

## Supplementary Material

Supplementary Figure S1.

Supplementary Figure S2.

Supplementary Figure S3.

Supplementary Figure S4.

Supplementary Table S1.

Supplementary Table S2.

Supplementary Table S3.

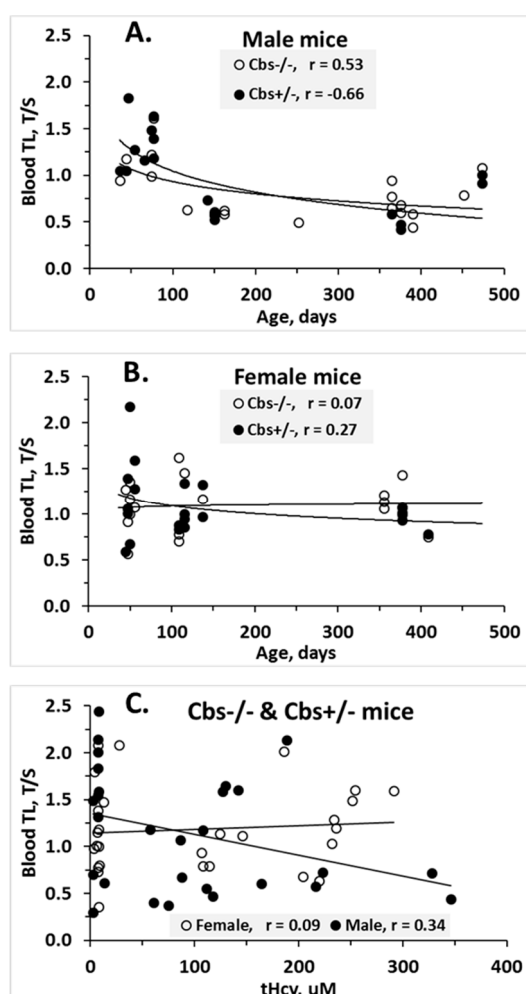
Supplementary Table S4.

Supplementary Table S5.

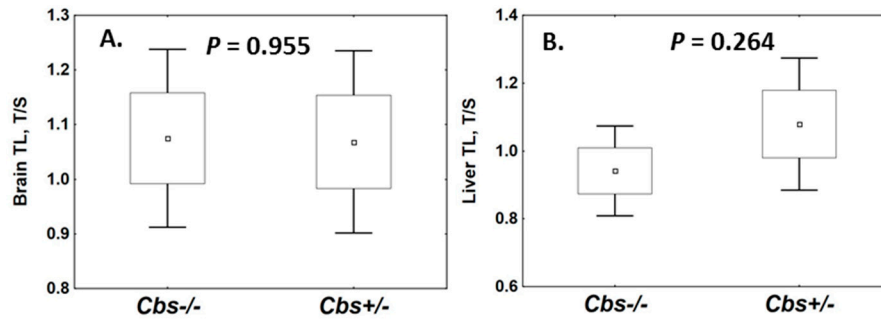
Supplementary Table S6.

Supplementary Table S7.

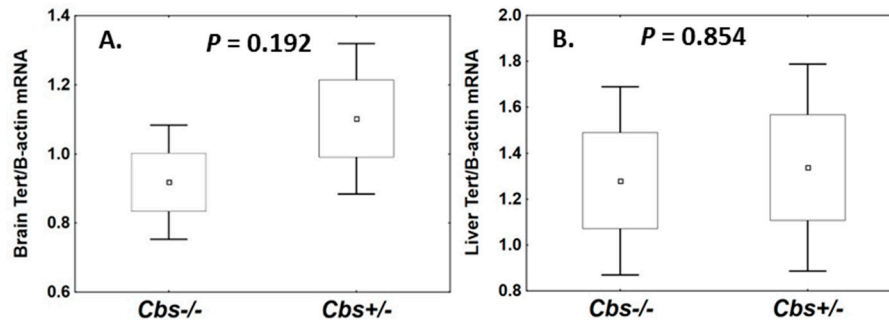
Supplementary Table S8.



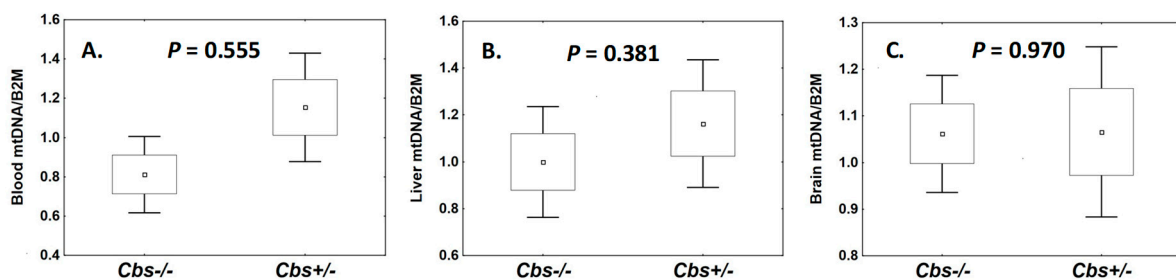
**Supplementary Figure S1.** Relationships between blood TL, age, and tHcy in *Cbs*<sup>-/-</sup> and *Cbs*<sup>+/-</sup> mice. Blood TL vs. age in (A) female and (B) male mice. (C) Blood TL vs. tHcy.



