Expanded View Figures

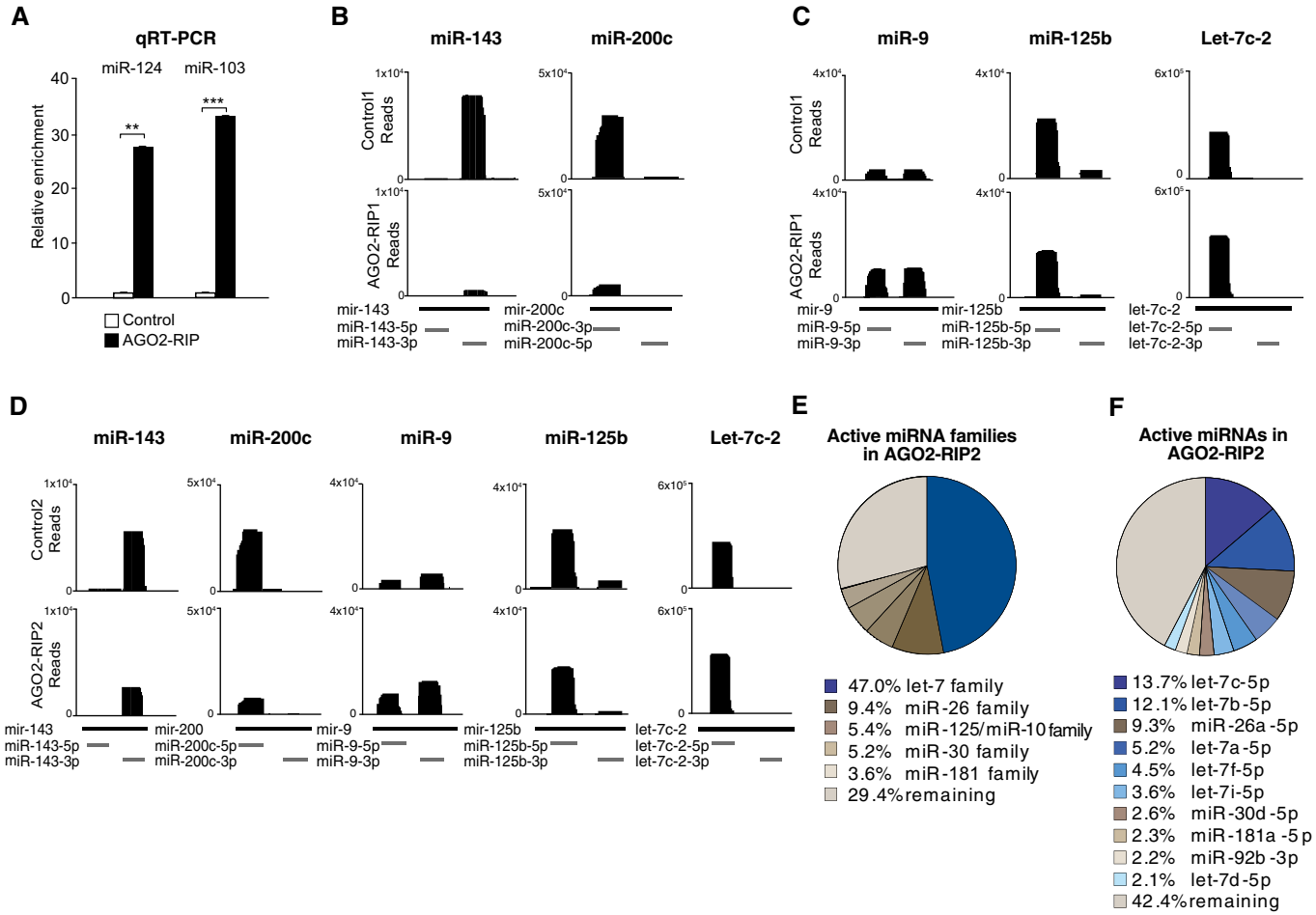

Figure EV1. Validation of RIP-seq on new-born neurons of the OB.

A qRT–PCR analysis showed that miRNAs are enriched in GFP-AGO2 RIP samples compared to sham-injected control samples; $n = 4$.

