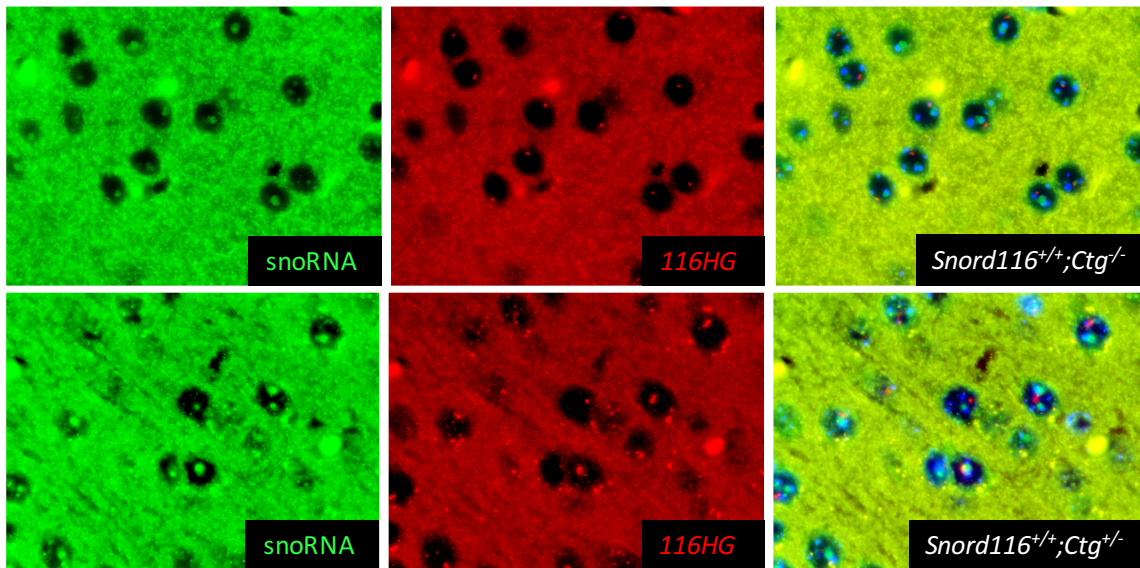
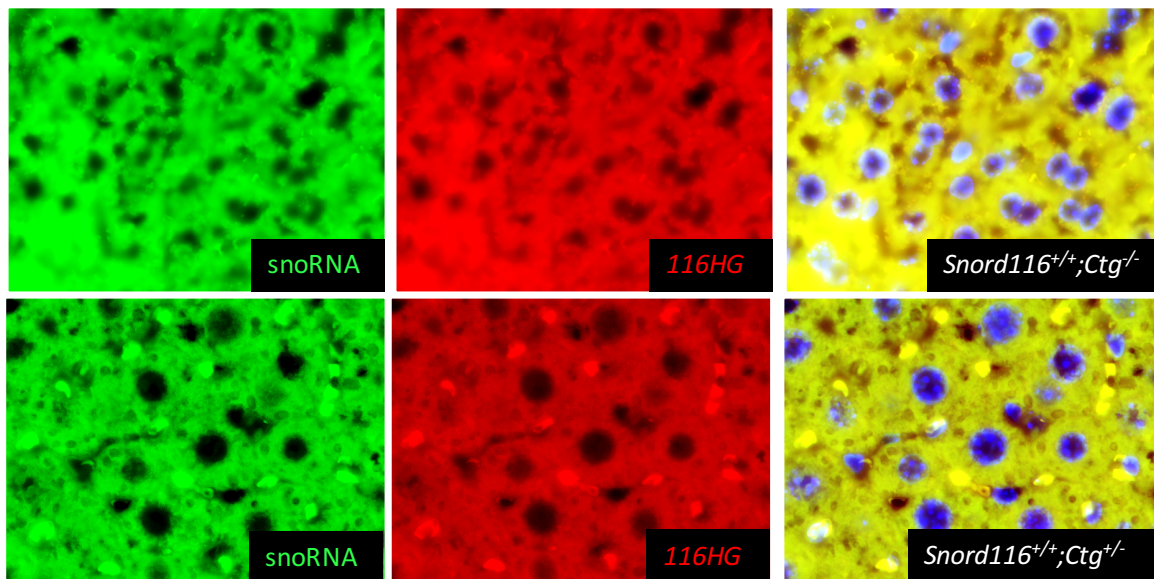


