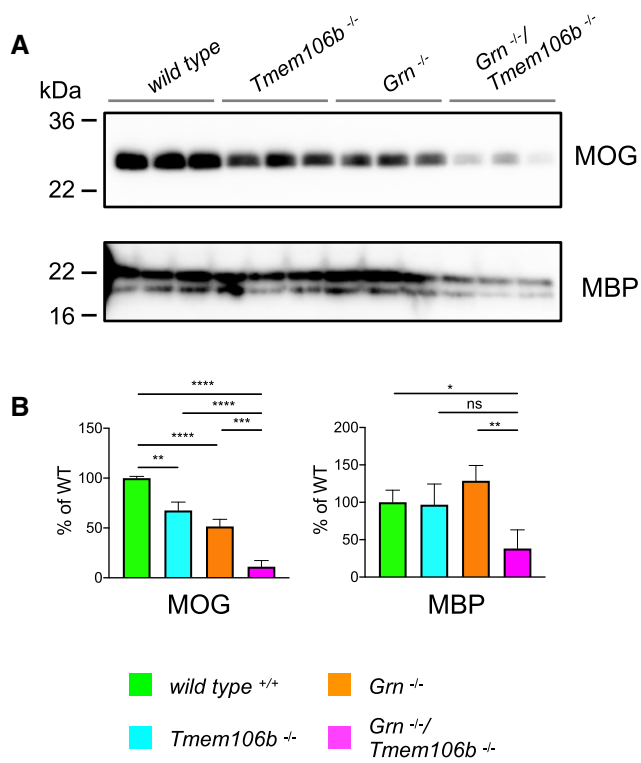


## Expanded View Figures



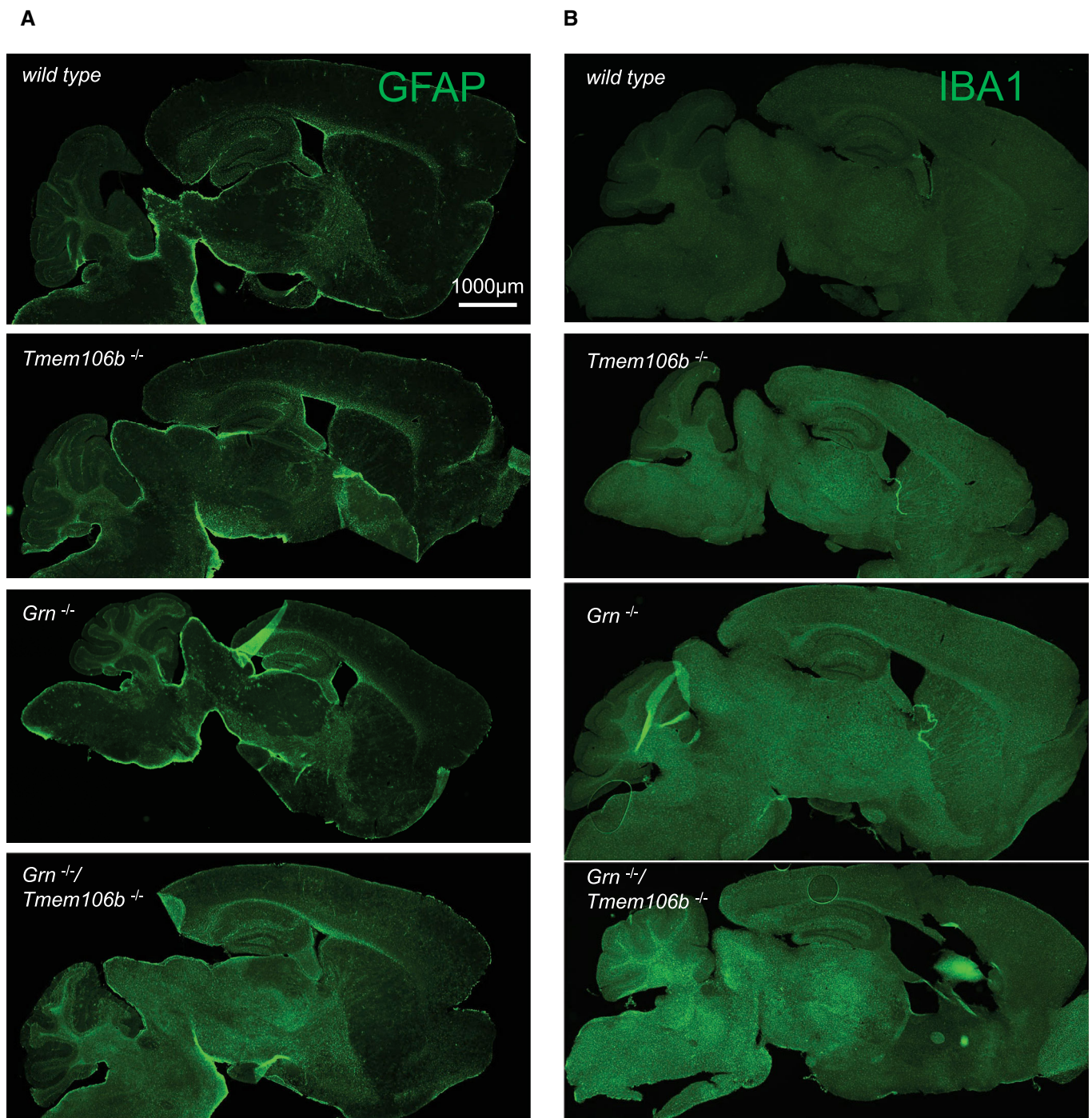
**Figure EV1. Reduced abundance of myelination-related proteins in  $Grn^{-/-}/Tmem106b^{-/-}$  mice.**