B Reads mapping to glia-enriched miR-143 and miR-200c in control (upper panel) and GFP-AGO2 RIP samples (lower panel).

C Reads mapping to miR-9, miR-125b, and let-7c in control (upper panel)- and LV.GFP-AGO2-injected mice (lower panel).

D Reads mapping to miR-143, miR-200c, miR-9, miR-125b, let-7c in an independent replicate of the GFP-AGO2 RIP.

E Pie chart of active miRNA families in new-born neurons in the AGO2-RIP2 from an independent replicate. Percentage of reads mapping to miRNA families are shown for the five most abundant miRNA families.

F Pie chart of active individual miRNAs in new-born neurons in the AGO2-RIP2 from an independent replicate. Percentage of reads mapping to miRNAs are shown for the ten most abundant miRNAs.

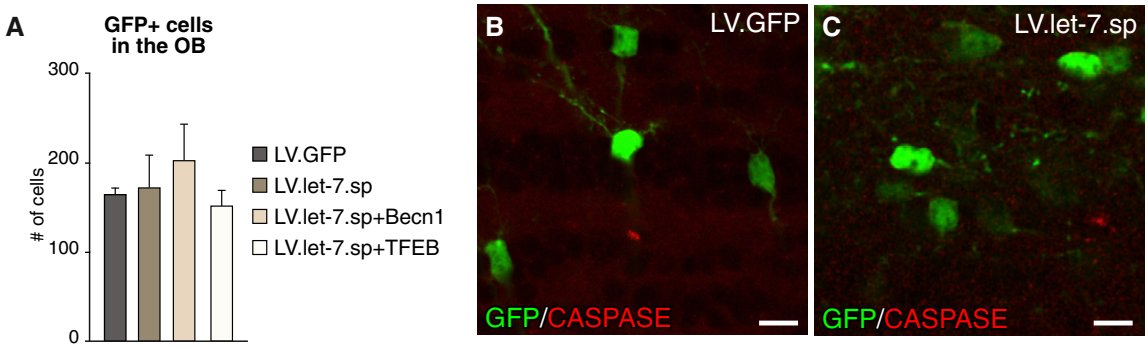

Figure EV2. Quantification of GFP-positive cells in the OB and caspase-3 staining.

A Total numbers of GFP-positive new-born neurons in the OB of LV.let-7.sp (n = 4 animals)-, LV.GFP (n = 4 animals)-, LV.let-7.sp + LV.Becn1 (n = 3 animals)-, and LV.let-7.sp + LV.TFEB (n = 3 animals)-injected brains. Data are presented as mean ± SEM.

B, C Caspase-3 staining on LV.let-7.sp- and LV.GFP-injected brains showed no differences between the two conditions. Scale bars: 10 μm.

Figure EV3. let-7 positively regulates autophagy by targeting autophagy-related genes.

A Previously identified let-7 targets in the amino acid-sensing pathway are marked with a star. Graphic is adapted from Dubinsky *et al* (2014).

B Genes in the amino acid-sensing pathway are expressed in the OB shown by qRT–PCR (n = 3).

C LC3 staining was conducted to identify and validate autophagic structures in the OB using electron microscopy. Gold particles are indicated with white arrows. Scale bars: 200 nm.

D Pictures for the quantification of autophagic structures were taken in close vicinity to the nuclei of GFP-positive cells. Nuclei are indicated with a star. Scale bars: 5 μm.

E Electron microscopy picture showing gold particles in the nucleus of a let-7.sp-expressing new-born neuron in the OB. Gold particles are highlighted with white arrows. Scale bar: 200 nm.

F Electron microscopy analysis and quantifications showed a decrease in the number of autophagosomes (APs) and late autophagic vesicles (AVs) in LV.let-7.sp-injected animals [n = 210 (two animals)] compared to LV.GFP control animals [n = 132 (three animals)].

Data information: Data are presented as mean ± SEM; unpaired, two-tailed t-test, ***$P < 0.001$.

