1.19757
ENSMUSG00000019820	Utrn	chr10	0.00416357	-1.08329
ENSMUSG00000046160	Olig1	chr16	0.00418629	-1.18584
ENSMUSG00000027562	Car2	chr3	0.00418629	-1.15592
ENSMUSG00000036907	C1ql2	chr1	0.00418629	-1.24378
ENSMUSG00000035441	Myo1d	chr11	0.00418629	-1.17974
ENSMUSG00000056966	Gjc3	chr5	0.00432233	-1.1296
ENSMUSG00000036644	Tbc1d9b	chr11	0.00432233	-1.08264
ENSMUSG00000031714	Gab1	chr8	0.00432233	-1.16612
ENSMUSG00000032841	Prr5l	chr2	0.00432233	-1.21533
ENSMUSG00000047797	Gjb1	chrX	0.00432233	-1.20703
ENSMUSG00000028082	Sh3d19	chr3	0.00447485	-1.11753
ENSMUSG00000078771	Evi2a	chr11	0.00457461	-1.14241
ENSMUSG00000035413	Tmem98	chr11	0.00467163	-1.19303
ENSMUSG00000060716	Plekhh1	chr12	0.00478522	-1.12667

ENSMUSG00000020411	Nipal4	chr11	0.00478522	-1.27989
ENSMUSG00000036098	Myrf	chr19	0.00484794	-1.15008
ENSMUSG00000030630	Fah	chr7	0.00485039	-1.1348
ENSMUSG00000041607	Mbp	chr18	0.00485039	-1.11133
ENSMUSG00000037458	Azin1	chr15	0.00485039	1.07391
ENSMUSG00000025584	Pde8a	chr7	0.00485039	-1.177
ENSMUSG00000033039	Micall1	chr15	0.00485039	-1.12024
ENSMUSG00000073680	Tmem88b	chr4	0.00485039	-1.17068
ENSMUSG00000000805	Car4	chr11	0.00514752	1.12386
ENSMUSG00000024187	Itfg3	chr17	0.00515316	-1.1043
ENSMUSG00000049092	Gpr137c	chr14	0.00515938	1.13975
ENSMUSG00000043448	Gjc2	chr11	0.00515938	-1.27688
ENSMUSG00000025504	Eps8l2	chr7	0.00517914	-1.15386
ENSMUSG00000001864	Aif1l	chr2	0.00524086	-1.22669
ENSMUSG00000052609	Plekhg3	chr12	0.00544526	-1.13777
ENSMUSG00000042625	Safb2	chr17	0.00574441	1.07757
ENSMUSG00000064325	Hhip	chr8	0.00657371	-1.30964
ENSMUSG00000007891	Ctsd	chr7	0.00657371	1.06854
ENSMUSG00000013698	Pea15a	chr1	0.0067914	-1.06386
ENSMUSG00000019880	Rspo3	chr10	0.0067914	1.17599
ENSMUSG00000037031	Tspan15	chr10	0.00718829	-1.14251
ENSMUSG00000060675	Pla2g16	chr19	0.00739811	-1.11055
ENSMUSG00000032135	Mcam	chr9	0.00739811	-1.21436
ENSMUSG00000055717	Slain1	chr14	0.00739811	-1.1128
ENSMUSG00000033557	Fam20b	chr1	0.00739811	-1.05268
ENSMUSG00000018449	Rpain	chr11	0.00768149	1.15395
ENSMUSG00000037166	Ppp1r14a	chr7	0.00768149	-1.22243
ENSMUSG00000081534	Slc48a1	chr15	0.00872803	-1.06303
ENSMUSG00000020486	Sept4	chr11	0.00872803	-1.09048
ENSMUSG00000017417	Plxdc1	chr11	0.00880978	-1.10698
ENSMUSG00000020846	Fam101b	chr11	0.0101713	-1.17585
ENSMUSG00000056515	Rab31	chr17	0.0105553	-1.06731
ENSMUSG00000031425	Plp1	chrX	0.0105637	-1.13494
ENSMUSG00000015755	Tab2	chr10	0.0113115	-1.05915
ENSMUSG00000027858	Tspan2	chr3	0.0117513	-1.13282
ENSMUSG00000021709	Erbb2ip	chr13	0.0117532	-1.11334
ENSMUSG00000031762	Mt2	chr8	0.0119488	1.37532
ENSMUSG00000015757	Ppil4	chr10	0.0123085	1.06244
ENSMUSG00000030751	Psma1	chr7	0.0124541	1.05126
ENSMUSG00000019899	Lama2	chr10	0.0125757	-1.12936
ENSMUSG00000030849	Fgfr2	chr7	0.0129867	-1.15497
ENSMUSG00000020536	Llgl1	chr11	0.0130109	-1.07583
ENSMUSG00000024816	Frmd8	chr19	0.0132594	-1.12572
ENSMUSG00000039316	Rftn1	chr17	0.0149621	-1.11979
ENSMUSG00000073982	Rhog	chr7	0.015412	-1.16694
ENSMUSG00000090083	Rnf8	chr17	0.0163712	-1.06224
ENSMUSG00000031628	Casp3	chr8	0.0163712	1.17511
ENSMUSG00000058835	Abi1	chr2	0.0173073	1.07001
ENSMUSG00000015451	C4a	chr17	0.0173073	1.20235
ENSMUSG00000045404	Kcnk13	chr12	0.0181938	-1.17602
ENSMUSG00000041935	AW549877	chr15	0.0184128	1.06839
ENSMUSG00000003934	Efnb3	chr11	0.0185397	-1.07886
ENSMUSG00000024268	Celf4	chr18	0.0185437	-1.0668
ENSMUSG00000037242	Clic4	chr4	0.0186651	-1.0917
ENSMUSG00000011877	Git1	chr11	0.0188527	-1.07853

ENSMUSG00000048537	Phldb1	chr9	0.0195804	-1.12093
ENSMUSG00000090121	Abhd12b	chr12	0.0195804	-1.38407
ENSMUSG00000024558	Mapk4	chr18	0.0195804	1.08588
ENSMUSG00000020932	Gfap	chr11	0.0206826	1.16646
ENSMUSG00000026203	Dnajb2	chr1	0.0208456	-1.06301
ENSMUSG00000027215	Cd82	chr2	0.0220344	-1.13454
ENSMUSG00000021143	Pacs2	chr12	0.022259	-1.10226
ENSMUSG00000020811	Wscd1	chr11	0.022259	-1.08792
ENSMUSG00000049807	Arhgap23	chr11	0.0227066	-1.09371
ENSMUSG00000030137	Tuba8	chr6	0.0240665	-1.12919
ENSMUSG00000028364	Tnc	chr4	0.0249303	-1.31023
ENSMUSG00000044447	Dock5	chr14	0.0253919	-1.18833
ENSMUSG00000040234	Tm7sf3	chr6	0.0253919	-1.08491
ENSMUSG00000019647	Sema6a	chr18	0.0253919	-1.13285
ENSMUSG00000020788	Atp2a3	chr11	0.0253919	-1.23844
ENSMUSG00000052155	Acvr2a	chr2	0.0258135	1.07658
ENSMUSG00000002831	Plin4	chr17	0.0266461	2.19007
ENSMUSG00000044258	Ctla2a	chr13	0.0272797	1.3388
ENSMUSG00000092021	Gbp11	chr5	0.0272797	-1.45112
ENSMUSG00000028971	Cort	chr4	0.027575	1.40669
ENSMUSG00000042066	Tmcc2	chr1	0.027575	-1.07969
ENSMUSG00000068882	Ssb	chr2	0.028348	1.07644
ENSMUSG00000036905	C1qb	chr4	0.0283812	1.13508
ENSMUSG00000041309	Nkx6-2	chr7	0.0286983	-1.14379
ENSMUSG00000024777	Ppp2r5b	chr19	0.0288173	1.07137
ENSMUSG00000037010	Apln	chrX	0.0288842	-1.25238
ENSMUSG00000025979	Mob4	chr1	0.0296954	1.0655
ENSMUSG00000087050	Dhrs13os	chr11	0.0297811	-1.08099
ENSMUSG00000027954	Efna1	chr3	0.0301765	-1.19544
ENSMUSG00000038351	Sgsm2	chr11	0.0313386	-1.07929
ENSMUSG00000062078	Qk	chr17	0.0318651	-1.0577
ENSMUSG00000090062	Galnt6os	chr15	0.0320293	-1.1959
ENSMUSG00000085008	Dbhos	chr2	0.0327938	-1.20123
ENSMUSG00000037656	Slc20a2	chr8	0.0327938	-1.13795
ENSMUSG00000020864	Ankrd40	chr11	0.0327938	-1.04307
ENSMUSG00000030513	Pcsk6	chr7	0.0327938	-1.14552
ENSMUSG00000026074	Map4k4	chr1	0.0327938	-1.06917
ENSMUSG00000031410	Nxf7	chrX	0.0327938	-1.70334
ENSMUSG00000070423	Olfr558	chr7	0.0327938	-1.7612
ENSMUSG00000071042	Rasgrp3	chr17	0.0343125	-1.14154
ENSMUSG00000024188	Luc7l	chr17	0.0343125	1.06504
ENSMUSG00000012609	Ttll5	chr12	0.0344909	-1.10634
ENSMUSG00000032599	Ip6k2	chr9	0.0351575	1.08407
ENSMUSG00000027288	Zfp106	chr2	0.0351575	-1.07033
ENSMUSG00000066687	Zbtb16	chr9	0.0353153	1.28698
ENSMUSG00000065514	Mir106b	chr5	0.0353153	-2.89311
ENSMUSG00000017009	Sdc4	chr2	0.0353153	1.14611
ENSMUSG00000032902	Slc16a1	chr3	0.0353153	-1.13572
ENSMUSG00000044037	Als2cl	chr9	0.0353153	1.12341
ENSMUSG00000020089	Ppa1	chr10	0.0369378	1.0699
ENSMUSG00000062604	Srpk2	chr5	0.0369378	1.03515
ENSMUSG00000042292	Mkl1	chr15	0.0369378	1.09541
ENSMUSG00000035093	Secisbp2l	chr2	0.0369378	-1.05598
ENSMUSG00000040850	Psme4	chr11	0.0369378	1.07577
ENSMUSG00000021696	Elovl7	chr13	0.0369378	-1.14536