A Western blot analysis of the myelin basic protein (MBP) and the myelin oligodendrocyte glycoprotein (MOG) in RIPA total brain lysates from 4.5-month-old mice with the indicated genotype ( $n = 3$  biological replicates per genotype).

B Quantification of (A). Protein expression was normalized to levels in wild-type animals. Data represent the mean  $\pm$  SD.

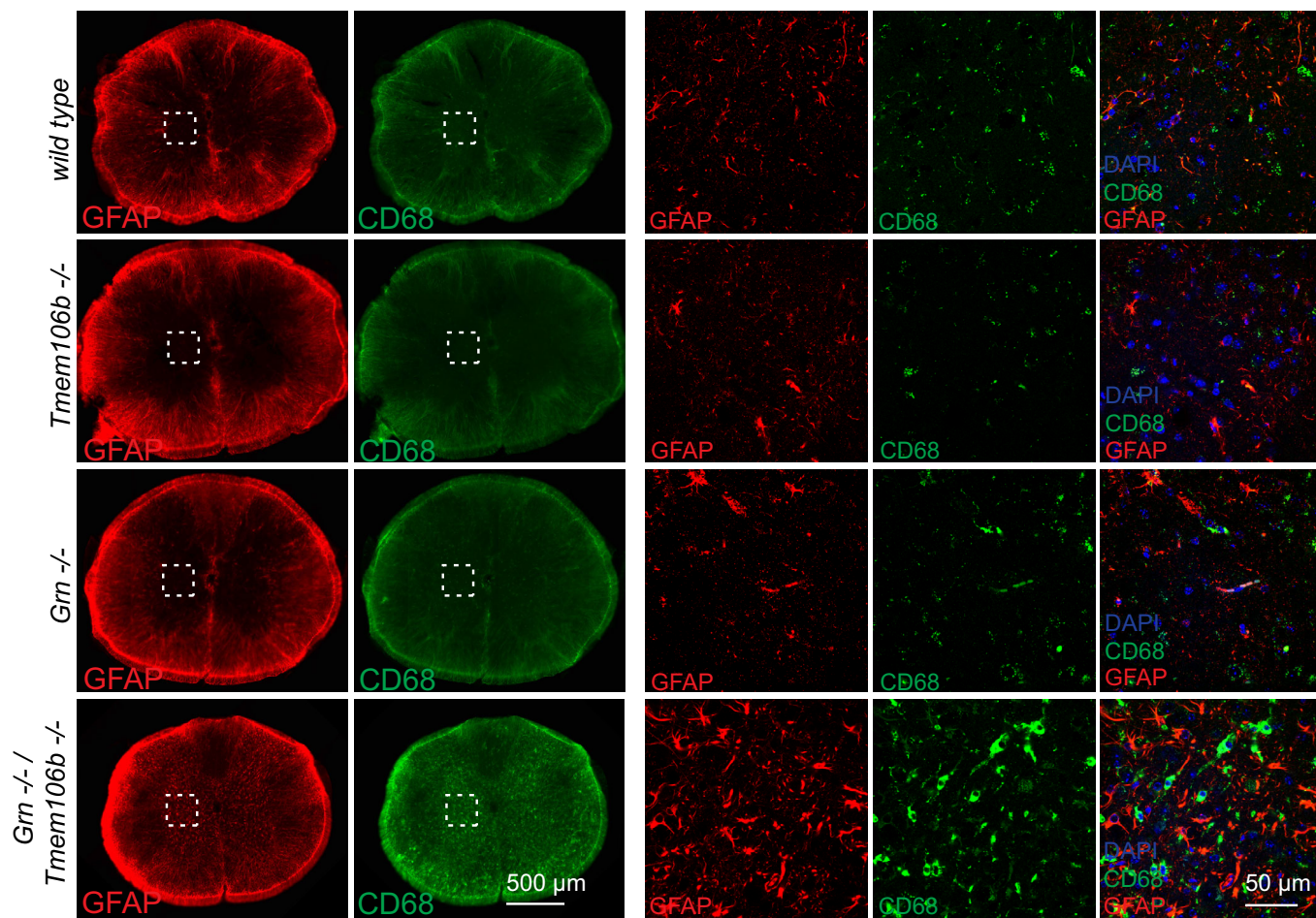
Data information: For statistical analysis of normalized data, one-way ANOVA with Tukey's *post hoc* test was used to compare individual genotypes. Significance is indicated; \* $P < 0.05$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$ ; and \*\*\*\* $P < 0.0001$ .

Source data are available online for this figure.