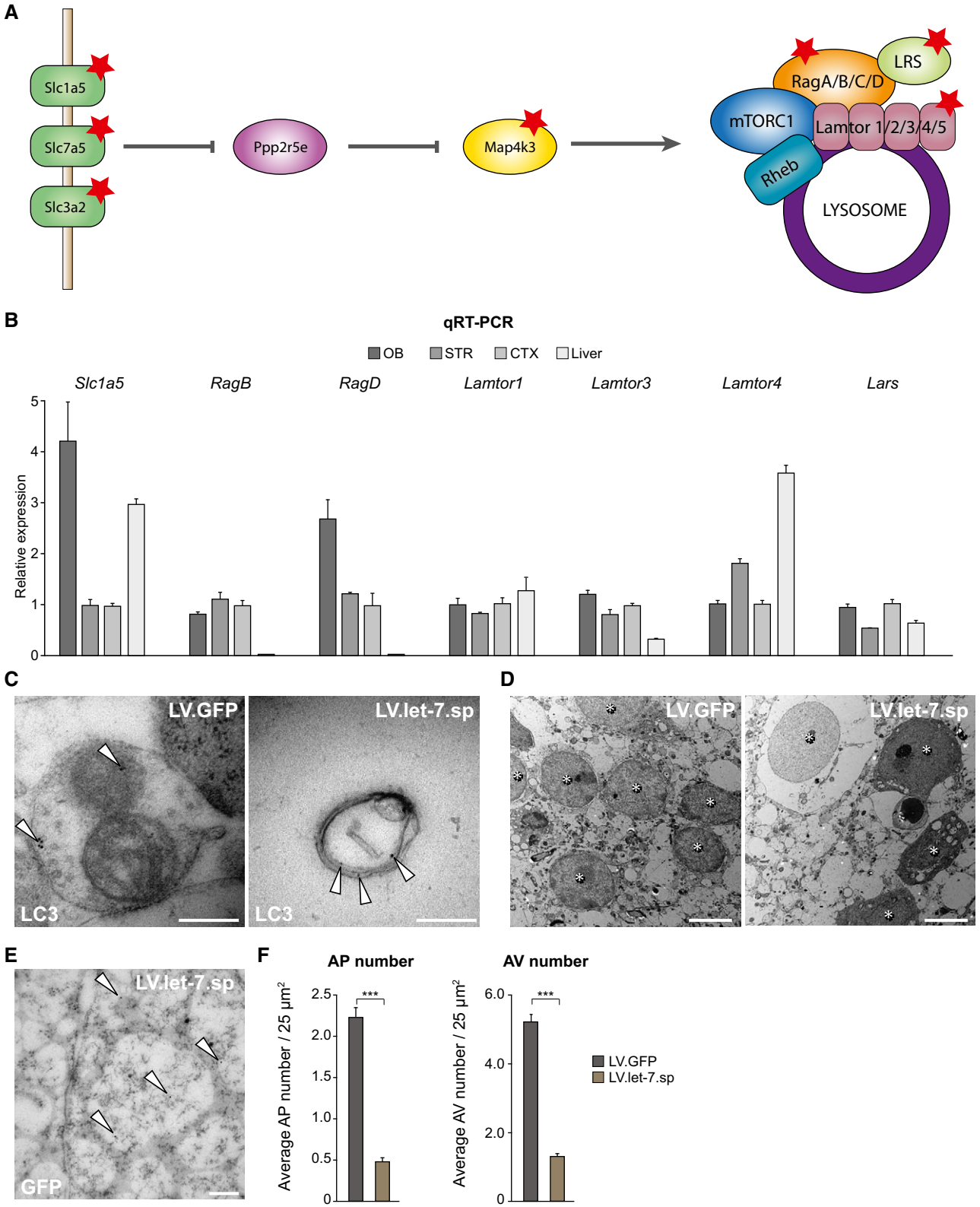

Figure EV3.