ENSMUSG00000064201	Krt2	chr15	0.037705	-1.4546
ENSMUSG00000019873	Reep3	chr10	0.037705	-1.09089
ENSMUSG00000027199	Gatm	chr2	0.037705	-1.10149
ENSMUSG00000012640	Zfp715	chr7	0.037705	1.08186
ENSMUSG00000024381	Bin1	chr18	0.037705	-1.08147
ENSMUSG00000057134	Ado	chr10	0.037705	-1.06751
ENSMUSG00000043496	Tril	chr6	0.037705	-1.11197
ENSMUSG00000007877	Tcap	chr11	0.037705	1.29297
ENSMUSG00000004328	Hif3a	chr7	0.037705	1.84648
ENSMUSG00000010048	Ifrd2	chr9	0.037705	1.14905
ENSMUSG00000022205	Sub1	chr15	0.0383259	1.06698
ENSMUSG00000074457	S100a16	chr3	0.0387143	-1.12779
ENSMUSG00000061762	Tac1	chr6	0.0393756	1.16201
ENSMUSG00000030256	Bhlhe41	chr6	0.0394173	1.1939
ENSMUSG00000031765	Mt1	chr8	0.0409994	1.09568
ENSMUSG00000025724	Sec11a	chr7	0.0420148	1.10169
ENSMUSG00000059149	Mfsd4	chr1	0.0420148	1.1096
ENSMUSG00000001348	Acp5	chr9	0.0433091	1.86573
ENSMUSG00000087141	Plcxd2	chr16	0.0445803	-1.09373
ENSMUSG00000011884	Gltp	chr5	0.0458169	-1.10387
ENSMUSG00000008035	Mid1ip1	chrX	0.0458169	-1.0913
ENSMUSG00000064496	DQ267101	chr12	0.0458169	2.36522
ENSMUSG00000022752	Tomm70a	chr16	0.0458169	1.05813
ENSMUSG00000071176	Arhgef10	chr8	0.0458169	-1.09911
ENSMUSG00000034480	Diap2	chrX	0.0458169	1.08905
ENSMUSG00000103344	GBP11	chr5	0.0458169	-1.43098
ENSMUSG00000001366	Fbxo9	chr9	0.0458169	1.07834
ENSMUSG00000008393	Carhsp1	chr16	0.0458169	-1.08352
ENSMUSG00000040596	Pogk	chr1	0.0458169	-1.05109
ENSMUSG00000017428	Psmd11	chr11	0.0458169	1.0604
ENSMUSG00000042328	Hps4	chr5	0.0458169	1.10558
ENSMUSG00000058070	Eml1	chr12	0.0458169	-1.08945
ENSMUSG00000014361	Mertk	chr2	0.0458169	1.1832
ENSMUSG00000038619	Ensa	chr3	0.0458257	1.06265
ENSMUSG00000051675	Trim32	chr4	0.0458257	1.05495
ENSMUSG00000021214	Akr1c18	chr13	0.0458257	-1.72371
ENSMUSG00000032060	Cryab	chr9	0.0462347	-1.16777
ENSMUSG00000036580	Spg20	chr3	0.0462347	-1.07961
ENSMUSG00000036634	Mag	chr7	0.0462347	-1.10002
ENSMUSG00000024066	Xdh	chr17	0.0464722	1.34967
ENSMUSG00000051617	Krt9	chr11	0.0466942	-1.15899
ENSMUSG00000021990	Spata13	chr14	0.047042	-1.09114
ENSMUSG00000022483	Col2a1	chr15	0.047864	-1.34711
ENSMUSG00000059602	Syn3	chr10	0.047864	1.10008
ENSMUSG00000076144	Mir709	chr8	0.0480931	2.37747
ENSMUSG00000058756	Thra	chr11	0.048867	-1.04984
ENSMUSG00000040848	Sft2d2	chr1	0.048867	-1.0962
ENSMUSG00000031775	Pllp	chr8	0.048867	-1.15664
ENSMUSG00000027434	Nkx2-2	chr2	0.048867	-1.16674
ENSMUSG00000021596	Mctp1	chr13	0.0497665	1.08087
ENSMUSG00000047412	Zbtb44	chr9	0.0497665	1.07404
ENSMUSG00000015090	Ptgds	chr2	0.0497665	1.10198

Supplementary Table 2. Differentially expressed genes (DEGs) between *Tmem106b-/-* and *Tmem106b+/-* animals.

Gene_ID	Symbol	Chr	Stepup p-value	Fold-Change
ENSMUSG00000029571	Tmem106b	chr6	1.06E-18	-2.06917
ENSMUSG00000032854	Ugt8a	chr3	1.30E-02	-1.22483
ENSMUSG00000090062	Galnt6os	chr15	4.63E-02	-1.22176
ENSMUSG00000033579	Fa2h	chr8	1.63E-04	-1.21426
ENSMUSG00000041828	Abca8a	chr11	4.19E-03	-1.21189
ENSMUSG00000006403	Adamts4	chr1	2.16E-03	-1.20084
ENSMUSG00000037280	Galnt6	chr15	2.44E-03	-1.19723
ENSMUSG00000028681	Ptch2	chr4	1.67E-02	-1.19163
ENSMUSG00000036777	Anln	chr9	1.52E-02	-1.19087
ENSMUSG00000047797	Gjb1	chrX	0.0277294	-1.18849
ENSMUSG00000039904	Gpr37	chr6	0.00548018	-1.18191
ENSMUSG00000038668	Lpar1	chr4	0.0107686	-1.17804
ENSMUSG00000030137	Tuba8	chr6	0.0129935	-1.16495
ENSMUSG00000026830	Ermn	chr2	0.0176258	-1.15258
ENSMUSG00000032554	Trf	chr9	0.0350375	-1.14865
ENSMUSG00000006782	Cnp	chr11	0.0129935	-1.1473
ENSMUSG00000027375	Mal	chr2	0.0129935	-1.14207
ENSMUSG00000037625	Cldn11	chr3	0.00151083	-1.13726
ENSMUSG00000031385	Plxnb3	chrX	0.0348441	-1.13054
ENSMUSG00000076439	Mog	chr17	0.0138916	-1.12798
ENSMUSG00000024816	Frmd8	chr19	0.0462895	-1.12564
ENSMUSG00000034714	Ttyh2	chr11	0.00151083	-1.09353
ENSMUSG00000041298	Katnal1	chr5	0.0462895	-1.05251
ENSMUSG00000007891	Ctsd	chr7	0.0176258	1.06975
ENSMUSG00000018651	Tada2a	chr11	0.0166744	1.09668
ENSMUSG00000025555	Farp1	chr14	0.0166744	1.11312
ENSMUSG00000000805	Car4	chr11	0.0129935	1.13233
ENSMUSG00000020932	Gfap	chr11	0.0166744	1.20072
ENSMUSG00000015451	C4a	chr17	0.0462895	1.20831
ENSMUSG00000073418	C4b	chr17	0.0277294	1.2195
ENSMUSG00000041062	Mslnl	chr17	0.0144737	1.76505

Supplementary Table 3. Oligodendrocyte enriched and myelination-related genes list[obtained from JAX Mouse Genome Informatics (http://www.informatics.jax.org/)].