**Figure EV2. Increased gliosis in sagittal brain sections of *Grn*<sup>-/-</sup>/*Tmem106b*<sup>-/-</sup> mice.**

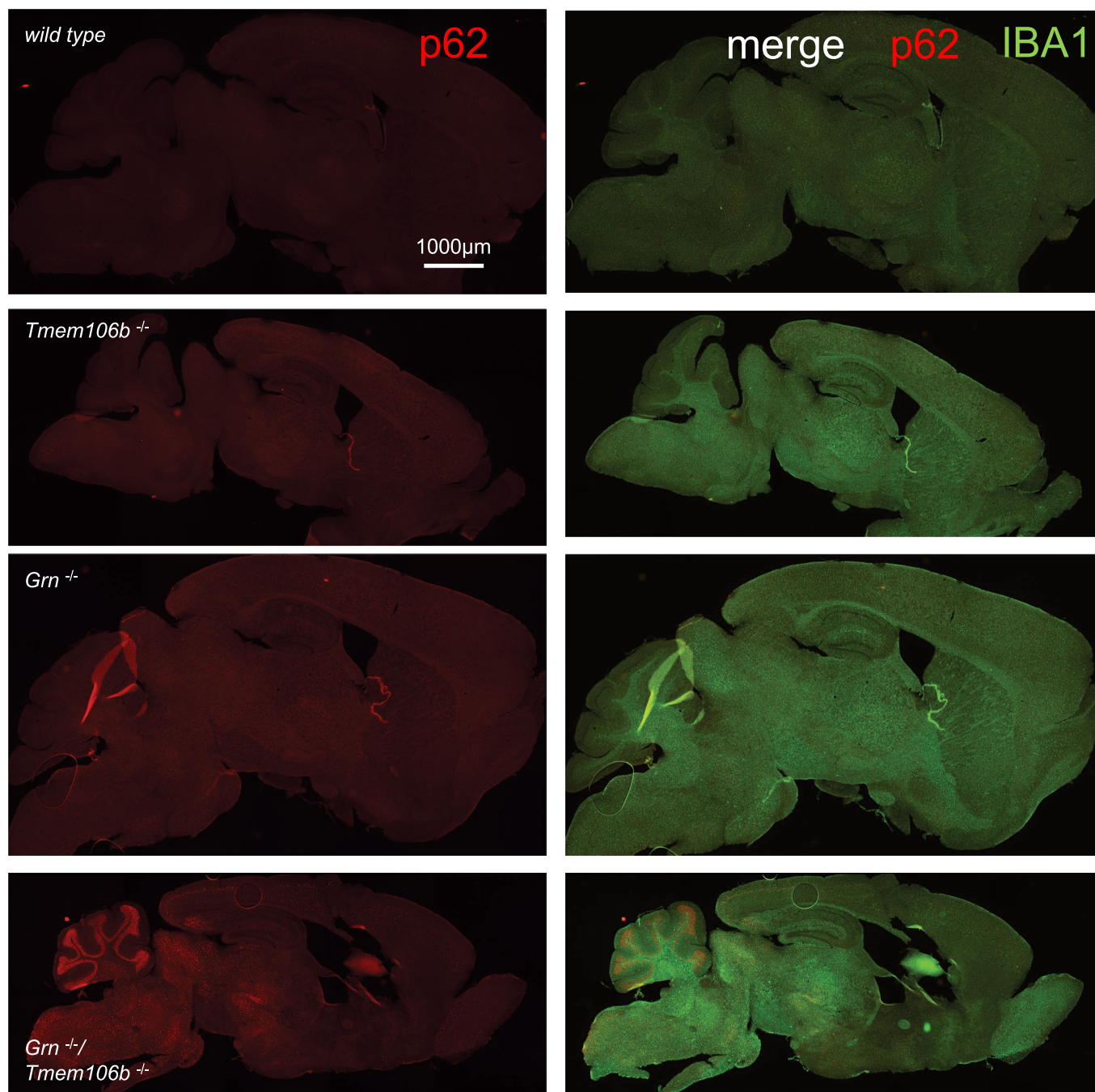
A, B Gliosis analyzed by immunofluorescence staining of GFAP (A) and IBA1 (B) in sagittal brain sections. Whole brain section of 4.5-month-old mice, all genotypes acquired by same acquisition conditions. Scale bar indicates 1,000  $\mu$ m.



**Figure EV3.** Increased gliosis in the spinal cord of *Grn*<sup>-/-</sup>/*Tmem106b*<sup>-/-</sup> mice.

Astrogliosis and microgliosis in spinal cord sections analyzed by immunofluorescence staining of GFAP and CD68. Scale bar indicates 500 µm in overview and 50 µm in insert.





**Figure EV4. Overview of brain regions with p62-positive aggregates.**

Immunofluorescence staining of p62 in sagittal brain sections. Merge of p62 and IBA1 staining from EV2. Whole brain section of 4.5-month-old mice, all images acquired by identical acquisition conditions. Scale bar indicates 1,000  $\mu\text{m}$ .

**Figure EV5. Enhanced TDP-43 aggregation in different brain regions of  $Grn^{-/-}/Tmem106b^{-/-}$  mice.**

Immunofluorescence analysis of TDP-43 in sagittal brain sections of 4.5-month-old mice. Representative images of indicated brain regions (CBX, cerebellum; CTX, cortex; MB, midbrain; MY, medulla; TH, thalamus). White arrow heads indicate TDP-43 aggregates. Scale bar indicates 100  $\mu\text{m}$ . Zoom in on TDP-43 aggregates in double knockout mouse brain sections of the midbrain, scale bar zoom in indicates 50  $\mu\text{m}$ .

