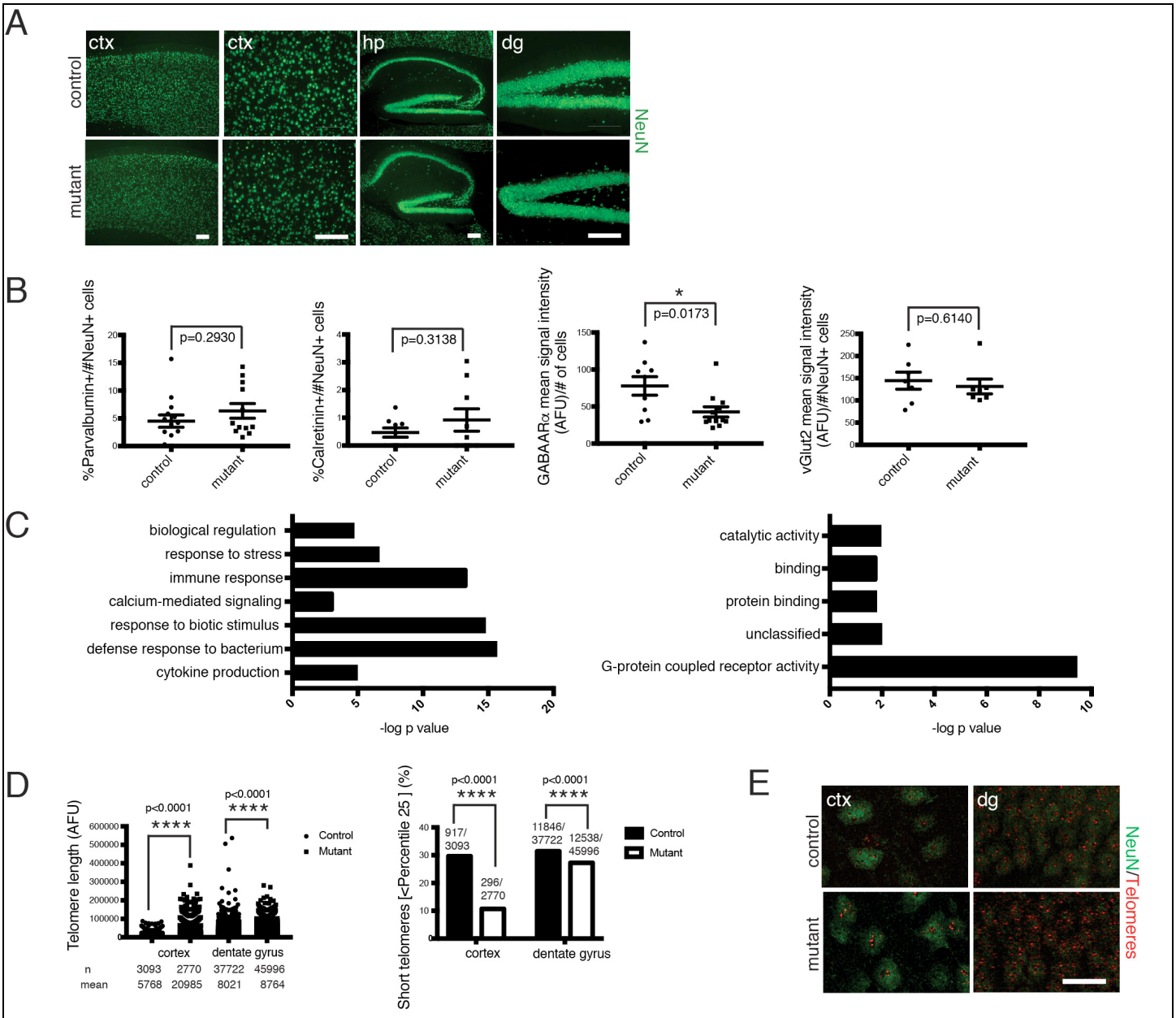