## Cortex



## Liver

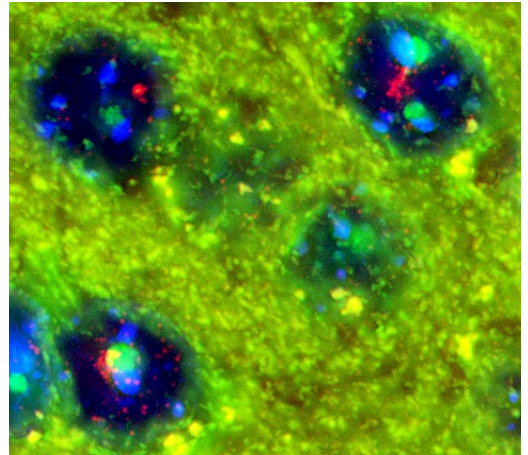
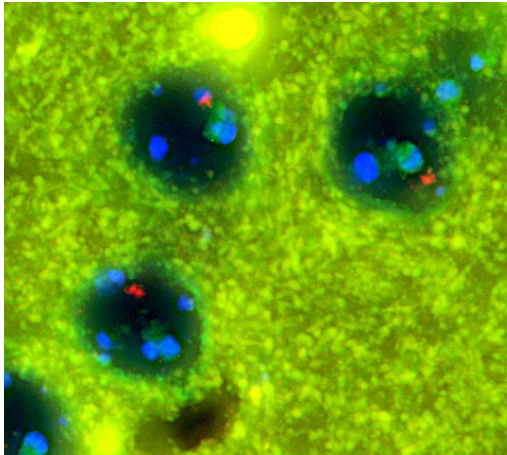


**Supplementary Figure 1.** Transgenic *Snord116* colocalizes with endogenous *Snord116* snoRNAs (green) and 116HG (red) in *Snord116<sup>+/-</sup>;Ctg<sup>+/-</sup>* cortical neurons, but not liver.

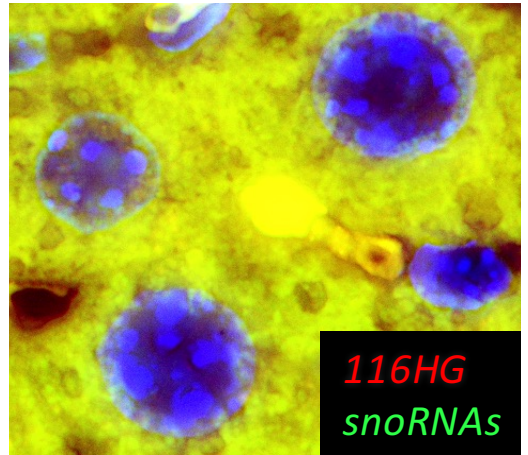
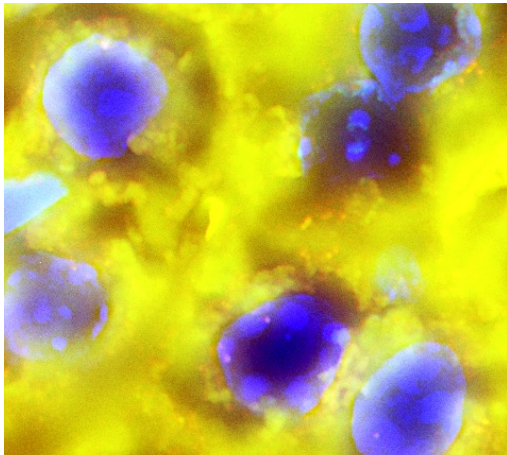
*Snord116*<sup>+/+</sup>;*Ctg*<sup>-/-</sup>