MGI Gene/Marker ID	Symbol	Chr
MGI:97435	Mog	17
MGI:1355334	Olig1	16
MGI:1355331	Olig2	16
MGI:2149955	Olig3	10
MGI:106586	Omg	11
MGI:106925	Cldn11	3
MGI:108511	Mobp	9
MGI:2657025	Opalin	19
MGI:99606	Abca2	2
MGI:1932576	Akap12	10
MGI:96919	Ascl1	10
MGI:87914	Aspa	11
MGI:1927169	B4galt5	2
MGI:1928380	B4galt6	18
MGI:88180	Bmp4	14
MGI:101765	Cdk5	5
MGI:88423	Clu	14
MGI:88437	Cnp	11
MGI:104518	Cntn2	1
MGI:1858201	Cntnap1	11
MGI:88276	Ctnnb1	9
MGI:109563	Cxcr4	1
MGI:1923691	Daam2	17
MGI:101864	Dag1	9
MGI:2177178	Dicer1	12
MGI:94901	Dlx1	2
MGI:94902	Dlx2	2
MGI:94925	Drd3	16
MGI:1927070	Dusp10	1
MGI:1934928	Dusp15	2
MGI:2384802	Eif2b1	5
MGI:2145118	Eif2b2	12
MGI:1313286	Eif2b3	4
MGI:95300	Eif2b4	5
MGI:2446176	Eif2b5	16
MGI:1321390	Enpp2	15
MGI:95410	Erbb2	11
MGI:95413	Ercc2	7
MGI:1096376	Exoc4	6
MGI:2443327	Fa2h	8
MGI:95524	Fgfr3	5
MGI:95660	Gas6	8

MGI:95729	Gli3	13
MGI:87940	Grk2	19
MGI:95843	Gsx2	5
MGI:108086	Hdac1	4
MGI:2385252	Hdac11	6
MGI:1097691	Hdac2	10
MGI:104853	Hes1	16
MGI:104876	Hes5	4
MGI:96397	Id2	12
MGI:99414	Id4	13
MGI:96432	Igf1	10
MGI:1923777	Il34	8
MGI:1194504	Kcnj10	1
MGI:1915522	Lingo1	9
MGI:96912	Mag	7
MGI:96949	Mdk	2
MGI:1926212	Med12	X
MGI:3618753	Mir219a-1	17
MGI:3618754	Mir219a-2	2
MGI:2676897	Mir23a	8
MGI:1928394	Mtor	4
MGI:2684944	Myrf	19
MGI:1891700	Ncstn	1
MGI:97306	Nf1	11
MGI:108067	Nkx2-1	12
MGI:97347	Nkx2-2	2
MGI:3652259	Nkx2-2os	2
MGI:1206039	Nkx6-1	5
MGI:1352738	Nkx6-2	7
MGI:2444609	Nlgn3	X
MGI:97363	Notch1	2
MGI:96083	Nrg1	8
MGI:97384	Ntrk2	13
MGI:97451	Otx2	14
MGI:97490	Pax6	2
MGI:97623	Plp1	X
MGI:97747	Pparg	6
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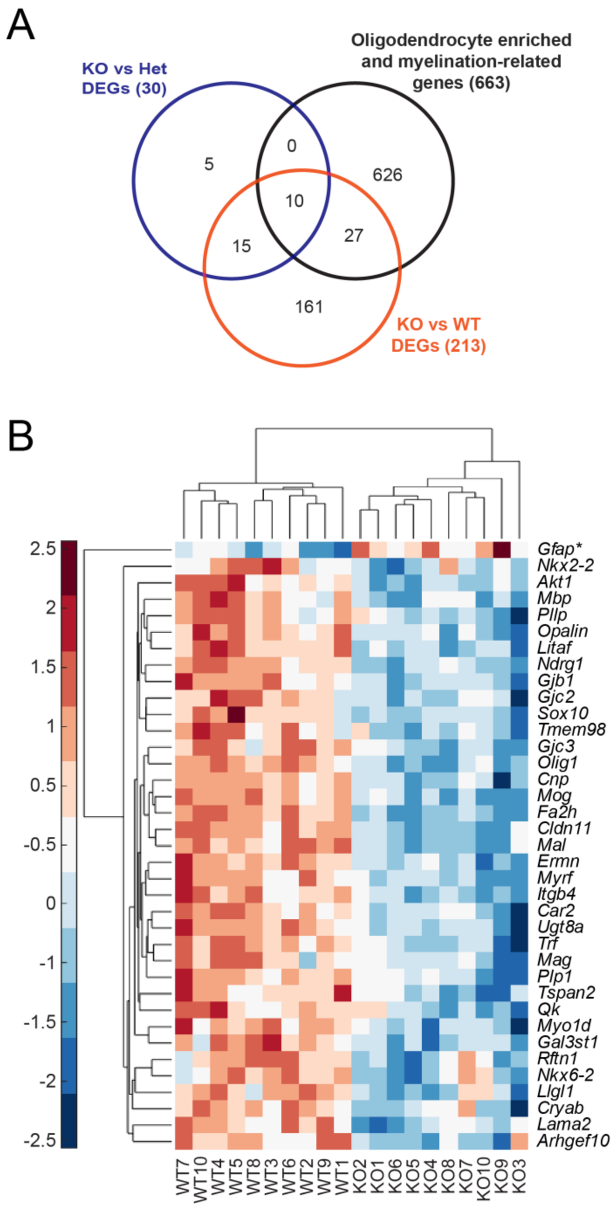
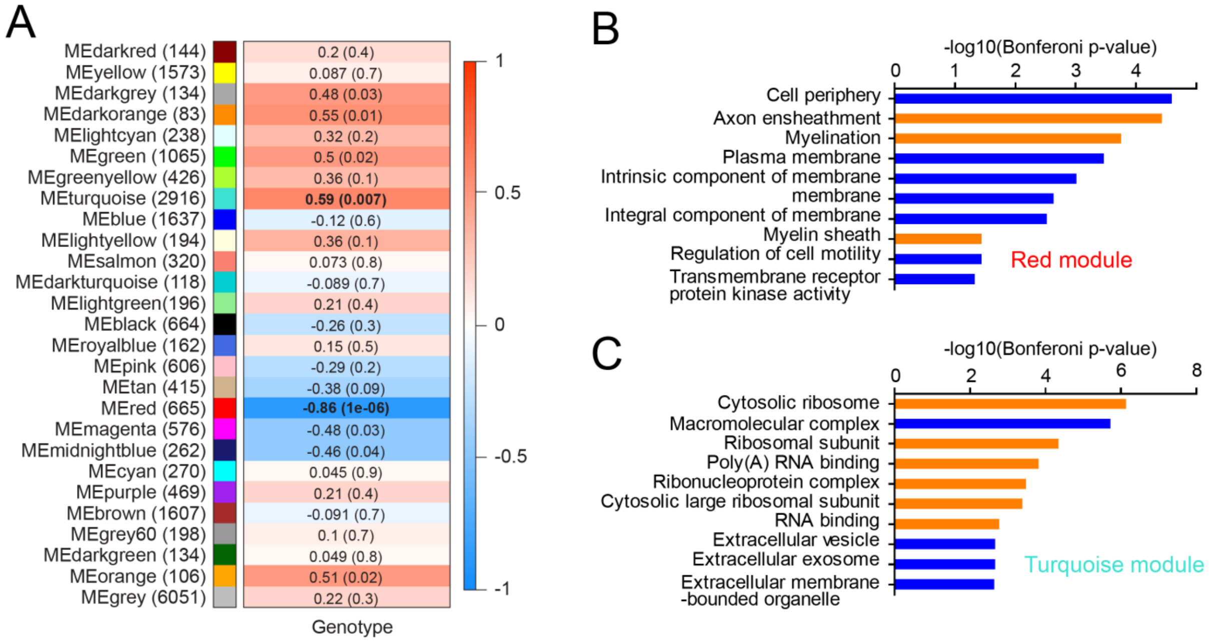
MGI:2676898	Mir23b	13
MGI:2676899	Mir24-1	13
MGI:3618755	Mir24-2	8
MGI:2676903	Mir27b	13
MGI:2676907	Mir30a	1
MGI:3619352	Mir338	11
MGI:3619363	Mir34a	4
MGI:105976	Myo5a	9
MGI:97323	Ngfr	11
MGI:97380	Ntf3	6
MGI:97385	Ntrk3	7
MGI:1335106	Pikfyve	1
MGI:107172	Ppp3r1	11
MGI:97856	Rara	11
MGI:97857	Rarb	14
MGI:97858	Rarg	15
MGI:97896	Reg2	6
MGI:98214	Rxra	2
MGI:98215	Rxrb	17
MGI:98216	Rxrg	1
MGI:98217	S100b	10
MGI:1920212	Tymp	15
MGI:103569	Xk	X
MGI:1289293	Zkscan6	11
MGI:1330262	Zpr1	9