**Supplementary Figure S2.** Telomere length (TL) in brains (A) and livers (B) of *Cbs*<sup>-/-</sup> and *Cbs*<sup>+/-</sup> mice. TL was quantified by qPCR in *Cbs*<sup>-/-</sup> mice ( $n = 21$ ) and sex- and age-matched control *Cbs*<sup>+/-</sup> siblings ( $n = 22$ ) as described in the Materials and Methods. Box and whiskers represent the mean  $\pm$  SEM and the mean  $\pm$  95% CI, respectively.



**Supplementary Figure S3.** *Tert* mRNA levels in brains (A) and livers (B) of *Cbs*<sup>-/-</sup> and *Cbs*<sup>+/-</sup> mice. *Tert* mRNA was quantified by qPCR in *Cbs*<sup>-/-</sup> mice ( $n = 21$ ) and sex- and age-matched control *Cbs*<sup>+/-</sup> siblings ( $n = 22$ ) as described in the Materials and Methods. Box and whiskers represent the mean  $\pm$  SEM and the mean  $\pm$  95% CI, respectively.



**Supplementary Figure S4.** mtDNA levels in blood (A), livers (B), and brains (C) of *Cbs*<sup>-/-</sup> and *Cbs*<sup>+/-</sup> mice. mtDNA was quantified by qPCR in *Cbs*<sup>-/-</sup> mice (blood,  $n = 40$ ; liver and brain,  $n = 21$ ) and sex- and age-matched control *Cbs*<sup>+/-</sup> siblings (blood,  $n = 40$ ; liver and brain,  $n = 22$ ) as described in the Materials and Methods. Box and whiskers represent the mean  $\pm$  SEM and the mean  $\pm$  95% CI, respectively.

Supplementary Table S1. Aging/senescence-related mRNAs in the liver of *Cbs*<sup>-/-</sup> and *Cbs*<sup>+/-</sup> mice stratified by sex and age.

