

Supplemental Table S1: Potential effects of *Osx-cre* in trabecular bone.

| Female Ts65Dn Trabecular Bone                                  |                     | AVERAGE              |                       |                   |
|--|---------------------|----------------------|-----------------------|-------------------|
|  | Percent bone volume | Trabecular thickness | Trabecular separation | Trabecular number |
| Euploid, <i>Dyrk1a</i> <sup>wt/wt</sup> , without Cre (n = 7)  | 24.66978            | 0.06931              | 0.172502857           | 3.527741429       |
| Euploid, <i>Dyrk1a</i> <sup>wt/wt</sup> , with Cre (n = 10)    | 25.92522            | 0.071803             | 0.173066              | 3.593003          |
| TTEST  | 0.687523764         | 0.282163395          | 0.966286491           | 0.851648124       |
|  |                     |                      |                       |                   |
| Trisomic, <i>Dyrk1a</i> <sup>wt/wt</sup> , without Cre (n = 7) | 23.61766429         | 0.068812857          | 0.189802857           | 3.34176           |
| Trisomic, <i>Dyrk1a</i> <sup>wt/wt</sup> , with Cre (n = 4)    | 18.918995           | 0.0643975            | 0.2075125             | 2.9536925         |
| TTEST  | 0.435821224         | 0.206134615          | 0.643229452           | 0.592789407       |
|  |                     |                      |                       |                   |
| Male Ts65Dn Trabecular Bone                                    |                     | Average              |                       |                   |
|  | Percent bone volume | Trabecular thickness | Trabecular separation | Trabecular number |
| Euploid, <i>Dyrk1a</i> <sup>wt/wt</sup> , without Cre (n = 3)  | 38.00312            | 0.07768              | 0.123517              | 4.888703          |
| Euploid, <i>Dyrk1a</i> <sup>wt/wt</sup> , with Cre (n = 6)     | 32.29261            | 0.079805             | 0.15032               | 3.975463          |
| TTEST  | 0.3688              | 0.7452               | 0.1957                | 0.1321            |
|  |                     |                      |                       |                   |
|  | Percent bone volume | Trabecular thickness | Trabecular separation | Trabecular number |
| Trisomic, <i>Dyrk1a</i> <sup>wt/wt</sup> , without Cre (n = 2) | 21.63789            | 0.06913              | 0.18444               | 3.086785          |
| Trisomic, <i>Dyrk1a</i> <sup>wt/wt</sup> , with Cre (n = 1)    | 16.16818            | 0.06498              | 0.20155               | 2.48816           |

Supplemental Table S2: Potential effects of *Osx-cre* in cortical bone.