*Snord116*<sup>+/+</sup>;*Ctg*<sup>+/-</sup>

Cortex

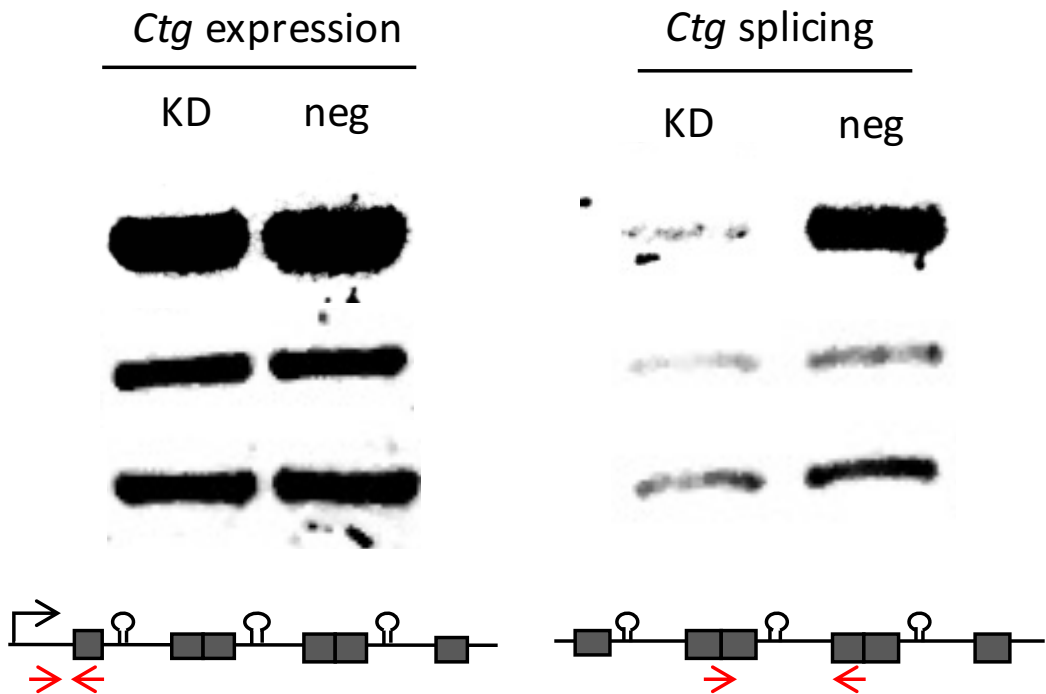


Liver

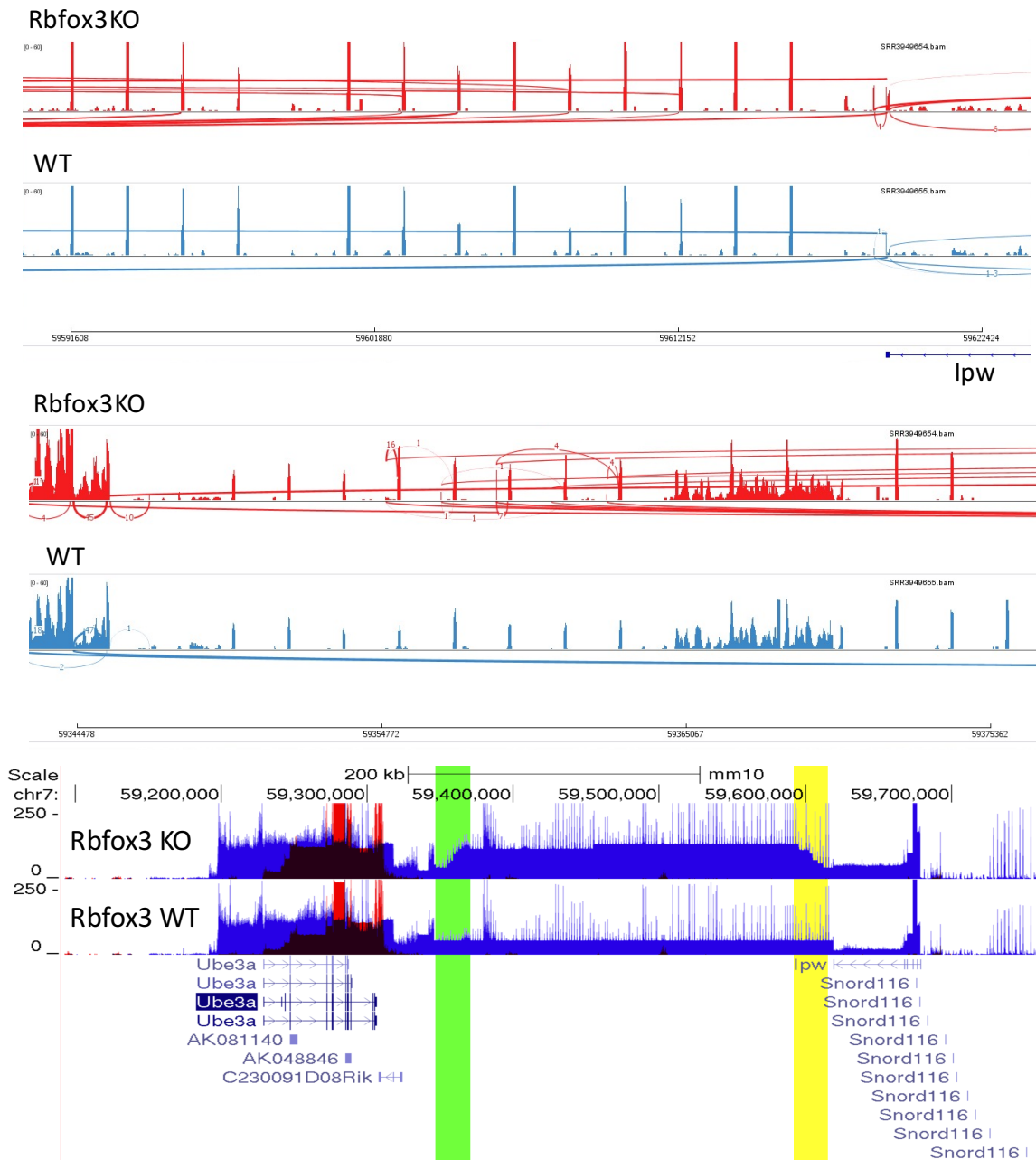


116HG  
snoRNAs

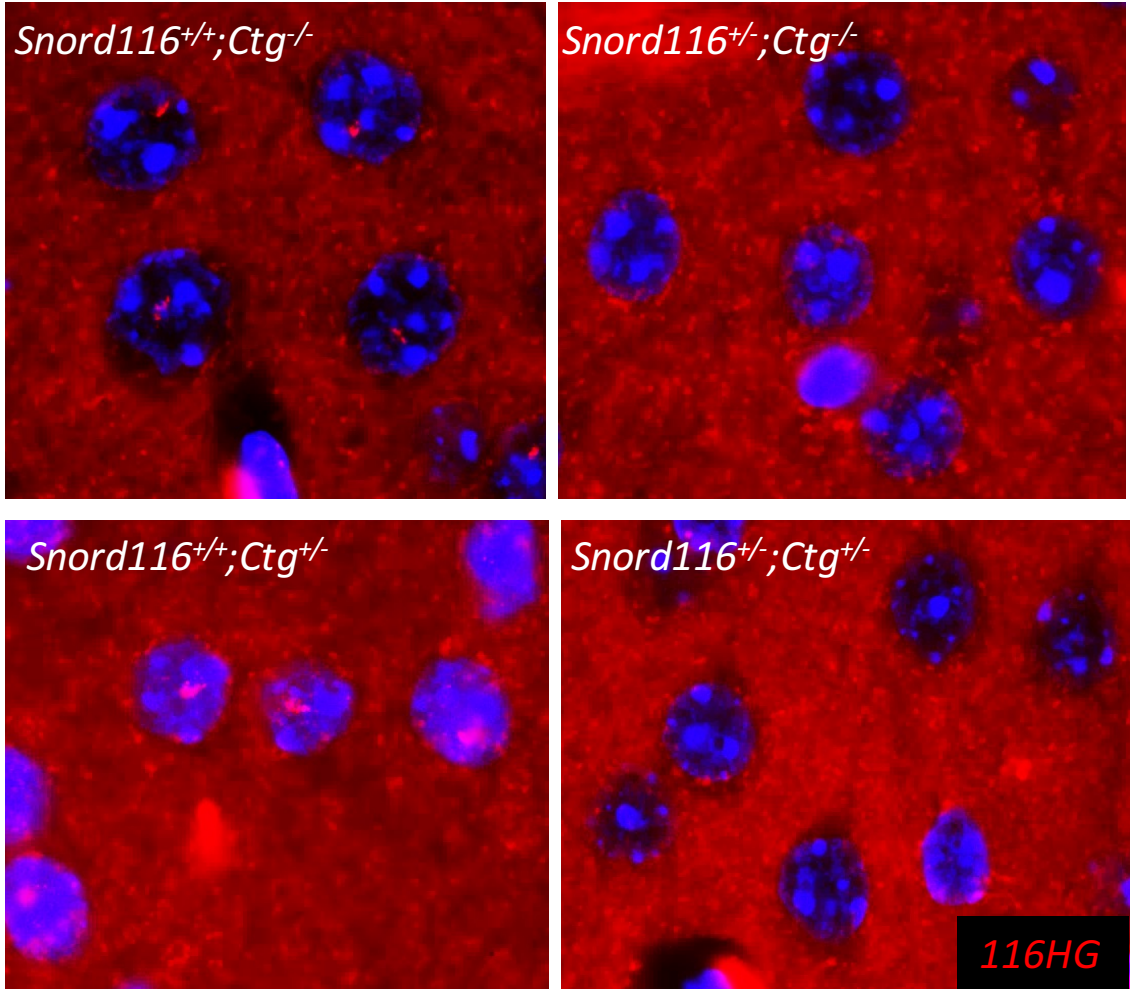
**Supplementary Figure 2.** Detailed view of colocalization of transgenic and endogenous *Snord116* snoRNAs and 116HG in *Snord116*<sup>+/+</sup>;*Ctg*<sup>+/-</sup> cortex. No signal is detected in the absence of endogenous *Snord116* expression in liver and *Snord116*<sup>+/-</sup>;*Ctg*<sup>+/-</sup> neurons.