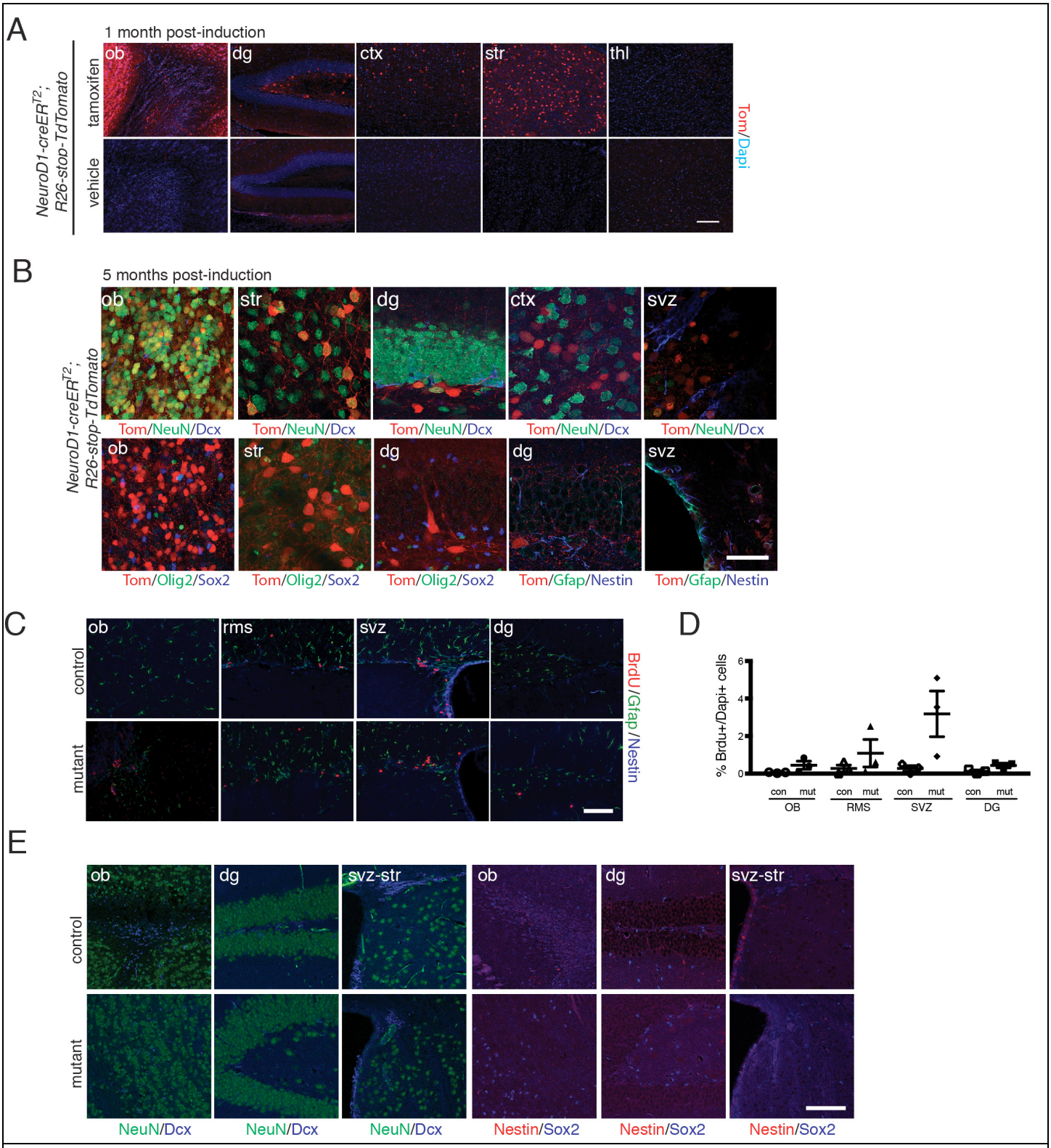