| Genotype (n)                      | Sex (n)   | Age*                                      | <i>Pai-1</i> /β-actin mRNA |                                                |                         | <i>p21</i> /β-actin mRNA |                                                |                         | <i>Mcp1</i> /β-actin mRNA |                                                |                         | <i>Il-6</i> /β-actin mRNA |                                                |                         |
|-----------------------------------|-----------|-------------------------------------------|----------------------------|------------------------------------------------|-------------------------|--------------------------|------------------------------------------------|-------------------------|---------------------------|------------------------------------------------|-------------------------|---------------------------|------------------------------------------------|-------------------------|
|                                   |           |                                           | Mean ± SD (n)              | FC <sup>#</sup> ; <i>P</i> <sub>genotype</sub> | <i>P</i> <sub>sex</sub> | Mean ± SD (n)            | FC <sup>#</sup> ; <i>P</i> <sub>genotype</sub> | <i>P</i> <sub>sex</sub> | Mean ± SD (n)             | FC <sup>#</sup> ; <i>P</i> <sub>genotype</sub> | <i>P</i> <sub>sex</sub> | Mean ± SD (n)             | FC <sup>#</sup> ; <i>P</i> <sub>genotype</sub> | <i>P</i> <sub>sex</sub> |
| <i>Cbs</i> <sup>+/-</sup> (18–20) | ♀ (9–10)  | Young                                     | 10.7 ± 6.4 (4)             | 10.7; <b>0.025</b>                             | 13.4; 0.060             | 5.3 ± 3.2 (4)            | 7.6; <b>0.016</b>                              | 0.87; 0.272             | 4.2 ± 2.2 (4)             | 11.0; <b>0.014</b>                             | 2.0; 0.202              | 0.78 ± 1.11 (3)           | 4.6; 0.311                                     | 0.55; 0.500             |
|                                   |           | Old                                       | 3.1 ± 1.5 (6)              | 4.4; <b>0.006</b>                              | 1.47; 0.318             | 6.3 ± 4.8 (6)            | 4.2; 0.059                                     | 1.75; 0.124             | 4.3 ± 1.8 (6)             | 1.4; 0.174                                     | 0.34; <b>0.004</b>      | 2.87 ± 1.50 (6)           | 0.8; 0.525                                     | 0.71; 0.252             |
|                                   |           | FC <sup>#</sup> ; <i>P</i> <sub>age</sub> | 0.29; <b>0.021</b>         |                                                |                         | 1.2; 0.589               |                                                |                         | 1.0; 0.906                |                                                |                         | 1.2; 0.072                |                                                |                         |
|                                   | ♂ (8–10)  | Young                                     | 1.3 ± 1.3 (3)              | 0.8; 0.571                                     |                         | 10.4 ± 7.5 (2)           | 8.7; <b>0.005</b>                              |                         | 2.1 ± 1.0 (3)             | 3.0; <b>0.005</b>                              |                         | 1.43 ± 1.05 (3)           | 8.4; <b>0.063</b>                              |                         |
|                                   |           | Old                                       | 4.5 ± 2.9 (5)              | 3.0; 0.106                                     |                         | 3.1 ± 2.8 (6)            | 2.4; 0.123                                     |                         | 12.7 ± 5.3 (6)            | 3.2; <b>0.034</b>                              |                         | 4.06 ± 1.98 (7)           | 1.0; 0.923                                     |                         |
|                                   |           | FC <sup>#</sup> ; <i>P</i> <sub>age</sub> | 3.5; 0.132                 |                                                |                         | 0.30; 0.065              |                                                |                         | 6.0; <b>0.013</b>         |                                                |                         | 3.0; 0.066                |                                                |                         |
| <i>Cbs</i> <sup>+/-</sup> (20–23) | ♀ (9)     | Young                                     | 1.0 ± 0.9 (4)              |                                                | 0.59; 0.230             | 0.70 ± 0.37 (5)          |                                                | 0.58; 0.124             | 0.38 ± 0.12 (4)           |                                                | 0.49; 0.307             | 0.17 ± 0.10 (4)           |                                                | 0.29; <b>0.010</b>      |
|                                   |           | Old                                       | 0.7 ± 0.2 (5)              |                                                | 0.45; 0.216             | 1.50 ± 0.62 (4)          |                                                | 1.15; 0.676             | 3.12 ± 0.39 (5)           |                                                | 0.69; 0.715             | 3.42 ± 1.29 (5)           |                                                | 0.88; 0.796             |
|                                   |           | FC <sup>#</sup> ; <i>P</i> <sub>age</sub> | 0.7; 0.384                 |                                                |                         | 2.1; <b>0.047</b>        |                                                |                         | 8.2; <b>0.000</b>         |                                                |                         | 20.1; <b>0.002</b>        |                                                |                         |
|                                   | ♂ (10–14) | Young                                     | 1.7 ± 0.8 (7)              |                                                |                         | 1.2 ± 0.5 (7)            |                                                |                         | 0.78 ± 0.62 (7)           |                                                |                         | 0.59 ± 0.24 (7)           |                                                |                         |
|                                   |           | Old                                       | 1.5 ± 1.4 (4)              |                                                |                         | 1.3 ± 0.9 (7)            |                                                |                         | 1.66 ± 1.58 (4)           |                                                |                         | 3.90 ± 3.72 (6)           |                                                |                         |
|                                   |           | FC <sup>#</sup> ; <i>P</i> <sub>age</sub> | 0.9; 0.784                 |                                                |                         | 1.1; 0.749               |                                                |                         | 2.1; 0.217                |                                                |                         | 6.6; <b>0.037</b>         |                                                |                         |

\* Young = 63- to 66-day-old; Old = 354- to 408-day-old. <sup>#</sup> FC, fold change.

Supplementary Table S2. Aging/senescence-related mRNAs in the brain of *Cbs*<sup>-/-</sup> and *Cbs*<sup>+/-</sup> mice stratified by sex and age.