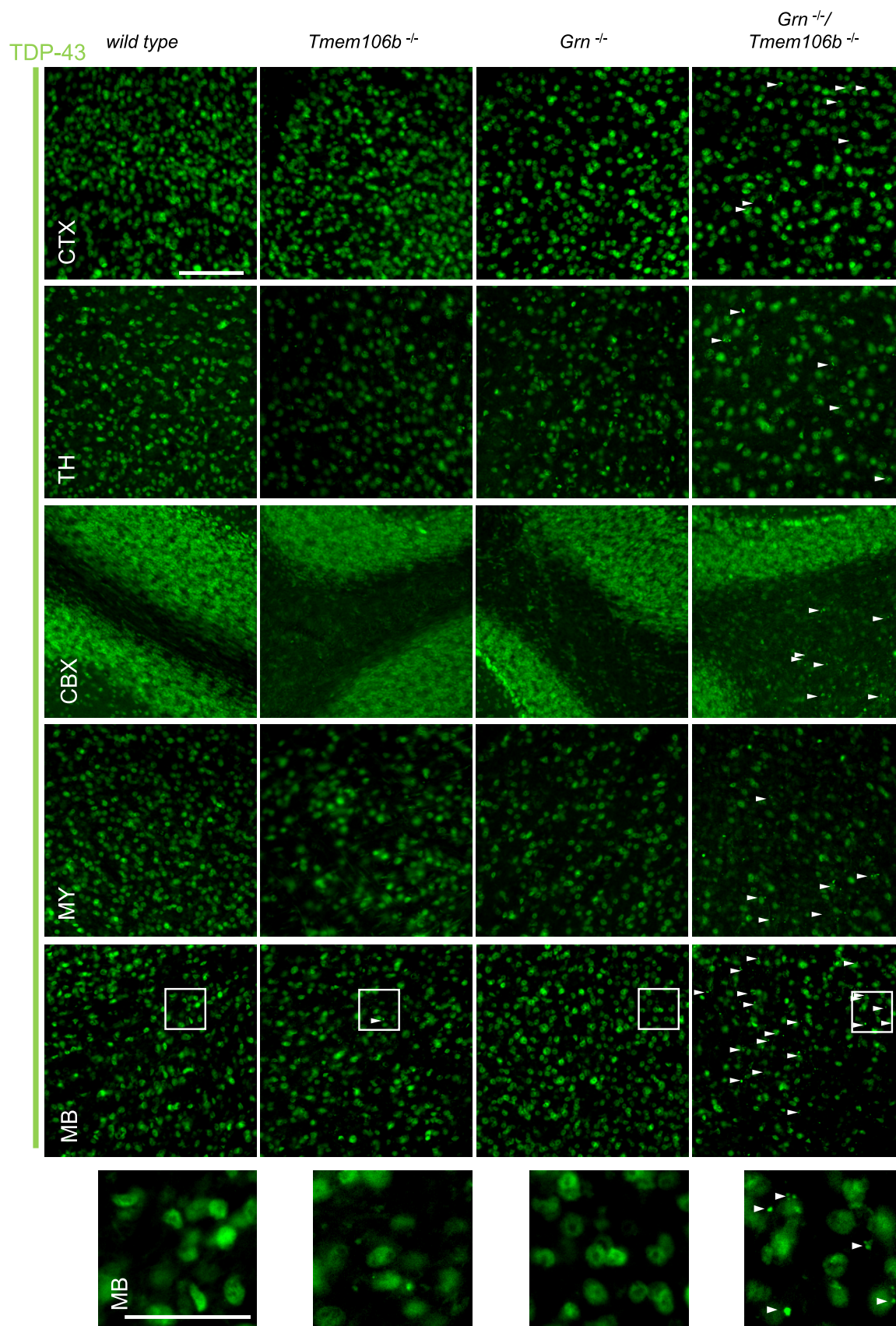


Figure EV5.