Supplementary figure 1



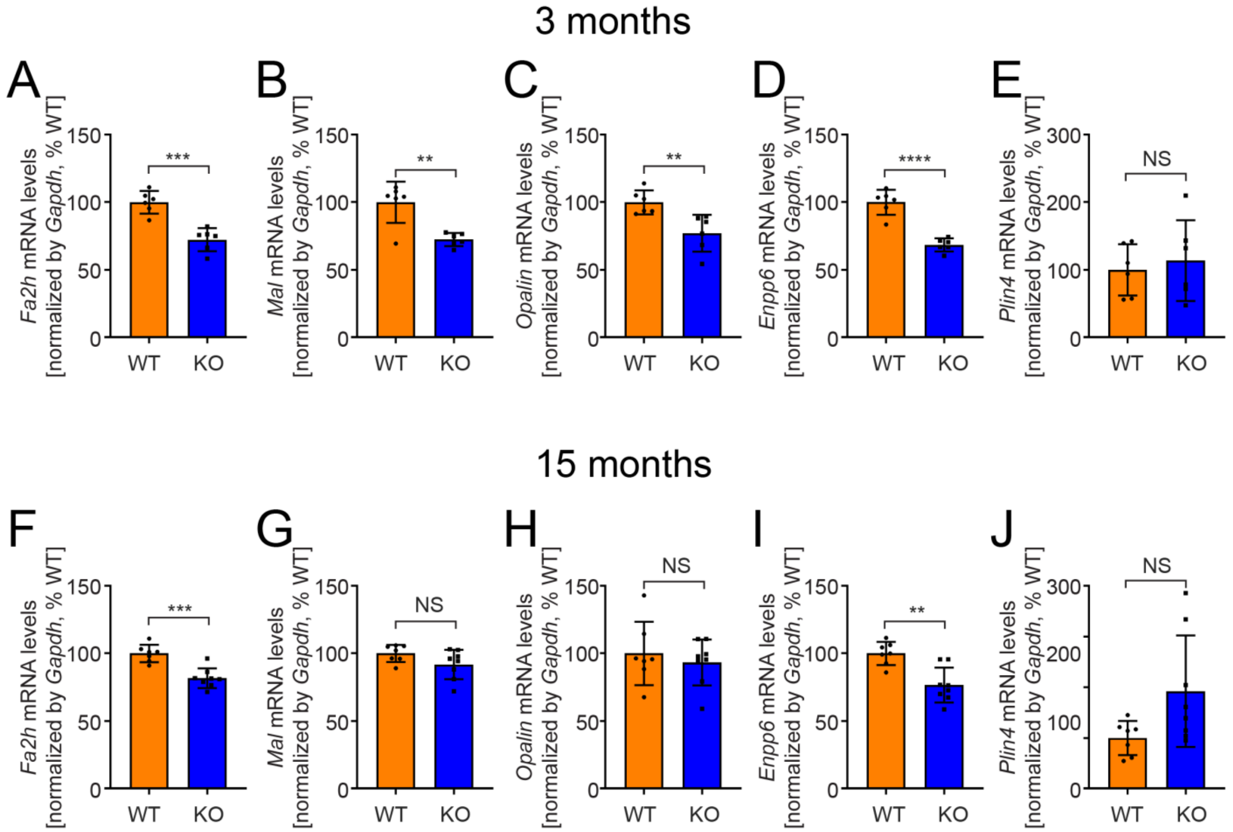
Supplementary Figure 1. DEGs in *Tmem106b-/-* mice overlap with myelination-related genes. (**A**) Venn diagram shows the overlap of DEGs of *Tmem106b-/- (*KO) vs *Tmem106b+/-* (Het), DEGs of *Tmem106b-/-* (KO) vs *Tmem106b+/+* (WT), and oligodendrocyte enriched and myelination-related genes (for detailed gene list, see Supplementary Table 3). (**B**) Hierarchical clustering of 37 overlapping genes between DEGs of KO vs WT mice and oligodendrocyte-enriched and myelination-related genes. * indicates the only upregulated gene.

Supplementary Figure 2



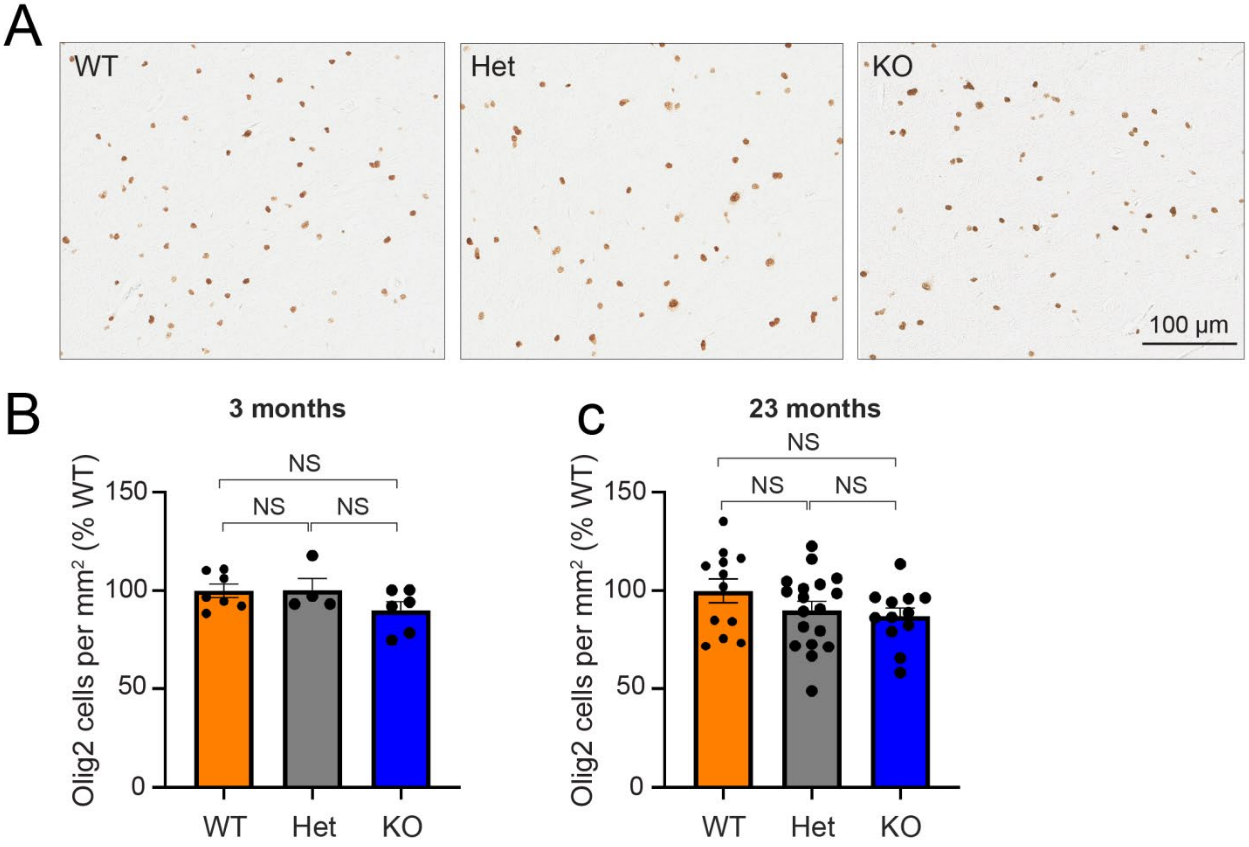
Supplementary Figure 2. Weighted gene co-expression network analysis (WGCNA) confirms myelination deficits in *Tmem106b-/-* mice. (**A**) Module-trait relationships are plotted for *Tmem106b+/+* (WT) and *Tmem106b-/-* (KO) mice. These plots are generated with WGCNA for groups of genes that increase (red) or decrease (blue) together. A unique color has been assigned to each of these groups (modules). Correlations and p-values are shown with respect to the *Tmem106b* genotype (KO vs WT). On the left, the color of the module and the number of member genes in each of the 27 co-expression modules are shown. (**B, C**) Top 10 GO terms of the red (B) and turquoise (C) modules identified in A. Myelination-related (in B) and translation-related (in C) cellular processes are highlighted in yellow.