| Genotype<br>( <i>n</i> )             | Sex ( <i>n</i> ) | Age*                                      | <i>Pai-1</i> /β-actin mRNA |                                              |                         | <i>p21</i> /β-actin mRNA  |                                              |                                              | <i>Mcp1</i> /β-actin mRNA |                                              |                         | <i>Il-6</i> /β-actin mRNA |                                              |                                              | <i>Kl</i> /β-actin mRNA   |                                              |                                              |
|--------------------------------------|------------------|-------------------------------------------|----------------------------|----------------------------------------------|-------------------------|---------------------------|----------------------------------------------|----------------------------------------------|---------------------------|----------------------------------------------|-------------------------|---------------------------|----------------------------------------------|----------------------------------------------|---------------------------|----------------------------------------------|----------------------------------------------|
|                                      |                  |                                           | Mean ± SD<br>( <i>n</i> )  | FC <sup>‡</sup> ;<br><i>P</i> <sub>gen</sub> | <i>P</i> <sub>sex</sub> | Mean ± SD ( <i>n</i> )    | FC <sup>‡</sup> ;<br><i>P</i> <sub>gen</sub> | FC <sup>‡</sup> ;<br><i>P</i> <sub>sex</sub> | Mean ± SD ( <i>n</i> )    | FC <sup>‡</sup> ;<br><i>P</i> <sub>gen</sub> | <i>P</i> <sub>sex</sub> | Mean ± SD ( <i>n</i> )    | FC <sup>‡</sup> ;<br><i>P</i> <sub>gen</sub> | FC <sup>‡</sup> ;<br><i>P</i> <sub>sex</sub> | Mean ± SD<br>( <i>n</i> ) | FC <sup>‡</sup> ;<br><i>P</i> <sub>gen</sub> | FC <sup>‡</sup> ;<br><i>P</i> <sub>sex</sub> |
| <i>Cbs</i> <sup>−/−</sup><br>(17–21) | ♀<br>(8–11)      | Young                                     | 1.38 ± 0.14 (3)            | 1.3;<br>0.404                                | 0.167                   | 1.87 ± 0.63 (4)           | <b>1.9</b> ;<br><b>0.035</b>                 | 0.206                                        | 0.66 ± 0.12 (3)           | 0.7;<br>0.259                                | 0.266                   | 1.54 ± 1.24 (4)           | 2.0;<br>0.286                                | 1.9;<br>0.383                                | 2.00 ± 0.34 (4)           | 1.4;<br>0.192                                | <b>2.5</b> ;<br><b>0.010</b>                 |
|                                      |                  | Old                                       | 0.97 ± 0.33 (5)            | 0.9;<br>0.361                                | 0.623                   | 1.83 ± 0.77 (7)           | <b>2.9</b> ;<br><b>0.004</b>                 | 0.360                                        | 1.03 ± 0.21 (7)           | <b>1.4</b> ;<br><b>0.020</b>                 | 0.622                   | 1.34 ± 0.29 (7)           | 0.83;<br>0.417                               | <b>1.6</b> ;<br><b>0.032</b>                 | 1.17 ± 0.56 (7)           | 1.4;<br>0.996                                | 0.168                                        |
|                                      |                  | FC <sup>‡</sup> ; <i>P</i> <sub>age</sub> | 0.7; 0.093                 |                                              | 1.0; 0.936              |                           |                                              | 1.6; <b>0.02</b>                             |                           |                                              | 0.9; 0.678              |                           |                                              | <b>0.6</b> ; <b>0.022</b>                    |                           |                                              |                                              |
|                                      | ♂<br>(8–10)      | Young                                     | 0.76 ± 0.60 (2)            | 0.5;<br>0.366                                |                         | 1.09 ± 0.80 (3)           | 0.750                                        |                                              | 0.89 ± 0.29 (3)           | 0.8;<br>0.421                                |                         | 0.81 ± 0.45 (3)           | 0.71;<br>0.520                               |                                              | 0.80 ± 0.46 (3)           | 0.53;<br>0.138                               |                                              |
|                                      |                  | Old                                       | 0.71 ± 0.54 (7)            | 0.7;<br>0.411                                |                         | 0.64 ± 0.46 (7)           | 0.818                                        |                                              | 1.16 ± 0.68 (5)           | 0.8;<br>0.773                                |                         | 0.83 ± 0.47 (7)           | 0.83;<br>0.495                               |                                              | 0.80 ± 0.41 (7)           | 0.99;<br>0.465                               |                                              |
|                                      |                  | <i>P</i> <sub>age</sub>                   | 0.911                      |                                              | 0.286                   |                           |                                              | 0.547                                        |                           |                                              | 0.949                   |                           |                                              | 0.996                                        |                           |                                              |                                              |
| <i>Cbs</i> <sup>±/−</sup><br>(19–22) | ♀<br>(8–9)       | Young                                     | 1.03 ± 0.63 (4)            |                                              | 0.527                   | 0.96 ± 0.23 (4)           |                                              | 0.254                                        | 0.95 ± 0.37 (4)           |                                              | 0.599                   | 0.77 ± 0.46 (4)           |                                              | 0.270                                        | 1.44 ± 0.69 (4)           |                                              | 0.878                                        |
|                                      |                  | Old                                       | 1.05 ± 0.29 (5)            |                                              | 0.989                   | 1.43 ± 0.66 (5)           | <b>2.1</b> ;<br><b>0.036</b>                 |                                              | 0.72 ± 0.08 (4)           |                                              | 0.052                   | 1.61 ± 0.77 (5)           |                                              | 0.121                                        | 0.83 ± 0.28 (4)           |                                              | 0.947                                        |
|                                      |                  | <i>P</i> <sub>age</sub>                   | 0.951                      |                                              | 0.231                   |                           |                                              | 0.273                                        |                           |                                              | 0.098                   |                           |                                              | 0.156                                        |                           |                                              |                                              |
|                                      | ♂<br>(10–13)     | Young                                     | 1.42 ± 1.04 (6)            |                                              |                         | 1.41 ± 0.69 (7)           |                                              |                                              | 1.07 ± 0.27 (6)           |                                              |                         | 1.14 ± 0.53 (7)           |                                              |                                              | 1.50 ± 0.65 (7)           |                                              |                                              |
|                                      |                  | Old                                       | 1.05 ± 0.55 (4)            |                                              |                         | 0.69 ± 0.28 (6)           |                                              |                                              | 1.41 ± 0.54 (6)           |                                              |                         | 1.00 ± 0.37 (6)           |                                              |                                              | 0.81 ± 0.54 (6)           |                                              |                                              |
|                                      |                  | FC <sup>‡</sup> ; <i>P</i> <sub>age</sub> | 0.7; 0.535                 |                                              |                         | <b>0.5</b> ; <b>0.038</b> |                                              |                                              | 1.3; 0.238                |                                              |                         | 0.9; 0.596                |                                              |                                              | 0.5; 0.064                |                                              |                                              |

