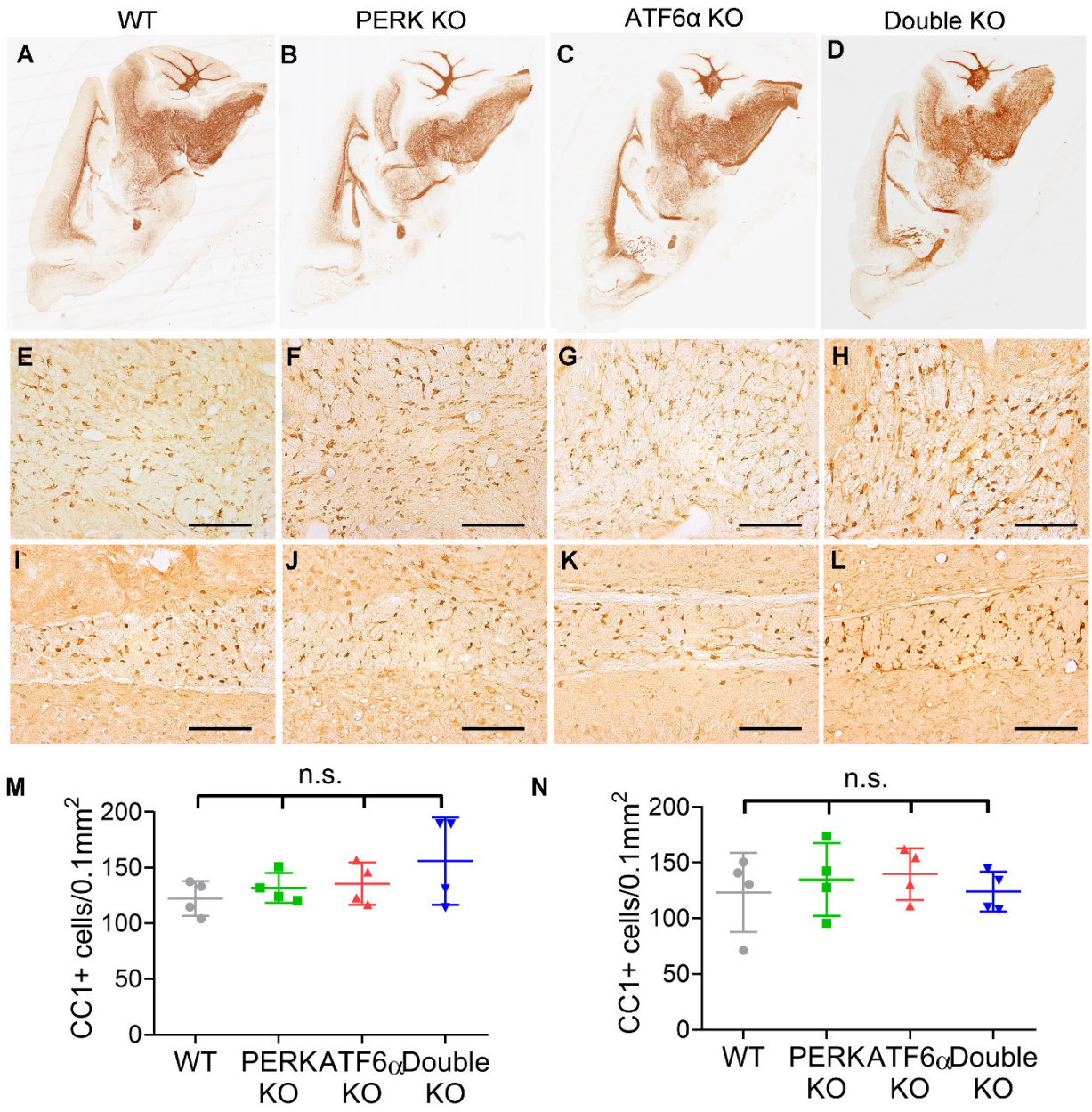
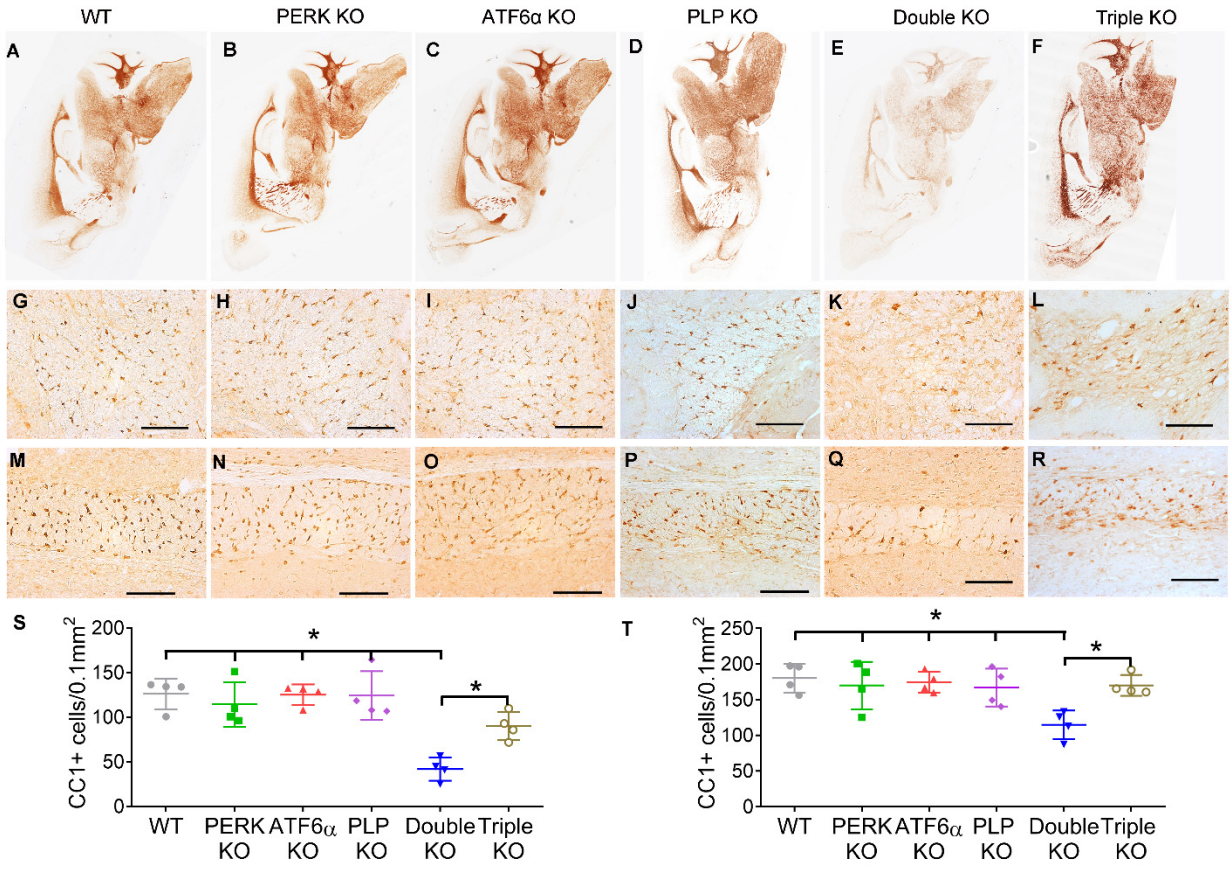
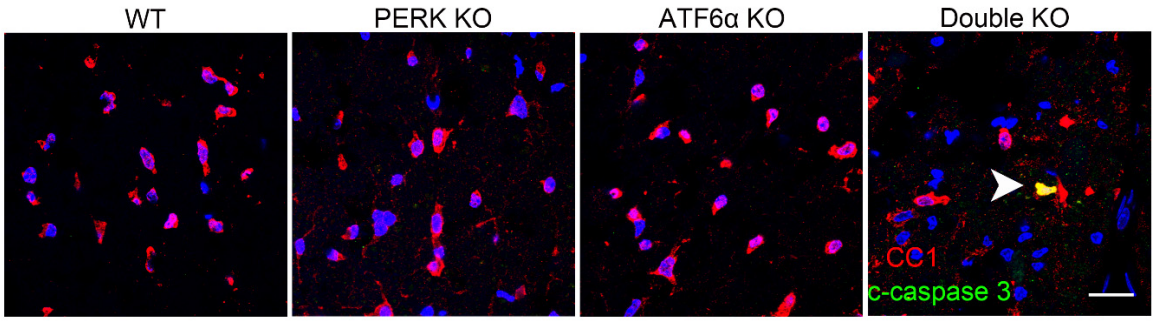


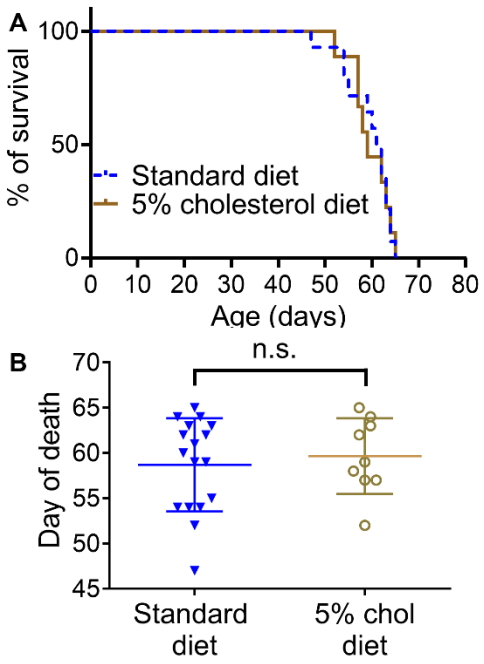
Supplemental Figure 1. Inactivation of PERK and ATF6α in oligodendrocytes did not affect developmental myelination of the CNS. A-D. MBP IHC showed that the degree of myelination in the brain of Double KO mice was comparable to WT mice, PERK-KO mice, and ATF6α-KO mice at P 21. **E-H, M.** CC1 IHC showed that oligodendrocyte numbers in the cerebellum of Double KO mice were comparable to WT mice, PERK-KO mice, and ATF6α-KO mice at P 21. **I-L, N.** CC1 IHC showed that oligodendrocyte numbers in the corpus callosum of Double-KO mice were comparable to WT mice, PERK-KO mice, and ATF6α-KO mice at P 21. Scale bars: 100 μm. N = 4 animals. Error bars represent SD. Statistical analyses were done with a 1-way ANOVA with a Tukey's posttest, n.s. not significant.



Supplemental Figure 2. Inactivation of PERK and ATF6α in oligodendrocytes led to late-onset dysfunction and death of mature oligodendrocytes, and PLP deficiency attenuated mature oligodendrocyte