Supplementary Figure 3



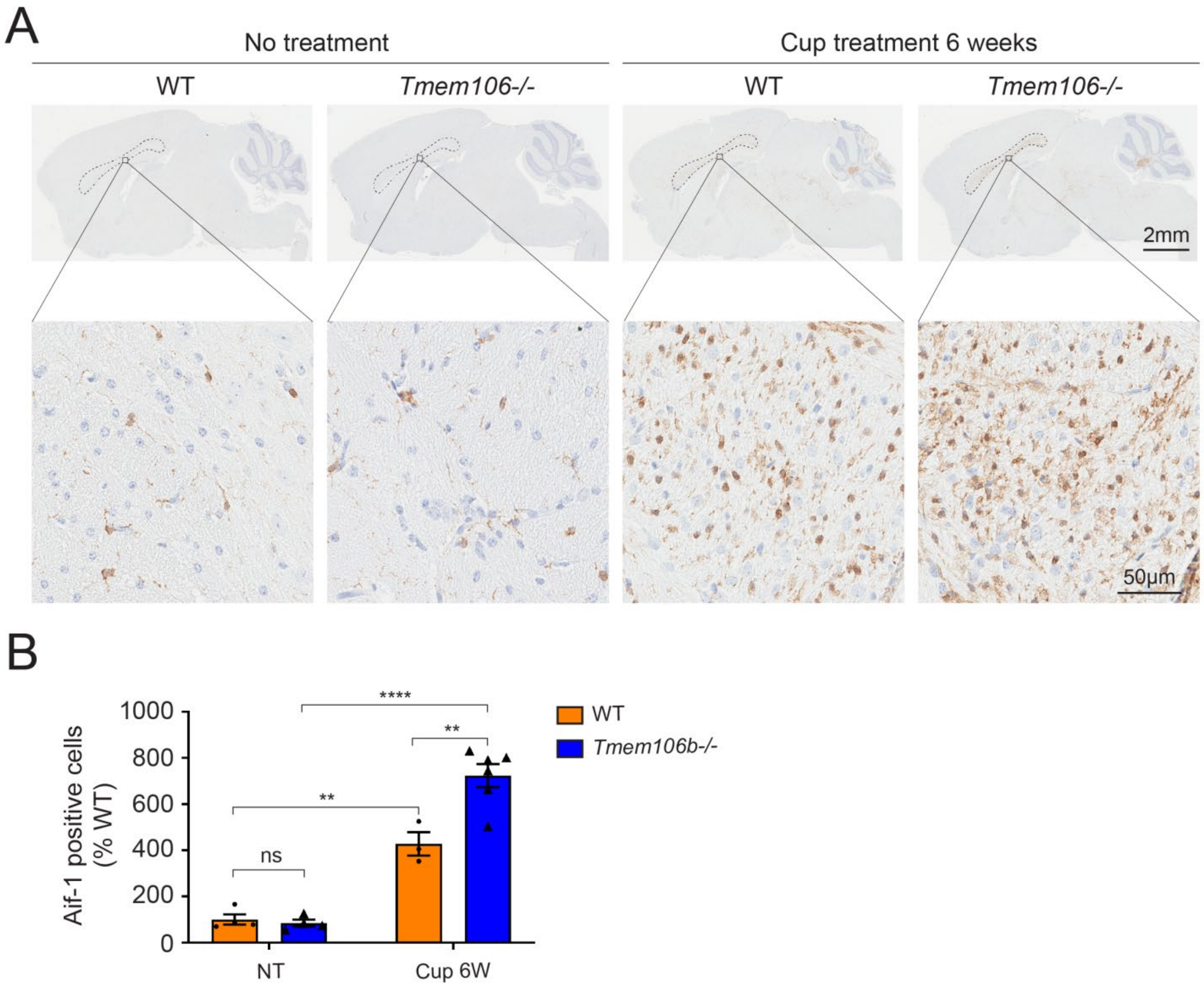
Supplementary Figure 3. q-PCR validation of top down- and up-regulated DEGs identified in WT and *Tmem106b-/-* mice at different ages. (**A-E**) 3-month-old WT and *Tmem106b-/-* brains. (**F-J**) 15-month-old WT and *Tmem106b-/-* brains. Graphs represent the mean ± S.E.M. Data was analyzed by Student's t-test (n = 6-8 per group). NS, not significant, $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, $****p < 0.0001$.

Supplementary Figure 4



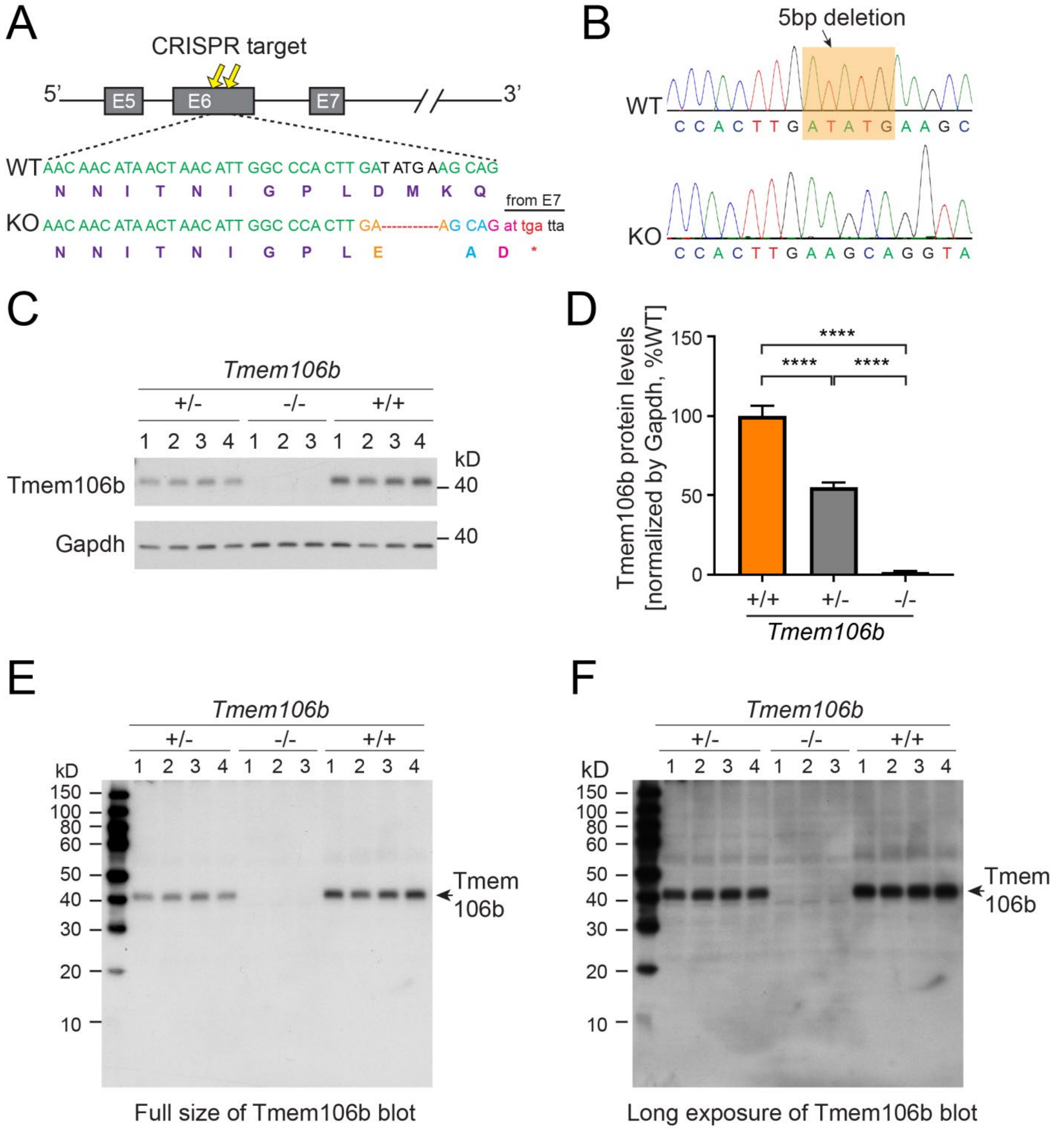
Supplementary Figure 4. Olig2 positive cell counts in the cortex region of *Tmem106b* deficiency mice. (**A**) Representative images of olig2 immunostaining in cortex of 3-month-old *Tmem106b+/+* (WT), *Tmem106b+/-* (Het), and *Tmem106b-/-* (KO) mouse brains. (**B**-**F**) Quantification of olig2 positive cells in the corpus callosum of the WT, Het, and KO mouse brains at indicated ages (n = 4-18 per group). The graph represents the mean ± S.E.M. Data was analyzed by one-way analysis of variance (ANOVA) followed by Bonferroni's multiple comparison test. NS, no significant.

Supplementary Figure 5



Supplementary Figure 5. Loss of Tmem106b increased cuprizone-diet induced microgliosis in corpus callosum. (**A**) Representative images of Aif-1(microglia marker) immunostaining of brains from *Tmem106b+/+* (WT) and *Tmem106b-/-* after normal diet (No treatment) and 6 weeks of cuprizone diet treatment (Cup treatment 6 weeks). The corpus callosum was highlighted in dashed lines. (**B**) Quantification of Aif-1 positive cells in the corpus callosum of the WT and *Tmem106b-/-* mouse brains in A (n = 3-6 per group). The graph represents the mean ± S.E.M. Data was analyzed by Student's t-test. ns, no significant, $**p < 0.01$, $***p < 0.001$.