\* Young = 63- to 66-day-old; Old = 354- to 408-day-old. <sup>‡</sup> FC, fold change.

**Supplementary Table S3. Blood TL, plasma tHcy levels in *Cbs*<sup>-/-</sup> and *Cbs*<sup>+/-</sup> mice stratified by sex and age.**

| Genotype (n)                   | Sex (n) | Age* (n)                | tHcy, $\mu$ M |                              |                         | TL, T/S          |                              |                         |
|--------------------------------|---------|-------------------------|---------------|------------------------------|-------------------------|------------------|------------------------------|-------------------------|
|                                |         |                         | Mean $\pm$ SD | <i>P</i> <sub>genotype</sub> | <i>P</i> <sub>sex</sub> | Mean $\pm$ SD    | <i>P</i> <sub>genotype</sub> | <i>P</i> <sub>sex</sub> |
| <i>Cbs</i> <sup>-/-</sup> (40) | ♀ (20)  | Young (12)              | 133 $\pm$ 64  | <b>&lt;0.000</b>             | 0.990                   | 1.08 $\pm$ 0.31  | 0.820                        | 0.507                   |
|                                |         | Old (8)                 | 238 $\pm$ 33  | <b>&lt;0.000</b>             | <b>0.044</b>            | 1.10 $\pm$ 0.19  | 0.374                        | <b>&lt;0.000</b>        |
|                                |         | <i>P</i> <sub>age</sub> | <b>0.002</b>  |                              |                         | 0.855            |                              |                         |
|                                | ♂ (20)  | Young (6)               | 133 $\pm$ 42  | <b>&lt;0.000</b>             |                         | 1.19 $\pm$ 0.27  | 0.335                        |                         |
|                                |         | Old (14)                | 156 $\pm$ 96  | <b>&lt;0.000</b>             |                         | 0.68 $\pm$ 0.17  | 0.615                        |                         |
|                                |         | <i>P</i> <sub>age</sub> | 0.531         |                              |                         | <b>&lt;0.000</b> |                              |                         |
| <i>Cbs</i> <sup>+/-</sup> (40) | ♀ (20)  | Young (14)              | 6.4 $\pm$ 1.8 |                              | 0.180                   | 1.12 $\pm$ 0.41  |                              | 0.165                   |
|                                |         | Old (6)                 | 8.7 $\pm$ 2.8 |                              | 0.669                   | 1.01 $\pm$ 0.18  |                              | <b>0.002</b>            |
|                                |         | <i>P</i> <sub>age</sub> | 0.096         |                              |                         | 0.564            |                              |                         |
|                                | ♂ (20)  | Young (10)              | 7.3 $\pm$ 0.2 |                              |                         | 1.34 $\pm$ 0.27  |                              |                         |
|                                |         | Old (10)                | 5.1 $\pm$ 5.4 |                              |                         | 0.64 $\pm$ 0.19  |                              |                         |
|                                |         | <i>P</i> <sub>age</sub> | 0.272         |                              |                         | <b>&lt;0.000</b> |                              |                         |

\* Young = 36- to 115-day-old; Old = 117- to 473-day-old; ♀ *Cbs*<sup>-/-</sup>, ♂ *Cbs*<sup>-/-</sup>, ♀ *Cbs*<sup>+/-</sup> and ♂ *Cbs*<sup>+/-</sup>.