**Supplementary Figure 3.** Replicates of Rbfox3 knockdown resulting in reduced splicing of the *Ctg* transgene in *Snord116<sup>+/-</sup>;Ctg<sup>+/-</sup>* NPC-derived neurons.



**Supplementary Figure 4.** Sashimi plots illustrating RNA sequencing of Rbfox3 knockout cortex (24) indicate disruption of splice junctions between *Snord116* and *Ube3a*.

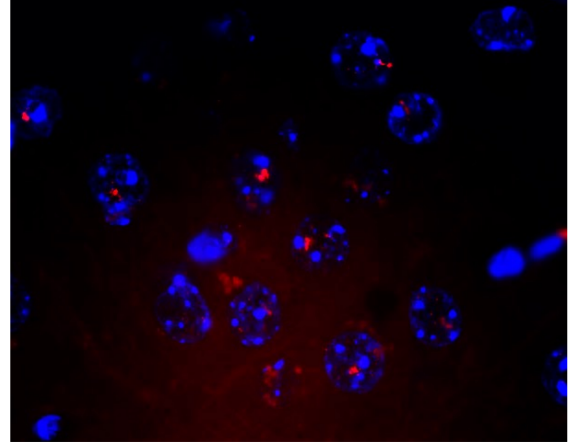
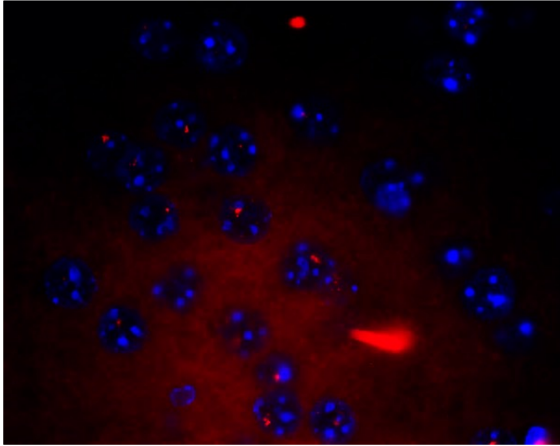


**Supplementary Figure 5.** Wide-field view of transgenic and endogenous 116HG colocalization in *Snord116*<sup>+/+</sup>;Ctg<sup>+/-</sup> cortical neurons shown in Figure 5. No RNA cloud is detected in liver or *Snord116*<sup>+/-</sup>;Ctg<sup>+/-</sup> neurons.

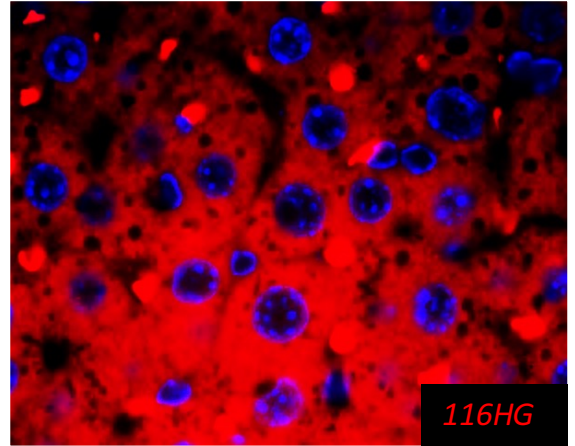
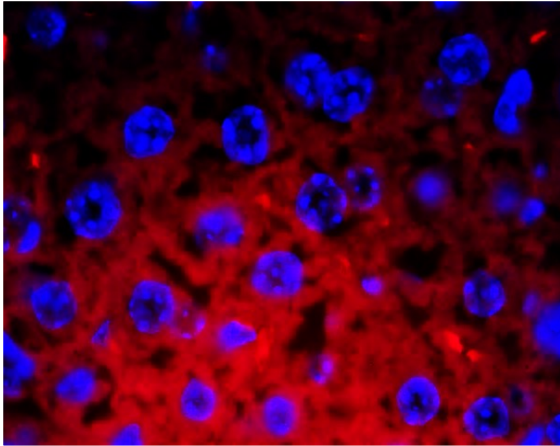
*Snord116*<sup>+/+</sup>;*Ctg*<sup>-/-</sup>

*Snord116*<sup>+/+</sup>;*Ctg*<sup>+/-</sup>

Cortex



Liver



116HG

**Supplementary Figure 6.** Verification of transgenic and endogenous *116HG* colocalization with a second RNA FISH probe.