Supplementary Figure 6

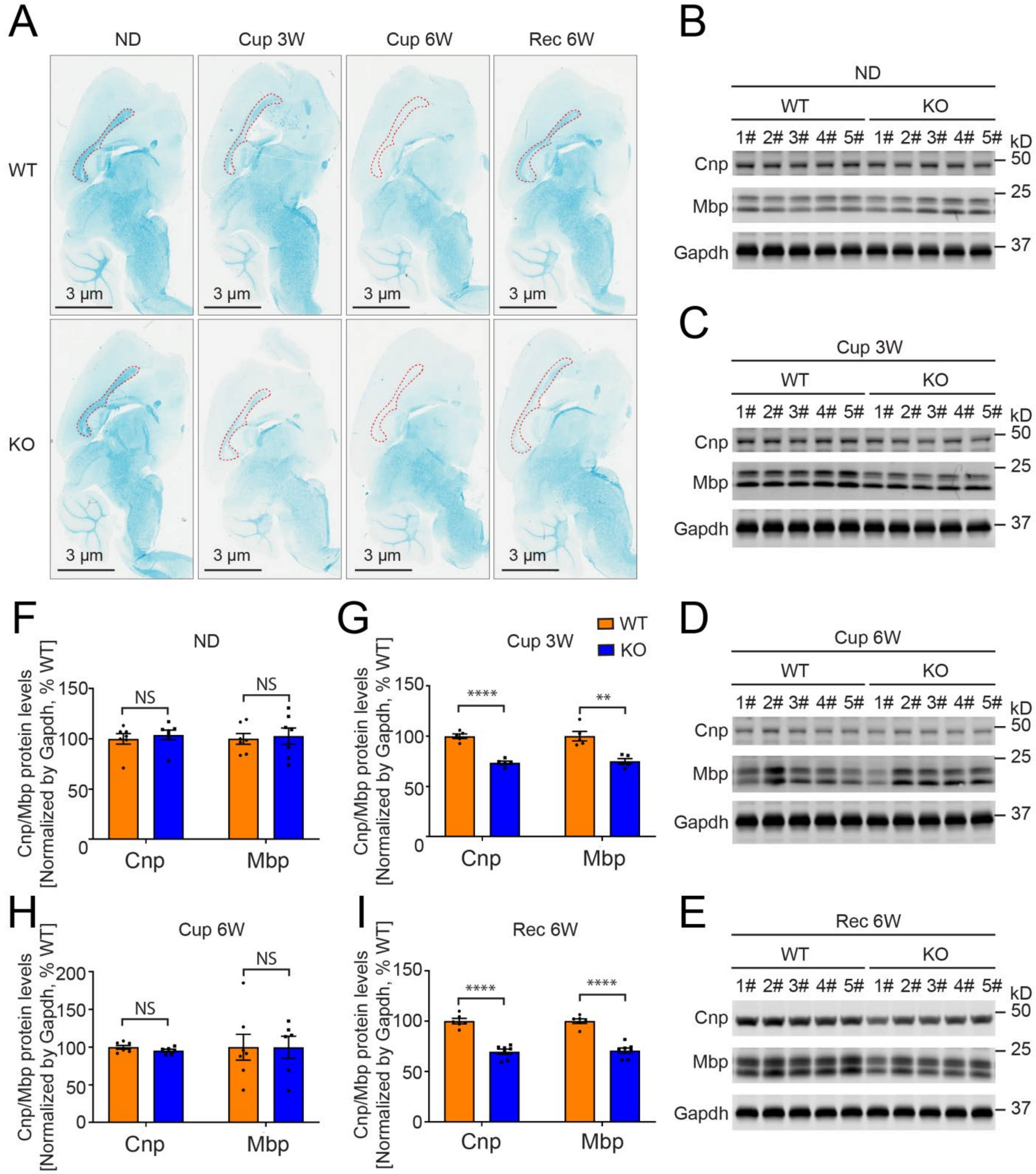


Full size of Tmem106b blot

Long exposure of Tmem106b blot

Supplementary Figure 6. Generation and characterization of Tmem106b CRSIPR knock-out (KO) mice. (**A**) A diagram shows the generation of *Tmem106b* CRISPR KO mice. CRISPR guide RNA targets exon 6 of *Tmem106b* and deletes 5bp (TATGA, highlighted in black color) leading to an immediate stop codon (*). (**B**) Sanger sequencing traces and sequences of WT and *Tmem106b* CRISPR KO (KO). (**C**) Western blot confirms a complete loss of Tmem106b protein in *Tmem106b* CRISPR KO brain tissues. (**D**) Quantification of Tmem106b protein levels in the blots in C. Graph represents the mean ± S.E.M. Data was analyzed by one-way analysis of variance (ANOVA) followed by Bonferroni's multiple comparison test ($n = 3\text{-}4$). ****$p < 0.0001$. (**E, F**) a full blot (E) and a long exposure blot (F) of Tmem106b blot in C.

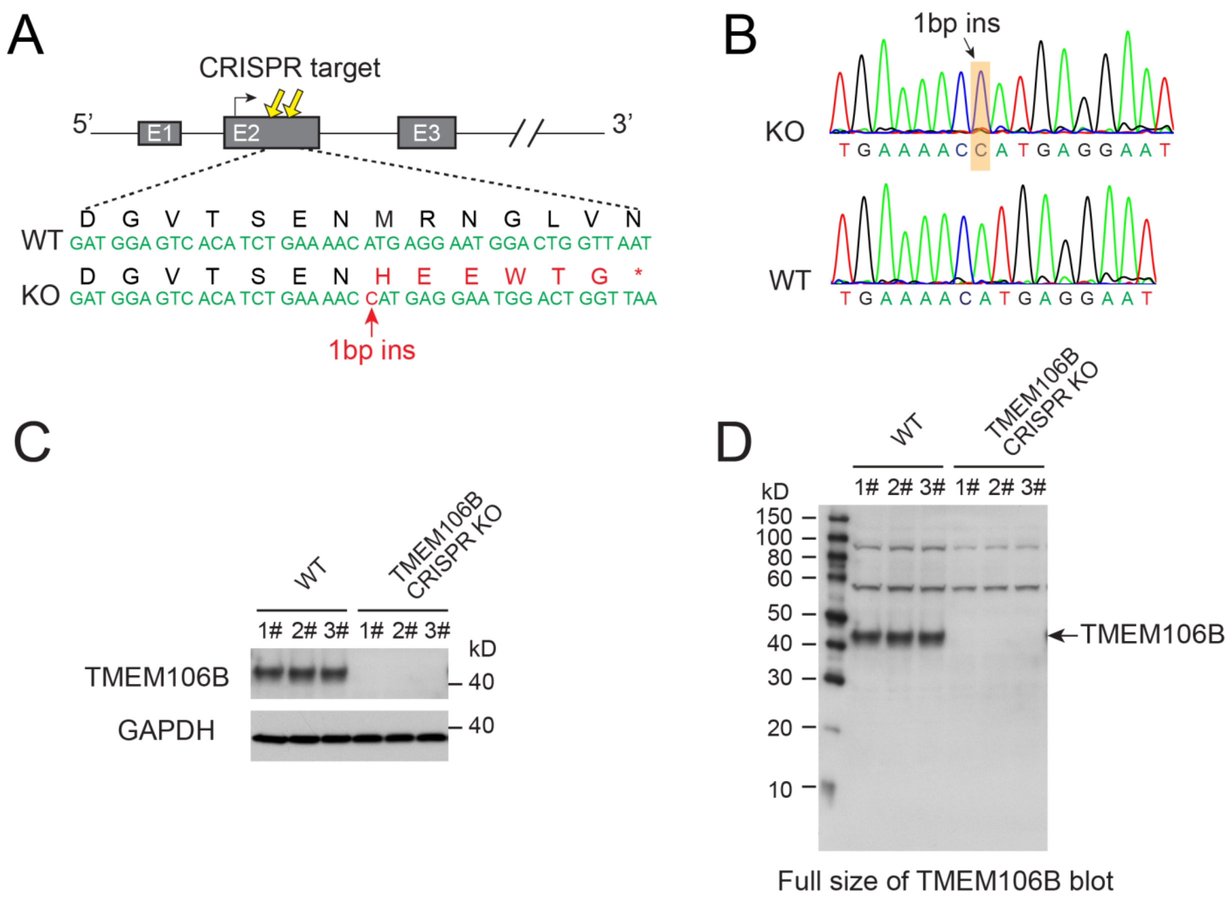
Supplementary Figure 7



Supplementary Figure 7. Increased de-myelination and re-myelination in *Tmem106b* CRISPR KO mice in a cuprizone-induced de- and re-myelination mouse model.