**Supplementary Table S4. Brain TL and *Tert* mRNA expression in *Cbs*<sup>-/-</sup> and *Cbs*<sup>+/-</sup> mice stratified by sex and age.**

| Genotype (n)                   | Sex (n) | Age*                    | Rel. brain TL, T/S |                              |                         | Rel. brain <i>Tert</i> /β-actin mRNA |                              |                         |
|--------------------------------|---------|-------------------------|--------------------|------------------------------|-------------------------|--------------------------------------|------------------------------|-------------------------|
|                                |         |                         | Mean $\pm$ SD      | <i>P</i> <sub>genotype</sub> | <i>P</i> <sub>sex</sub> | Mean $\pm$ SD                        | <i>P</i> <sub>genotype</sub> | <i>P</i> <sub>sex</sub> |
| <i>Cbs</i> <sup>-/-</sup> (19) | ♀ (10)  | young                   | 0.73 $\pm$ 0.09    | 0.527                        | 0.159                   | 1.29 $\pm$ 0.33                      | 0.916                        | <b>0.017</b>            |
|                                |         | old                     | 0.95 $\pm$ 0.22    | 0.948                        | <b>0.010</b>            | 0.87 $\pm$ 0.35                      | 0.275                        | 0.352                   |
|                                |         | <i>P</i> <sub>age</sub> | 0.095              |                              |                         | 0.154                                |                              |                         |
|                                | ♂ (9)   | young                   | 0.94 $\pm$ 0.22    | 0.504                        |                         | 0.55 $\pm$ 0.17                      | <b>0.035</b>                 |                         |
|                                |         | old                     | 1.53 $\pm$ 0.34    | 0.155                        |                         | 0.78 $\pm$ 0.23                      | 0.423                        |                         |
|                                |         | <i>P</i> <sub>age</sub> | 0.063              |                              |                         | 0.184                                |                              |                         |
| <i>Cbs</i> <sup>+/-</sup> (24) | ♀ (10)  | young                   | 1.00 $\pm$ 0.78    |                              | 0.746                   | 1.27 $\pm$ 0.32                      |                              | 0.978                   |
|                                |         | old                     | 0.96 $\pm$ 0.32    |                              | 0.273                   | 1.28 $\pm$ 0.61                      |                              | 0.067                   |
|                                |         | <i>P</i> <sub>age</sub> | 0.916              |                              |                         | 0.977                                |                              |                         |
|                                | ♂ (14)  | young                   | 1.11 $\pm$ 0.24    |                              |                         | 1.26 $\pm$ 0.39                      |                              |                         |
|                                |         | old                     | 1.17 $\pm$ 0.26    |                              |                         | 0.66 $\pm$ 0.21                      |                              |                         |
|                                |         | <i>P</i> <sub>age</sub> | 0.702              |                              |                         | <b>0.022</b>                         |                              |                         |

\* Young = 63- to 66-day-old; Old = 354- to 408-day-old.

Supplementary Table S5. Liver TL and *Tert* mRNA expression in *Cbs*<sup>-/-</sup> and *Cbs*<sup>+/-</sup> mice stratified by sex and age.

| Genotype<br>( <i>n</i> ) | Sex ( <i>n</i> ) | Age*                    | Rel. liver TL, T/S |                              |                         | Rel. liver <i>Tert</i> /β-actin mRNA |                              |                         |
|--------------------------|------------------|-------------------------|--------------------|------------------------------|-------------------------|--------------------------------------|------------------------------|-------------------------|
|                          |                  |                         | Mean ± SD          | <i>P</i> <sub>genotype</sub> | <i>P</i> <sub>sex</sub> | Mean ± SD                            | <i>P</i> <sub>genotype</sub> | <i>P</i> <sub>sex</sub> |
| Cbs <sup>-/-</sup> (19)  | ♀ (10)           | young                   | 1.08 ± 0.36        | 0.909                        | 0.353                   | 0.24 ± 0.10                          | 0.264                        | <b>0.020</b>            |
|                          |                  | old                     | 1.11 ± 0.30        | 0.186                        | <b>0.014</b>            | 2.22 ± 0.81                          | 0.512                        | <b>0.029</b>            |
|                          |                  | <i>P</i> <sub>age</sub> | 0.892              |                              |                         | <b>0.001</b>                         |                              |                         |
|                          | ♂ (9)            | young                   | 0.81 ± 0.35        | 0.415                        |                         | 0.43 ± 0.03                          | 0.859                        |                         |
|                          |                  | old                     | 0.75 ± 0.19        | 0.735                        |                         | 1.43 ± 0.47                          | 0.428                        |                         |
|                          |                  | <i>P</i> <sub>age</sub> | 0.737              |                              |                         | <b>0.008</b>                         |                              |                         |
| Cbs <sup>+/-</sup> (24)  | ♀ (10)           | young                   | 1.12 ± 0.47        |                              | 0.681                   | 0.90 ± 0.79                          |                              | 0.318                   |
|                          |                  | old                     | 1.50 ± 0.58        |                              | <b>0.018</b>            | 2.89 ± 1.07                          |                              | <b>0.012</b>            |
|                          |                  | <i>P</i> <sub>age</sub> | 0.325              |                              |                         | <b>0.010</b>                         |                              |                         |
|                          | ♂ (14)           | young                   | 1.01 ± 0.40        |                              |                         | 0.56 ± 0.14                          |                              |                         |
|                          |                  | old                     | 0.78 ± 0.23        |                              |                         | 1.43 ± 0.39                          |                              |                         |
|                          |                  | <i>P</i> <sub>age</sub> | 0.228              |                              |                         | <b>0.000</b>                         |                              |                         |