|           | numDF | denDF | F-value    | p-value  |
|-----------|-------|-------|------------|----------|
| condition | 7     | 14    | 141.758893 | 6.62E-12 |

| contrast                          | estimate   | SE         | df | t.ratio    | p.value      |
|-----------------------------------|------------|------------|----|------------|--------------|
| Ctg/Prad cortex - Ctg/Prad kidney | -0.8648687 | 0.57004385 | 14 | -1.52E+00  | 0.78711643   |
| Ctg/Prad cortex - Ctg/WT cortex   | -4.0495482 | 0.57004385 | 14 | -7.10E+00  | 0.0001089 *  |
| Ctg/Prad cortex - Ctg/WT kidney   | -1.7681941 | 0.57004385 | 14 | -3.1018562 | 1.05E-01     |
| Ctg/Prad cortex - Prad cortex     | 5.37215337 | 0.57004385 | 14 | 9.42E+00   | 4.17E-06 *   |
| Ctg/Prad cortex - Prad kidney     | 8.08847674 | 0.57004385 | 14 | 1.42E+01   | 2.34E-08 *   |
| Ctg/Prad cortex - WT cortex       | -4.2283749 | 0.57004385 | 14 | -7.42E+00  | 6.76E-05 *   |
| Ctg/Prad cortex - WT kidney       | 6.19210966 | 0.57004385 | 14 | 1.09E+01   | 7.25E-07 *   |
| Ctg/Prad kidney - Ctg/WT cortex   | -3.1846795 | 0.57004385 | 14 | -5.5867272 | 0.00128766 * |
| Ctg/Prad kidney - Ctg/WT kidney   | -0.9033253 | 0.57004385 | 14 | -1.58E+00  | 7.52E-01     |
| Ctg/Prad kidney - Prad cortex     | 6.23702209 | 0.57004385 | 14 | 1.09E+01   | 6.63E-07 *   |
| Ctg/Prad kidney - Prad kidney     | 8.95334546 | 0.57004385 | 14 | 15.7064152 | 5.91E-09 *   |
| Ctg/Prad kidney - WT cortex       | -3.3635062 | 0.57004385 | 14 | -5.90E+00  | 7.56E-04 *   |
| Ctg/Prad kidney - WT kidney       | 7.05697838 | 0.57004385 | 14 | 1.24E+01   | 1.39E-07 *   |
| Ctg/WT cortex - Ctg/WT kidney     | 2.28135418 | 0.57004385 | 14 | 4.00E+00   | 2.15E-02 *   |
| Ctg/WT cortex - Prad cortex       | 9.42170159 | 0.57004385 | 14 | 16.5280294 | 2.97E-09 *   |
| Ctg/WT cortex - Prad kidney       | 12.138025  | 0.57004385 | 14 | 2.13E+01   | 1.28E-10 *   |
| Ctg/WT cortex - WT cortex         | -0.1788267 | 0.57004385 | 14 | -0.3137069 | 1.00E+00     |
| Ctg/WT cortex - WT kidney         | 10.2416579 | 0.57004385 | 14 | 1.80E+01   | 1.02E-09 *   |
| Ctg/WT kidney - Prad cortex       | 7.14034742 | 0.57004385 | 14 | 12.5259616 | 1.20E-07 *   |
| Ctg/WT kidney - Prad kidney       | 9.85667079 | 0.57004385 | 14 | 1.73E+01   | 1.65E-09 *   |
| Ctg/WT kidney - WT cortex         | -2.4601808 | 0.57004385 | 14 | -4.3157747 | 1.22E-02 *   |
| Ctg/WT kidney - WT kidney         | 7.96030371 | 0.57004385 | 14 | 1.40E+01   | 2.90E-08 *   |
| Prad cortex - Prad kidney         | 2.71632337 | 0.57004385 | 14 | 4.76511299 | 5.44E-03 *   |
| Prad cortex - WT cortex           | -9.6005283 | 0.57004385 | 14 | -16.841736 | 2.32E-09 *   |
| Prad cortex - WT kidney           | 0.81995629 | 0.57004385 | 14 | 1.43840914 | 8.26E-01     |
| Prad kidney - WT cortex           | -12.316852 | 0.57004385 | 14 | -21.606849 | 1.05E-10 *   |
| Prad kidney - WT kidney           | -1.8963671 | 0.57004385 | 14 | -3.3267039 | 7.12E-02     |
| WT cortex - WT kidney             | 10.4204845 | 0.57004385 | 14 | 18.2801454 | 8.25E-10 *   |

**Supplementary Table 1.** ANOVA with Tukey correction for *Snord116* expression (endogenous + transgenic) (Figure 2e). Starred (\*) comparisons are significant at  $p < 0.05$  corrected and significant biologically important comparisons are highlighted.