Supplementary Figure 1

Histologic and molecular analysis of *iCK-cre* mutants.

A. Immunoflourescence staining for NeuN in different brain regions. **B.** Quantification of indicated neuronal lineage markers in *iCK-cre* mutant (M) vs. control (C) brains. (Left-most panel) Parvalbumin, n=12M,14C, p=0.2930; (Middle-left panel) Calretinin, n=9M,9C, p=0.3138; (Middle-right panel) GABAARα, n=12M,9C, p=0.0173; (Right-most panel) vGlut2, n=7M,7C, p=0.6140. *p<0.05. Two-tailed unpaired Student's *t*-test. Data is presented as mean +/- SEM. **C.** Gene ontology analysis of gene events (n=239 unique genes; listed in Table S1) in *iCK-cre* mutants (n=3) compared to controls (n=3) by PANTHER, showing functional annotations by biologic process (left panel) and molecular function (right panel) using Fisher's Exact Test with false discovery rate adjustment. **D.** Quantification of mean telomere length (left panel) and % of short telomeres (right panel) of cortical and dentate gyrus (dg) neurons in *iCK-cre* mutants (cortex: n=2770; dg: n=45996) vs. controls (cortex: n=3093; dg: n=37722). ****p<0.0001 using two tailed unpaired Students *t*-test and Chi-square test, respectively. Telomere length is presented as mean+/- SEM, while % short telomeres is presented as a ratio of number of short telomeres (below 25th percentile) over total number of telomeres. **E.** Telomere FISH images of *iCK-cre* mutants vs. controls in the cortex and dentate gyrus. All scale bars=100 μm. In A and E, experiments were independently repeated with similar results at least

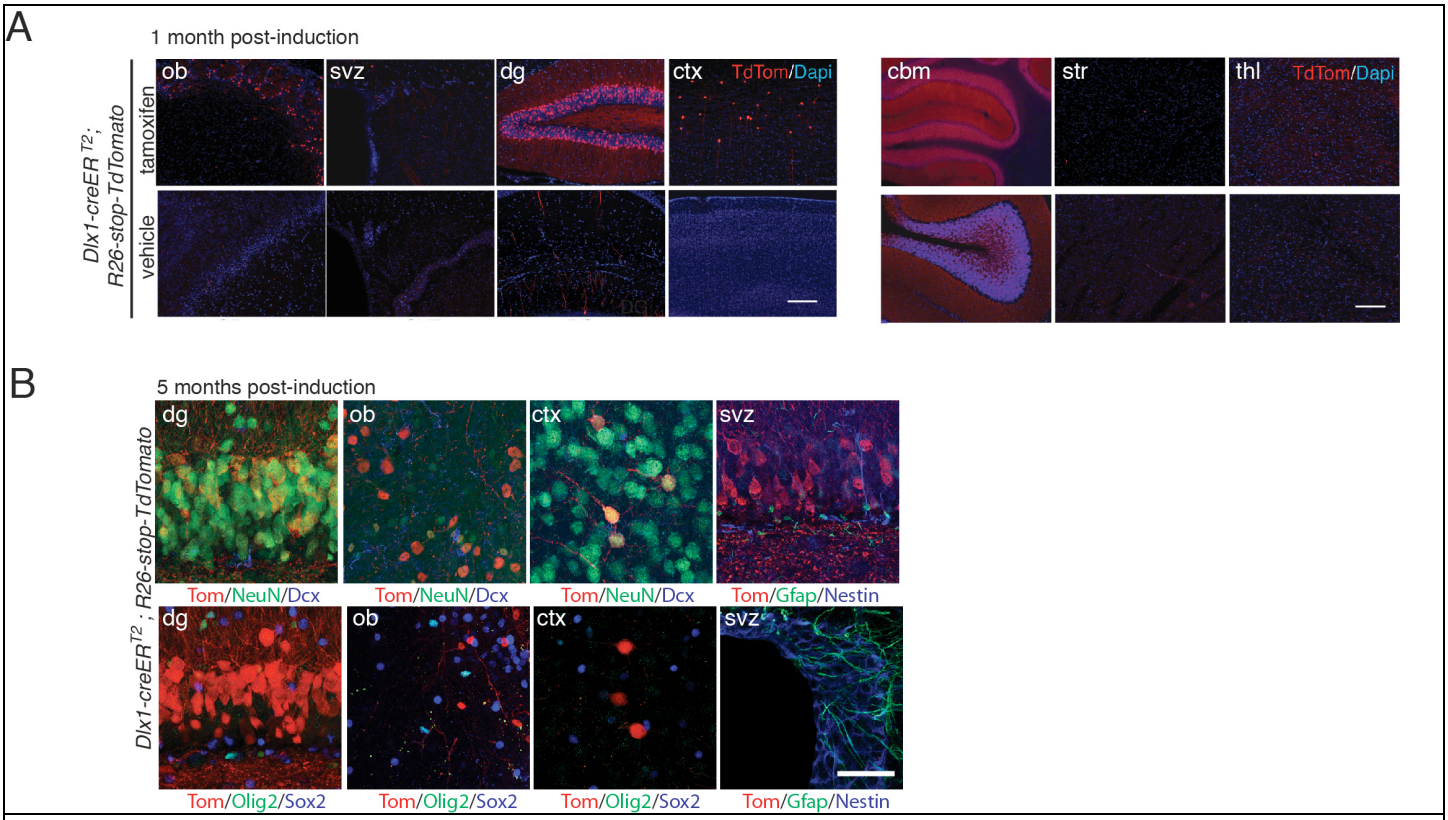
n=3 times using at least n=3 different mouse tissue samples for each group.