\* Young = 63- to 66-day-old; Old = 354- to 408-day-old.

| Supplementary Table S6. mtDNA levels in the blood, brain, and liver of <i>Cbs</i> <sup>-/-</sup> and <i>Cbs</i> <sup>+/-</sup> mice stratified by sex and age. |                     |                         |                          |                                     |                         |                                                       |                                     |                         |                          |                                     |                         |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|-------------------------|--------------------------|-------------------------------------|-------------------------|-------------------------------------------------------|-------------------------------------|-------------------------|--------------------------|-------------------------------------|-------------------------|
| Genotype<br>( <i>n</i> )                                                                                                                                       | Sex<br>( <i>n</i> ) | Age*                    | Rel. blood mtDNA/B2M DNA |                                     |                         | Rel. brain mtDNA/B2M DNA                              |                                     |                         | Rel. liver mtDNA/B2M DNA |                                     |                         |
|                                                                                                                                                                |                     |                         | Mean ± SD ( <i>n</i> )   | FC;<br><i>P</i> <sub>genotype</sub> | <i>P</i> <sub>sex</sub> | Mean ± SD ( <i>n</i> )                                | FC;<br><i>P</i> <sub>genotype</sub> | <i>P</i> <sub>sex</sub> | Mean ± SD ( <i>n</i> )   | FC;<br><i>P</i> <sub>genotype</sub> | <i>P</i> <sub>sex</sub> |
| <i>Cbs</i> <sup>-/-</sup><br>(21–39)                                                                                                                           | ♀<br>(11–19)        | Young                   | 1.39 ± 0.78 (8)          | 0.9;<br>0.861                       | 0.322                   | 0.73 ± 0.08 (4)                                       | 0.9;<br>0.269                       | <b>0.045</b>            | 0.44 ± 0.29 (4)          | 0.7;<br>0.321                       | 0.250                   |
|                                                                                                                                                                |                     | Old                     | 0.68 ± 0.13 (11)         | 0.8;<br>0.139                       | 0.613                   | 0.98 ± 0.23 (7)                                       | 1.0;<br>0.916                       | <b>0.002</b>            | 1.12 ± 0.49 (7)          | 0.6;<br>0.059                       | 0.525                   |
|                                                                                                                                                                |                     | <i>P</i> <sub>age</sub> | <b>0.004</b>             |                                     |                         | 0.062                                                 |                                     |                         | <b>0.036</b>             |                                     |                         |
|                                                                                                                                                                | ♂<br>(10–20)        | Young                   | 1.51 ± 1.09 (6)          | 0.7;<br>0.118                       |                         | 0.95 ± 0.14 (3)                                       | 1.1;<br>0.514                       |                         | 0.75 ± 0.32 (3)          | 1.1;<br>0.897                       |                         |
|                                                                                                                                                                |                     | Old                     | 0.76 ± 0.40 (14)         | 0.9;<br>0.641                       |                         | 1.38 ± 0.14 (7)                                       | 0.94;<br>0.922                      |                         | 1.31 ± 0.58 (7)          | 0.8;<br>0.426                       |                         |
|                                                                                                                                                                |                     | <i>P</i> <sub>age</sub> | <b>0.046</b>             |                                     |                         | <b>0.002</b>                                          |                                     |                         | 0.160                    |                                     |                         |
| <i>Cbs</i> <sup>+/-</sup><br>(22–38)                                                                                                                           | ♀<br>(9–20)         | Young                   | 1.46 ± 0.72 (14)         |                                     | <b>0.041</b>            | 0.84 ± 0.17 (4)                                       |                                     | 0.561                   | 0.68 ± 0.25 (4)          |                                     | 0.858                   |
|                                                                                                                                                                |                     | Old                     | 0.84 ± 0.75 (6)          |                                     | 0.927                   | 1.00 ± 0.38 (5)                                       |                                     | 0.264                   | 1.75 ± 0.53 (5)          |                                     | 0.620                   |
|                                                                                                                                                                |                     | <i>P</i> <sub>age</sub> | 0.103                    |                                     |                         | 0.463                                                 |                                     |                         | <b>0.004</b>             |                                     |                         |
|                                                                                                                                                                | ♂<br>(13–18)        | Young                   | 2.15 ± 0.96 (10)         |                                     |                         | 0.89 ± 0.13 (7)                                       |                                     |                         | 0.68 ± 0.22 (7)          |                                     |                         |
|                                                                                                                                                                |                     | Old                     | 0.87 ± 0.62 (8)          |                                     |                         | 1.40 ± 0.60 (7)                                       |                                     |                         | 1.58 ± 0.69 (6)          |                                     |                         |
|                                                                                                                                                                |                     | <i>P</i> <sub>age</sub> | <b>0.003</b>             |                                     |                         | <b>0.048</b>                                          |                                     |                         | <b>0.004</b>             |                                     |                         |
| * Young = 44 to 77-day-old; Old = 108–390-day-old.                                                                                                             |                     |                         |                          |                                     |                         | * Young = 63 to 66-day-old; Old = 354 to 408-day-old. |                                     |                         |                          |                                     |                         |