|                  | numDF | denDF | F-value    | p-value    |
|------------------|-------|-------|------------|------------|
| genotype         | 3     | 30    | 2.1598359  | 0.11350099 |
| measure          | 8     | 238   | 192.460696 | 0          |
| genotype:measure | 24    | 238   | 2.67134024 | 7.97E-05   |

| contrast          | week | estimate   | SE         | df | t.ratio      | p.value     | p.adjust    |
|-------------------|------|------------|------------|----|--------------|-------------|-------------|
| WT - Prad         | 3    | 2.05961538 | 1.2067992  | 30 | 1.706676133  | 0.098214848 | 0.203984685 |
| WT - Prad/Ctg     | 3    | 3.03653846 | 1.2067992  | 30 | 2.516191984  | 0.017445423 | 0.06728949  |
| WT - WT/Ctg       | 3    | 2          | 1.49244119 | 30 | 1.340086309  | 0.190279489 | 0.270397168 |
| Prad - Prad/Ctg   | 3    | 0.97692308 | 0.82785742 | 30 | 1.180061995  | 0.247248447 | 0.325644297 |
| Prad - WT/Ctg     | 3    | -0.0596154 | 1.2067992  | 30 | -0.049399589 | 0.960928286 | 0.960928286 |
| Prad/Ctg - WT/Ctg | 3    | -1.0365385 | 1.2067992  | 30 | -0.85891544  | 0.397198391 | 0.498807282 |
| WT - Prad         | 4    | 0.37692308 | 1.2067992  | 30 | 0.312332887  | 0.756948241 | 0.826584848 |
| WT - Prad/Ctg     | 4    | 2          | 1.2067992  | 30 | 1.657276544  | 0.107886453 | 0.213495695 |
| WT - WT/Ctg       | 4    | 2.175      | 1.49244119 | 30 | 1.457343862  | 0.155410418 | 0.24682831  |
| Prad - Prad/Ctg   | 4    | 1.62307692 | 0.82785742 | 30 | 1.960575441  | 0.059272007 | 0.16073498  |
| Prad - WT/Ctg     | 4    | 1.79807692 | 1.2067992  | 30 | 1.489955354  | 0.146675492 | 0.242127497 |
| Prad/Ctg - WT/Ctg | 4    | 0.175      | 1.2067992  | 30 | 0.145011698  | 0.88567152  | 0.91510513  |
| WT - Prad         | 5    | 1.46346154 | 1.2067992  | 30 | 1.21268024   | 0.234715476 | 0.316865893 |
| WT - Prad/Ctg     | 5    | 3.56346154 | 1.2067992  | 30 | 2.952820612  | 0.006066888 | 0.032761193 |
| WT - WT/Ctg       | 5    | 2.45       | 1.49244119 | 30 | 1.641605729  | 0.111115385 | 0.213495695 |
| Prad - Prad/Ctg   | 5    | 2.1        | 0.82785742 | 30 | 2.536668699  | 0.016630544 | 0.06728949  |
| Prad - WT/Ctg     | 5    | 0.98653846 | 1.2067992  | 30 | 0.817483526  | 0.420097481 | 0.515574181 |
| Prad/Ctg - WT/Ctg | 5    | -1.1134615 | 1.2067992  | 30 | -0.922656845 | 0.363547522 | 0.467418242 |
| WT - Prad         | 6    | 2.26730769 | 1.2067992  | 30 | 1.878777928  | 0.07002263  | 0.172796088 |
| WT - Prad/Ctg     | 6    | 3.38269231 | 1.2067992  | 30 | 2.803028309  | 0.008787774 | 0.039544982 |
| WT - WT/Ctg       | 6    | 2.425      | 1.49244119 | 30 | 1.62485465   | 0.114655096 | 0.213495695 |
| Prad - Prad/Ctg   | 6    | 1.11538462 | 0.82785742 | 30 | 1.347314877  | 0.187967621 | 0.270397168 |
| Prad - WT/Ctg     | 6    | 0.15769231 | 1.2067992  | 30 | 0.130669881  | 0.896908769 | 0.91510513  |
| Prad/Ctg - WT/Ctg | 6    | -0.9576923 | 1.2067992  | 30 | -0.793580499 | 0.433671985 | 0.518802824 |
| WT - Prad         | 7    | 2.95576923 | 1.2067992  | 30 | 2.449263508  | 0.020371999 | 0.073339198 |