Supplementary Figure 2

Expression analysis of *iND-cre* Tomato reporter and mutant/control brains.

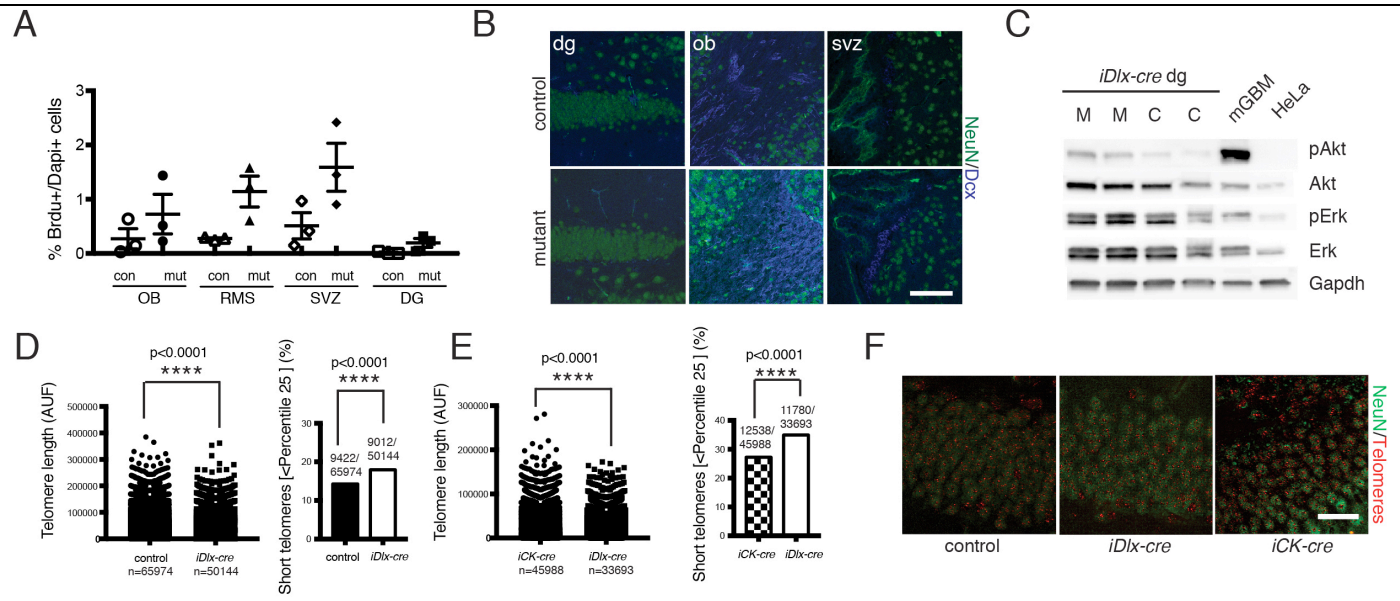
A. Tomato staining of *iND-cre; R26-stop-TdTomato* reporter and control at 4 weeks post-induction. **B.** Immunostaining of *iND-cre* reporter with lineage markers at 5 months post-induction **C.** Immunoflourescence staining of *iND-cre* mutant vs. control at 10 weeks post-induction. **D.** Quantification of % BrdU-positive cells in aged *iND-cre* mutants (n=3) vs. controls (n=3) in each of the indicated brain regions. Data is presented as mean +/- SEM. **E.** Immunoflourescence staining of aged *iND-cre* mutant vs. control at >6 months post-induction. All scale bars=100 μm. In A, B, C and E, experiments were independently repeated with similar results at least n=3 times using at least n=3 different mouse tissue samples for each group.