**Supplementary Table S7. Determinants of *Tert* mRNA in the brain and liver of *Cbs*<sup>-/-</sup> and *Cbs*<sup>+/-</sup> mice: Multiple regression analysis.**

| Variable                                         | <i>Tert</i> mRNA |                                                  |             |              |
|--------------------------------------------------|------------------|--------------------------------------------------|-------------|--------------|
|                                                  | Brain            |                                                  | Liver       |              |
|                                                  | $\beta$          | $p$                                              | $\beta$     | $p$          |
| Female ( $n = 19$ )                              |                  |                                                  |             |              |
| Age*                                             | -0.18            | 0.438                                            | <b>0.81</b> | <b>0.000</b> |
| <i>Cbs</i> genotype                              | 0.23             | 0.343                                            | 0.08        | 0.531        |
| TL                                               | 0.08             | 0.765                                            | <b>0.34</b> | <b>0.015</b> |
| F = 0.83, $p = 0.451$ ,<br>R <sup>2</sup> = 0.09 |                  | F = 25.6, $p = 0.000$ ,<br>R <sup>2</sup> = 0.76 |             |              |
| Male ( $n = 22$ )                                |                  |                                                  |             |              |
| Age*                                             | -0.31            | 0.207                                            | <b>0.84</b> | <b>0.000</b> |
| <i>Cbs</i> genotype                              | 0.41             | 0.100                                            | 0.02        | 0.908        |
| TL                                               | 0.15             | 0.716                                            | 0.13        | 0.380        |
| F = 1.9, $p = 0.187$ ,<br>R <sup>2</sup> = 0.21  |                  | F = 18.1, $p = 0.003$ ,<br>R <sup>2</sup> = 0.61 |             |              |
| All ( $n = 41$ )                                 |                  |                                                  |             |              |
| Sex                                              | <b>-0.43</b>     | <b>0.006</b>                                     | -0.13       | 0.194        |
| Age*                                             | -0.22            | 0.152                                            | <b>0.72</b> | <b>0.000</b> |
| <i>Cbs</i> genotype                              | 0.24             | 0.115                                            | 0.07        | 0.484        |
| TL                                               | 0.05             | 0.796                                            | <b>0.37</b> | <b>0.000</b> |
| F = 4.3, $p = 0.011$ ,<br>R <sup>2</sup> = 0.28  |                  | F = 28.9, $p = 0.000$ ,<br>R <sup>2</sup> = 0.69 |             |              |
| *Mouse age varied from 63 to 408 days.           |                  |                                                  |             |              |

**Supplementary Table S8. List of primers used for mouse mRNA quantification by RT-qPCR.**

| Gene name                       | Forward 5'→3'             | Reverse 5'→3'            |
|---------------------------------|---------------------------|--------------------------|
| <i>Tert</i>                     | GTGAACAGCCTCCAGACAG       | TTCCTAACACGCTGGTCAAA     |
| <i>Pai-1</i>                    | ACGCCTGGTGCTGGTGAATGC     | ACGGTGCTGCCATCAGACTTGTG  |
| <i>Mcp1</i>                     | GGGATCATCTTGCTGGTGAA      | AGGTCCCTGTCATGCTTCTG     |
| <i>p21</i>                      | GGCAGACCAGCCTGACAGAT      | TTCAGGGTTTTCTCTTGCAGAAG  |
| <i>Il-6</i>                     | TGGTACTCCAGAAGACCAGAGG    | AACGATGATGCACTTGCAGA     |
| <i>Kl</i>                       | TGTATGTGACAGCCAATGGAATCG  | GAATACGCAAAGTAGCCACAAAGG |
| <i>p16</i>                      | GAATCTTTTCGGTCGTACCC      | CGAATCTGCACCGTAGTTGA     |
| <i>Il-1<math>\beta</math></i>   | CAACCAACAAGTGATATTCTCCATG | GATCCACACTCTCCAGCTGCA    |
| <i><math>\beta</math>-actin</i> | TGTTACCAACTGGGACGACA      | GGGGTGTGAAGGTCTCAAA      |
| <i>Gapdh</i>                    | CGTCCCGTAGACAAAATGGT      | TTGATGGCAACAATCTCCAC     |