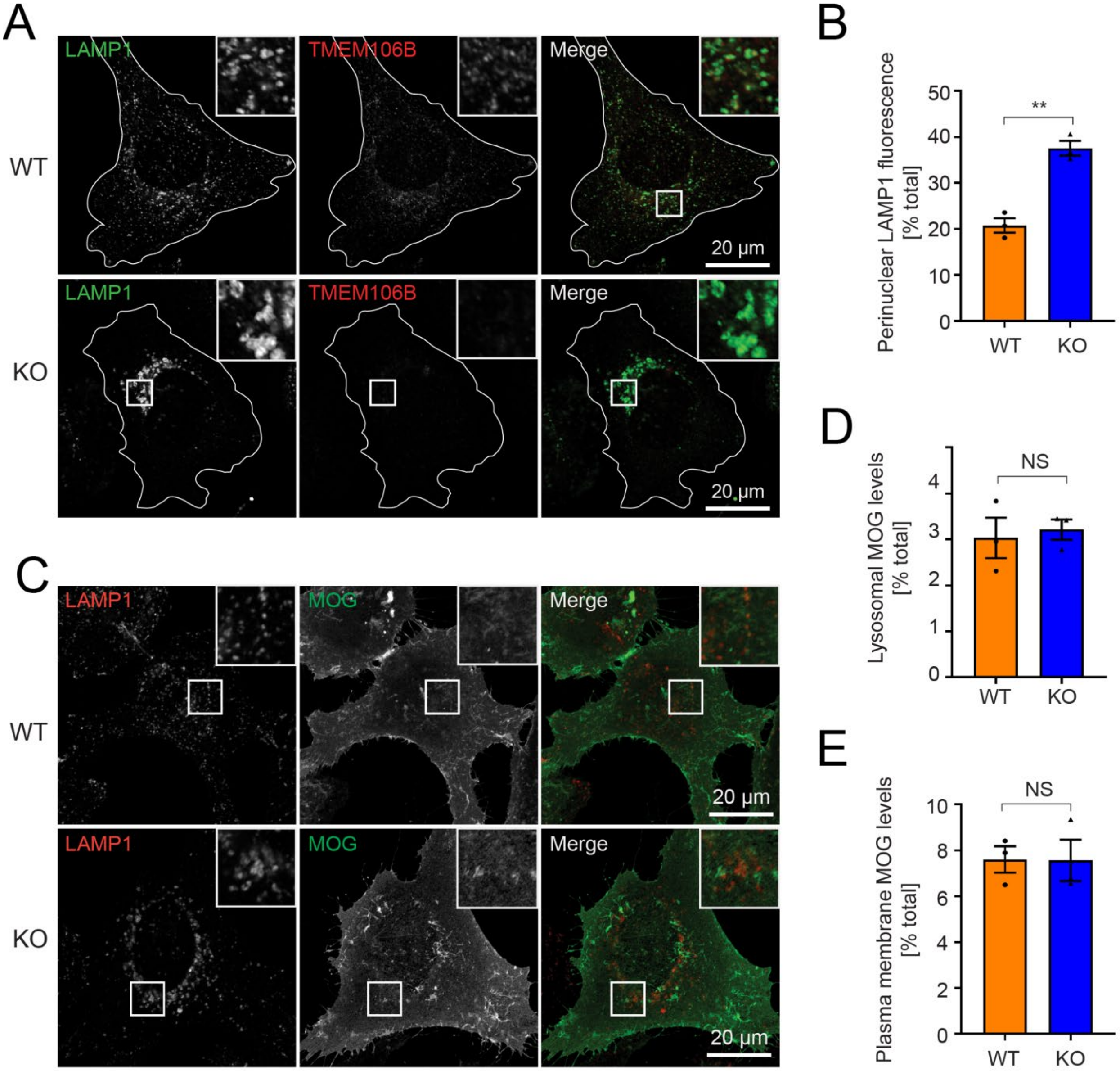
(**A**) Representative images of the Luxol fast blue (LFB) staining of corpus callosum from WT and *Tmem106b* CRISPR KO mice treated with indicated diets: ND, normal diet; Cup 3W, 3 weeks of cuprizone diet, Cup 6W, 6 weeks of cuprizone diet, Rec 6W, 6 weeks of cuprizone diet plus 6 weeks of normal diet. (**B-E**) Western blots show protein levels of Cnp, Mbp, and Gapdh in WT and *Tmem106b* CRISPR KO (KO) mice treated with normal diet (ND, B), 3 weeks of cuprizone diet (Cup 3w, C), 6 weeks of cuprizone diet (Cup 6w, D), and 6 weeks of cuprizone diet plus 6 weeks of normal diet (Rec 6w, E), respectively. Unmodified full-length blots in Supplementary Figure 14. (**F-I**) Quantification of the blots in B-E, respectively. Graphs represent the mean ± S.E.M. Data was analyzed by Student's t-test ($n = 5$-7 per group). NS, not significant, $^{**}p < 0.01$, $^{****}p < 0.0001$.

Supplementary Figure 8



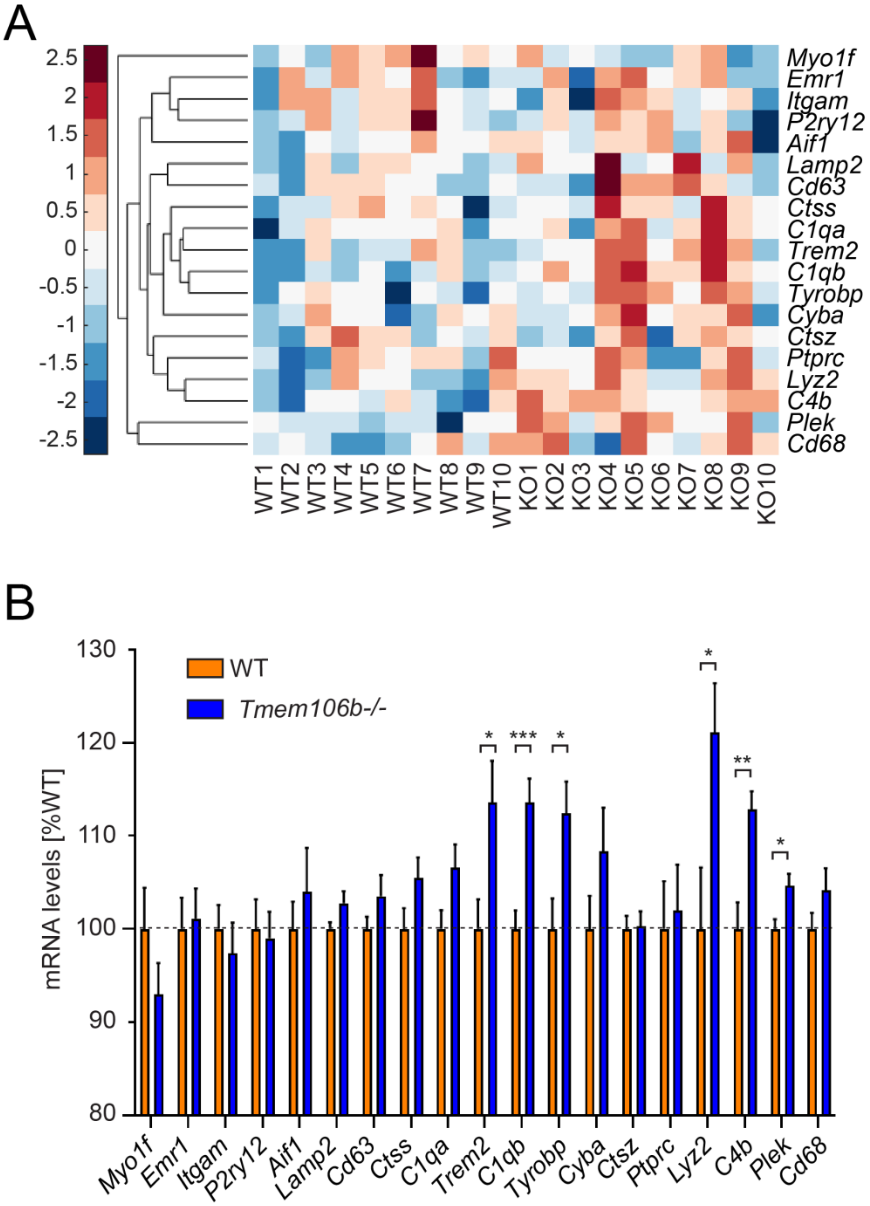
Supplementary Figure 8. Generation and characterization of *TMEM106b* CRISPR knock-out (KO) HeLa cell line. (**A**) Diagram shows the generation of *Tmem106b* CRISPR KO cells. CRISPR guide RNA targets the exon 1 of TMEM106B and inserts 1bp, highlighted in red color) leading to a stop codon (*). (**B**) Sanger sequencing traces and sequences of WT and *TMEM106B* CRISPR KO (KO) cells. (**C**) Western blot confirms a complete loss of TMEM106B protein in *TMEM106B* CRISPR KO HeLa cells. (**D**) Full TMEM106B blot shows no residual TMEM106B fragments in the KO cells.

Supplementary Figure 9



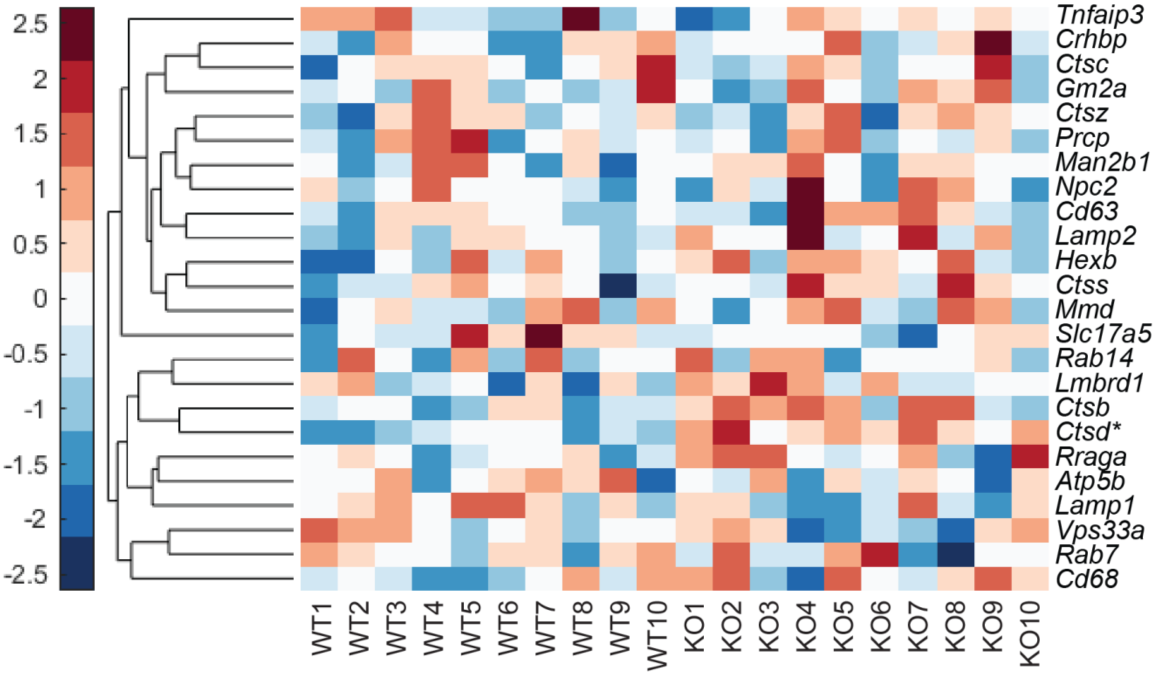
Supplementary Figure 9. No effect of TMEM106B on MOG trafficking. (**A**) Representative immunofluorescence staining images of LAMP1 and TMEM106B from WT HeLa and TMEM106B CRISPR KO (KO) HeLa cells. (**B**) Quantification of perinuclear-distributed LAMP1+ compartments. (**C**) Representative immunofluorescent images of LAMP1 and PLP1 from WT HeLa and TMEM106B CRISPR KO (KO) HeLa cells 24 h after MOG transfection. (**D, E**) Quantification of lysosomal (D) and plasma membrane (E) localized MOG in C. Graphs in B, D, and E represent the mean ± S.E.M. Data was analyzed by Student's t-test. NS, not significant, $^{**}p<0.01$, ($n = 3$).