Supplementary Figure 3

Expression analysis of *iDlx-cre* Tomato reporter.

A. Tomato staining of tamoxifen- and vehicle-treated *iDlx-cre;R26-stop-TdTomato* reporter at 1 month post-induction. **B**. Immunostaining of *iDlx-cre;R26-stop-TdTomato* reporter with lineage markers at 5 months post-induction. All scale bars=100 μm. In A and B, experiments were independently repeated with similar results at least n=3 times using at least n=3 different mouse tissue samples for each group.

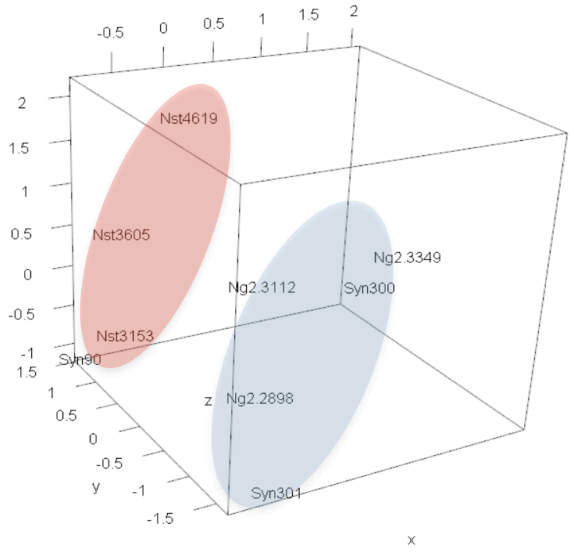


Supplementary Figure 4

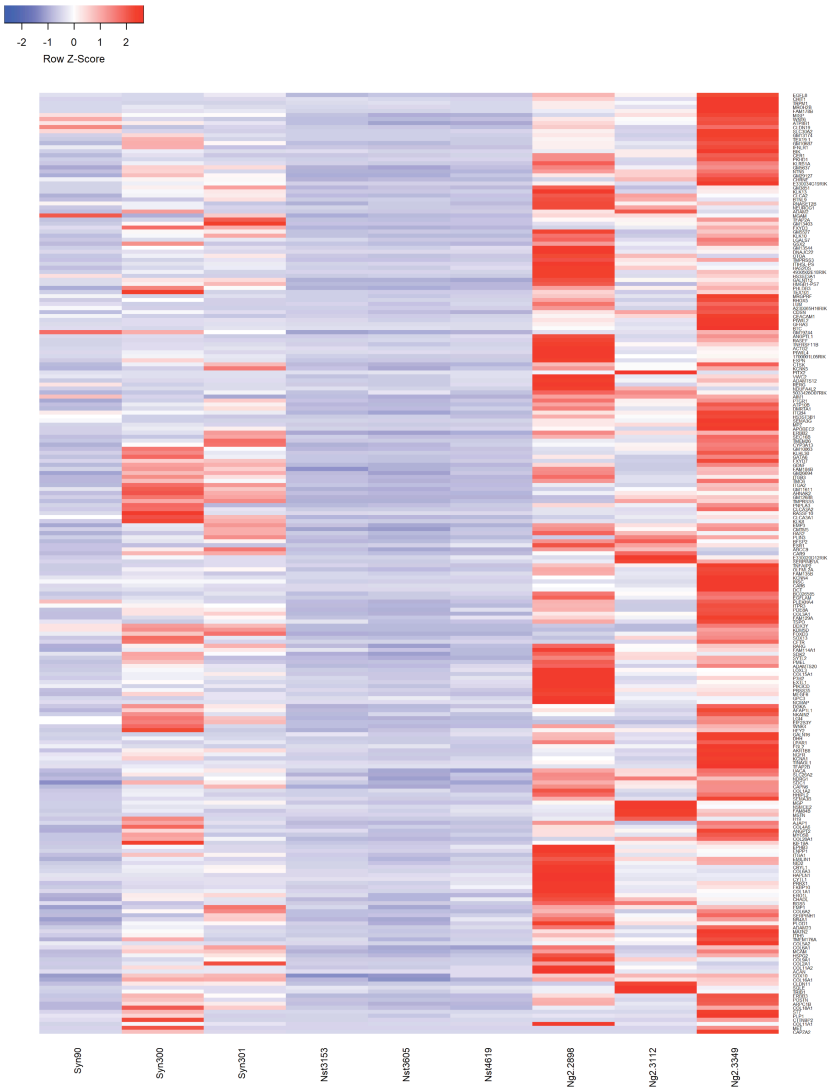
Molecular and histologic analysis of *iDlx-cre* mutants.

A. Quantification of % BrdU-positive cells in aged *iDlx-cre* mutants (n=3) vs. controls (n=3) in each of the indicated brain regions. Data is presented as mean +/- SEM. **B.** Immunostaining of aged *iDlx-cre* mutants and controls with lineage markers. **C**. Western blot analysis of MAPK and PI3K pathway components in *iDlx-cre* mutant (M) and control (C) brains. Mouse GBM (mGBM) and HeLa cell lysates were used as positive controls. **D.** Quantification of mean telomere length (left panel) and % of short telomeres (right panel) of dentate gyrus neurons in *iDlx-cre* mutants (n=50144) vs. controls (n=65974). **E.