| WT - Prad/Ctg     | 7    | 4.37115385 | 1.2067992  | 30 | 3.62210537   | 0.001066123 | 0.009595109 |
| WT - WT/Ctg       | 7    | 2.8        | 1.49244119 | 30 | 1.876120833  | 0.070398406 | 0.172796088 |
| Prad - Prad/Ctg   | 7    | 1.41538462 | 0.82785742 | 30 | 1.709696119  | 0.097647946 | 0.203984685 |
| Prad - WT/Ctg     | 7    | -0.1557692 | 1.2067992  | 30 | -0.129076346 | 0.898158739 | 0.91510513  |
| Prad/Ctg - WT/Ctg | 7    | -1.5711538 | 1.2067992  | 30 | -1.301918208 | 0.202852664 | 0.28087292  |
| WT - Prad         | 8    | 3.63846154 | 1.2067992  | 30 | 3.014968482  | 0.005190602 | 0.031143611 |
| WT - Prad/Ctg     | 8    | 4.90769231 | 1.2067992  | 30 | 4.066701673  | 0.000317788 | 0.003432112 |
| WT - WT/Ctg       | 8    | 3.275      | 1.49244119 | 30 | 2.194391332  | 0.036087713 | 0.114631558 |
| Prad - Prad/Ctg   | 8    | 1.26923077 | 0.82785742 | 30 | 1.533151411  | 0.135717796 | 0.236411645 |
| Prad - WT/Ctg     | 8    | -0.3634615 | 1.2067992  | 30 | -0.301178141 | 0.76535634  | 0.826584848 |
| Prad/Ctg - WT/Ctg | 8    | -1.6326923 | 1.2067992  | 30 | -1.352911333 | 0.186192744 | 0.270397168 |
| WT - Prad         | 9    | 4.16538462 | 1.2067992  | 30 | 3.45159711   | 0.001678865 | 0.011332339 |
| WT - Prad/Ctg     | 9    | 5.58846154 | 1.2067992  | 30 | 4.630813112  | 6.59E-05    | 0.001780451 |
| WT - WT/Ctg       | 9    | 3.225      | 1.49244119 | 30 | 2.160889174  | 0.038813959 | 0.116441876 |
| Prad - Prad/Ctg   | 9    | 1.42307692 | 0.82785742 | 30 | 1.718987946  | 0.095920915 | 0.203984685 |
| Prad - WT/Ctg     | 9    | -0.9403846 | 1.2067992  | 30 | -0.779238683 | 0.441943147 | 0.518802824 |
| Prad/Ctg - WT/Ctg | 9    | -2.3634615 | 1.2067992  | 30 | -1.958454685 | 0.059531474 | 0.16073498  |
| WT - Prad         | 10   | 4.19423077 | 1.2067992  | 30 | 3.475500137  | 0.001575952 | 0.011332339 |
| WT - Prad/Ctg     | 10   | 5.37237616 | 1.21032341 | 30 | 4.438793887  | 0.000112988 | 0.002033775 |
| WT - WT/Ctg       | 10   | 3.575      | 1.49244119 | 30 | 2.395404278  | 0.02304658  | 0.077782208 |
| Prad - Prad/Ctg   | 10   | 1.17814539 | 0.83298641 | 30 | 1.414363269  | 0.167550549 | 0.258506562 |
| Prad - WT/Ctg     | 10   | -0.6192308 | 1.2067992  | 30 | -0.513118315 | 0.611626713 | 0.688080052 |
| Prad/Ctg - WT/Ctg | 10   | -1.7973762 | 1.21032341 | 30 | -1.485037917 | 0.147966804 | 0.242127497 |
| WT - Prad         | 11   | 5.06923077 | 1.2067992  | 30 | 4.200558625  | 0.000219448 | 0.002962549 |
| WT - Prad/Ctg     | 11   | 6.39737616 | 1.21032341 | 30 | 5.285674969  | 1.04E-05    | 0.000561142 |
| WT - WT/Ctg       | 11   | 4.2        | 1.49244119 | 30 | 2.81418125   | 0.00855103  | 0.039544982 |
| Prad - Prad/Ctg   | 11   | 1.32814539 | 0.83298641 | 30 | 1.594438235  | 0.121320534 | 0.218376961 |
| Prad - WT/Ctg     | 11   | -0.8692308 | 1.2067992  | 30 | -0.720277883 | 0.476928931 | 0.547960899 |
| Prad/Ctg - WT/Ctg | 11   | -2.1973762 | 1.21032341 | 30 | -1.815528095 | 0.079450996 | 0.186537121 |

**Supplementary Table 2.** Repeated measures ANOVA, Benjamini-Hochberg post-hoc correction (p.adjust) for mouse weights (Figure 6a). Highlighted comparisons are significant \*p<0.05 corrected