Supplementary Figure 10



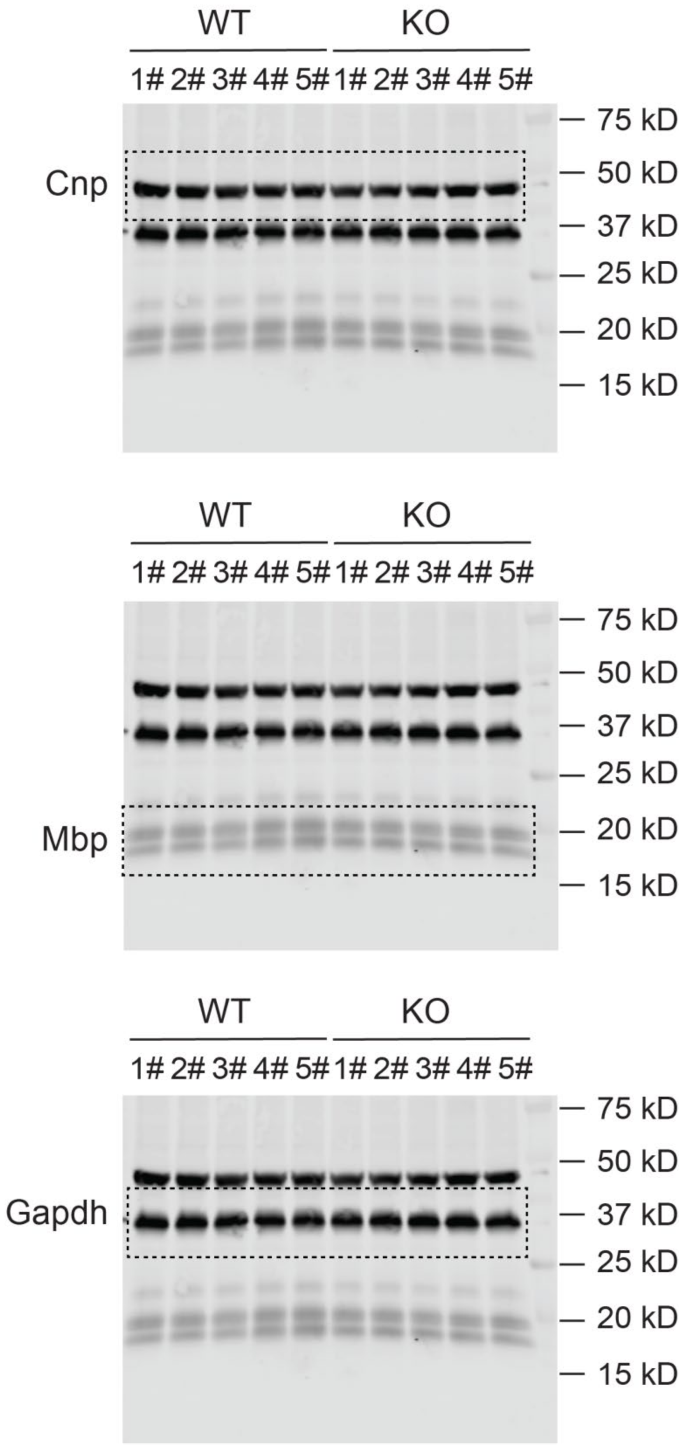
Supplementary Figure 10. Increased expression of *TYROBP* network genes (TNGs) in *Tmem106b-/-* mice. (**A**) Hierarchical clustering of 19 TNGs. (**B**) Expression values of the TNGs in WT and *Tmem106b-/-* mice. Graphs represent the mean ± S.E.M. Asterisks indicate significant differences between WT and *Tmem106b-/-* mice (*unadjusted $p<0.05$, ** unadjusted $p<0.01$, ** unadjusted $p<0.001$) (n =10 per group).

Supplementary Figure 11

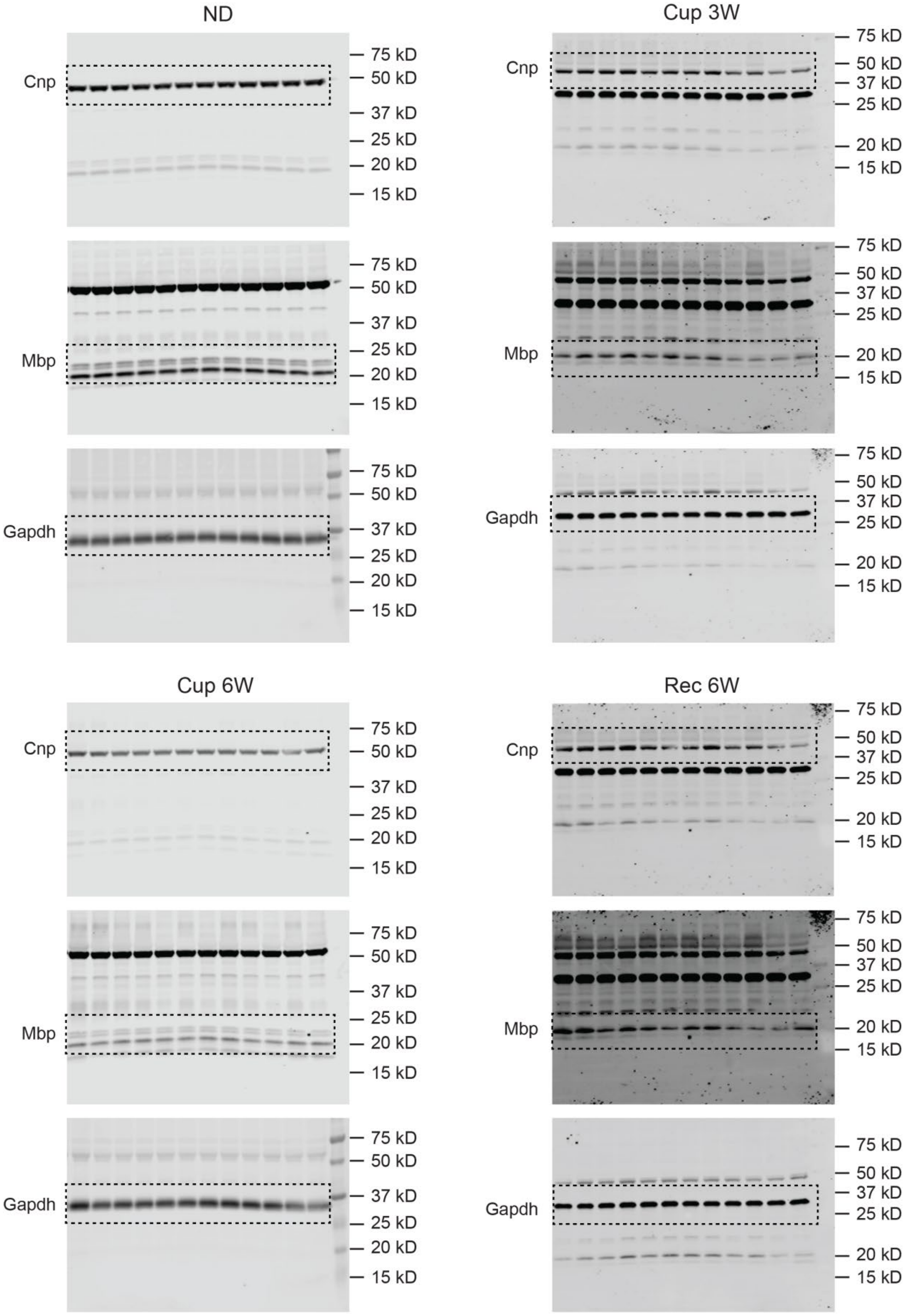


Supplementary Figure 11. Expression of progranulin-deficiency associated lysosomal genes in *Tmem106b-/-* mice. Hierarchical clustering of 24 progranulin-deficiency associated lysosomal genes in *Tmem106b+/+* (WT) and *Tmem106b-/-* (KO) mice. *p<0.05, n=10.

Supplementary Figure 12 unmodified full-length blots in Figure 2 G



Supplementary Figure 13 unmodified full-length blots in Figure 4 A, C, E, G



Supplementary Figure 14 unmodified full-length blots in Supplementary Figure 7 B-E