** Quantification of mean telomere length (left panel) and % of short telomeres (right panel) of dentate gyrus neurons in *iDlx-cre* (n=33693) vs. *iCK-cre* (n=45988) mutants. In D and E, telomere length is presented as mean +/- SEM, while % short telomeres is presented as a ratio of the number of short telomeres (below 25th percentile) over total number of telomeres. ****p<0.0001 using two tailed unpaired Student's *t*-test and Chi-square test, respectively. **H.** Telomere FISH images of *iDlx-cre* and *iCK-cre* mutants and controls in the dentate gyrus. All scale bars=100 μm. In B, C, and H, experiments were independently repeated with similar results at least n=3 times using at least n=3 different mouse tissue samples for each group.

A


Nst4619
Nst3605
Nst3153
Syn90
Ng2.3112
Syn300
Ng2.3349
Ng2.2898
Syn301
x
y
z

B


Row Z-Score
Syn90
Syn300
Syn301
Nst3153
Nst3605
Nst4619
Ng2.2898
Ng2.3112
Ng2.3349

Supplementary Figure 5

Molecular Profiling of *Syn-cre* Tumors.

RNA Sequencing analysis of *Syn-cre*, *Nestin-creER^{T2}*, and *NG2-creER^{TM}* tumors. **A**. Dimension reduction analysis of *Syn-cre* (n=3), *Nestin-creER^{T2}* (n=3), and *NG2-creER^{TM}* (n=3) mutant tumors. **B**. Heat map showing expression of *NG2-creER^{TM}* tumor signature genes (also listed in Table S2) in *Syn-cre* (n=3), *Nestin-creER^{T2}* (n=3), and *NG2-creER^{TM}* (n=3) tumors.