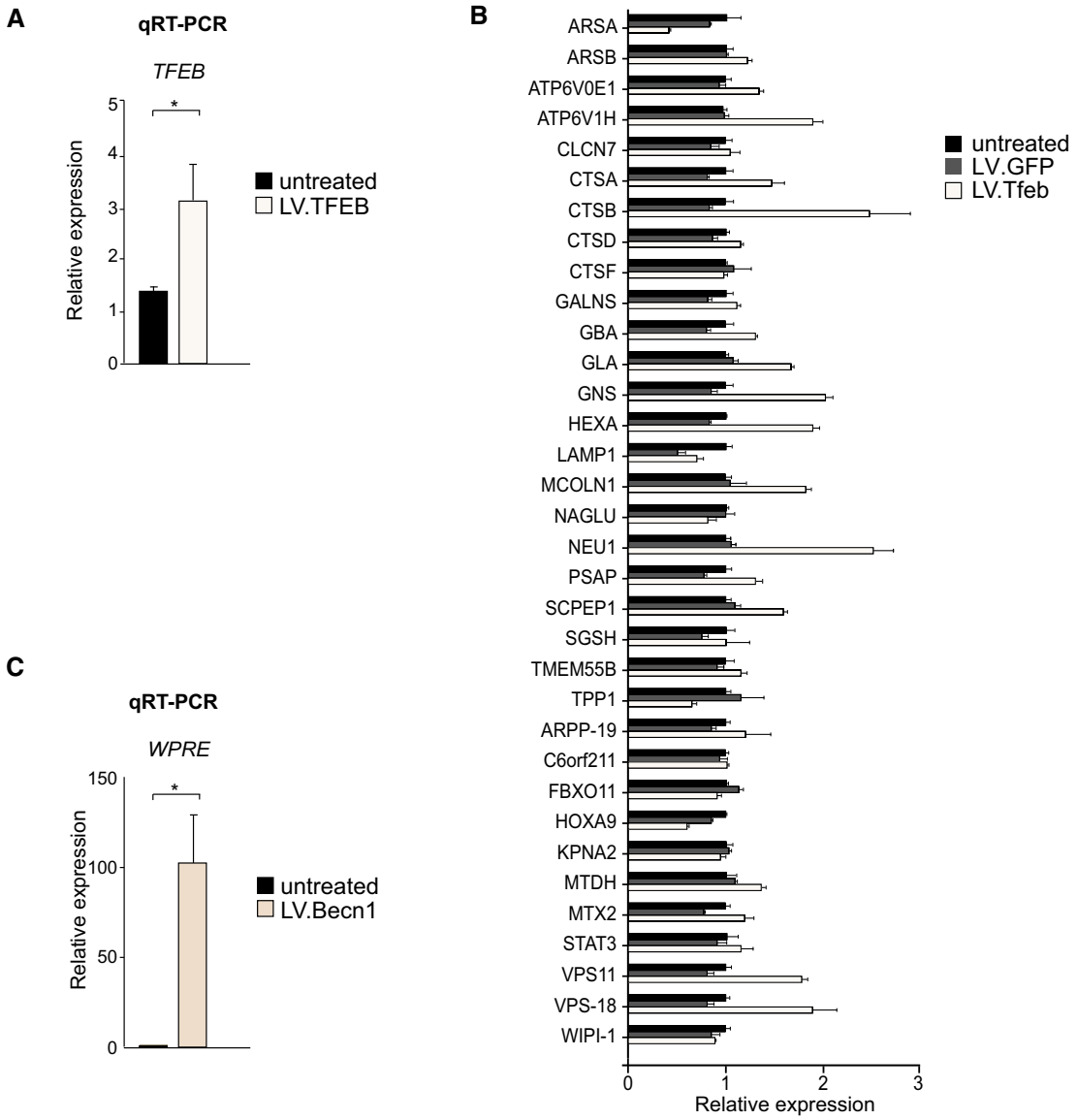

Figure EV4. Validation of LV.TFEB- and LV.Becn1-overexpressing constructs.

A Levels of *TFEB* in mouse neural progenitor cells upon LV.TFEB transduction shown by qRT–PCR; $n = 2$.

B Levels of lysosome- and autophagy-related genes upon LV.TFEB transduction of 293T cells shown by qRT–PCR; $n = 3$.

C Levels of WPRE sequence upon LV.Becn1 transduction of mouse neural progenitor cells shown by qRT–PCR; $n = 2$.

Data information: Data are presented as mean ± SEM; unpaired, two-tailed *t*-test, $*P < 0.05$.