dysfunction and death in Double-KO mice. A-F. MBP IHC reveals severe myelin loss in the brain of Double-KO mice compared to WT mice, PERK-KO mice, ATF6α-KO mice, and PLP-KO mice at P 45. Interestingly, myelin loss was noticeably attenuated in the brain of Triple KO mice compared to Double-KO mice at P 45. **G-L, S.** CC1 IHC showed that the number of oligodendrocytes was significantly reduced in the cerebellum of Double-KO mice compared to WT mice, PERK-KO mice, ATF6α-KO mice, and PLP-KO mice at P 45; however, the soma of oligodendrocytes was markedly enlarged in Double-KO mice. Interestingly, oligodendrocyte loss was significantly attenuated in the cerebellum of Triple-KO mice compared to Double-KO mice at P 45. **M-R, T.** CC1 IHC showed that the number of oligodendrocytes was significantly reduced in the corpus callosum of Double-KO mice compared to WT mice, PERK-KO mice, ATF6α-KO mice, and PLP-KO mice at P 45; however, the soma of oligodendrocytes was markedly enlarged in Double-KO mice. Interestingly, oligodendrocyte loss was significantly attenuated in the corpus callosum of Triple-KO mice compared to Double-KO mice at P 45. Scale bars: 100 μm. N = 4 animals. Error bars represent SD. Statistical analyses were done with a 1-way ANOVA with a Tukeys posttest, $*P < 0.05$.



Supplemental Figure 3. Inactivation of PERK and ATF6α induced mature oligodendrocyte apoptosis in the CNS of Double-KO mice at P 45. CC1 and cleaved-caspase-3 double immunostaining showed that there was no CC1 and cleaved-caspase-3 double positive cells in the spinal cord of WT mice, PERK-KO mice, and ATF6α-KO mice at P 45, but there were a few CC1 and cleaved-caspase-3 double positive cells (arrow) in Double-KO mice.



Supplementary Figure 4. A. high cholesterol diet did not affect the disease progression or lifespan of Double-KO mice. Double-KO mice were fed a 5% cholesterol diet starting between P 0 and P 21. The high cholesterol diet did not alter the onset of the tremoring phenotype, the severity of the tremor, or the life span of Double-KO mice (**A, B**). N = 17 animals fed standard diet, N = 9 animals fed 5% cholesterol diet. Error bars represent SD. Statistical analyses were done with a 2 tailed *t*-test, n.s. not significant.