| Female Ts65Dn Cortical Bone                                    |                     | AVERAGE               |                         |                            |                       |                         |
|--|---------------------|-----------------------|-------------------------|----------------------------|-----------------------|-------------------------|
|  | Total CSA<br>(mm^2) | Marrow Area<br>(mm^2) | Cortical Area<br>(mm^2) | Cortical<br>Thickness (mm) | Periosteal BS<br>(mm) | Endocortical BS<br>(mm) |
| Euploid, <i>Dyrk1a</i> <sup>wt/wt</sup> , without Cre (n = 7)  | 1.487927225         | 0.758576568           | 0.729350657             | 0.197531852                | 5.142633937           | 3.806404556             |
| Euploid, <i>Dyrk1a</i> <sup>wt/wt</sup> , with Cre (n = 10)    | 1.394176879         | 0.715162401           | 0.679014478             | 0.189641532                | 4.993670831           | 3.674091913             |
| TTEST  | 0.188586643         | 0.327784207           | 0.145894728             | 0.22764112                 | 0.182866807           | 0.225663145             |
|  |                     |                       |                         |                            |                       |                         |
| Trisomic, <i>Dyrk1a</i> <sup>wt/wt</sup> , without Cre (n = 7) | 1.385034276         | 0.694305233           | 0.690729043             | 0.19402097                 | 5.014592042           | 3.663213009             |
| Trisomic, <i>Dyrk1a</i> <sup>wt/wt</sup> , with Cre (n = 4)    | 1.165305149         | 0.618837131           | 0.546468018             | 0.165553084                | 4.609058042           | 3.410917317             |
| TTEST  | 0.003190947         | 0.118581785           | 0.000856245             | 0.005145779                | 0.001164143           | 0.040335489             |
|  |                     |                       |                         |                            |                       |                         |
| Male Ts65Dn Cortical Bone                                      |                     | AVERAGE               |                         |                            |                       |                         |
|  | Total CSA<br>(mm^2) | Marrow Area<br>(mm^2) | Cortical Area<br>(mm^2) | Cortical<br>Thickness (mm) | Periosteal BS<br>(mm) | Endocortical BS<br>(mm) |
| Euploid, <i>Dyrk1a</i> <sup>wt/wt</sup> , without Cre (n = 3)  | 1.8408              | 0.9072                | 0.9336                  | 0.2288                     | 5.7052                | 4.1598                  |
| Euploid, <i>Dyrk1a</i> <sup>wt/wt</sup> , with Cre (n = 6)     | 1.6099              | 0.8185                | 0.7914                  | 0.2053                     | 5.3143                | 3.8938                  |
| TTEST  | 0.1087              | 0.2865                | 0.0461                  | 0.0358                     | 0.0663                | 0.1894                  |
|  |                     |                       |                         |                            |                       |                         |
| AVERAGE  |                     |                       |                         |                            |                       |                         |
|  | Total CSA<br>(mm^2) | Marrow Area<br>(mm^2) | Cortical Area<br>(mm^2) | Cortical<br>Thickness (mm) | Periosteal BS<br>(mm) | Endocortical BS<br>(mm) |
| Trisomic, <i>Dyrk1a</i> <sup>wt/wt</sup> , without Cre (n = 2) | 1.4292              | 0.6746                | 0.7546                  | 0.211                      | 5.0925                | 3.5646                  |
| Trisomic, <i>Dyrk1a</i> <sup>wt/wt</sup> , with Cre (n = 1)    | 1.0887              | 0.5323                | 0.5564                  | 0.1765                     | 4.4812                | 3.1757                  |

Supplemental Table S3: Potential effects of *Osx-cre* in mechanical parameters.

| Female Mechanical Testing                                     |             |             | AVERAGE         |                    |                            |                             |                        |                  |                    |                     |                 |                    |                       |                      |                   |               |                  |                 |  |
|---|-------------|-------------|-----------------|--------------------|----------------------------|-----------------------------|------------------------|------------------|--------------------|---------------------|-----------------|--------------------|-----------------------|----------------------|-------------------|---------------|------------------|-----------------|--|
|   | I_ap (mm^4) | c_med (μm)  | Yield Force (N) | Ultimate Force (N) | Displacement to Yield (μm) | Postyield Displacement (μm) | Total Displacment (μm) | Stiffness (N/mm) | Work to Yield (mJ) | Postyield Work (mJ) | Total Work (mJ) | Yield Stress (MPa) | Ultimate Stress (MPa) | Strain to Yield (μ?) | Total Strain (μ?) | Modulus (GPa) | Resilience (MPa) | Toughness (MPa) |  |
| Euploid, <i>Dyrk1a</i> <sup>wt/wt</sup> ,without Cre (n = 6)  | 0.099302    | 805.1038667 | 6.687666667     | 11.39416667        | 113.0123333                | 1076.333333                 | 1189.345667            | 63.556           | 0.4327             | 8.9532              | 9.3859          | 80.925             | 141.55                | 30535                | 318842            | 2.977         | 1.3705           | 31.039          |  |
| Euploid, <i>Dyrk1a</i> <sup>wt/wt</sup> ,with Cre (n = 7)     | 0.087256714 | 777.7667286 | 6.066857143     | 10.92285714        | 103.3204429                | 939                         | 1042.320443            | 64.124           | 0.3287             | 7.1869              | 7.5156          | 81.827             | 146.27                | 26745                | 270782            | 3.3232        | 1.1528           | 27.078          |  |
| TTEST   | 0.28209725  | 0.28209725  | 0.281369349     | 0.494886693        | 0.643662933                | 0.438399096                 | 0.512064086            | 0.4778           | 0.914              | 0.3543              | 0.1754          | 0.1586             | 0.8853                | 0.5735               | 0.3261            | 0.3888        | 0.1754           | 0.4508          |  |
|   |             |             |                 |                    |                            |                             |                        |                  |                    |                     |                 |                    |                       |                      |                   |               |                  |                 |  |
| Trisomic, <i>Dyrk1a</i> <sup>wt/wt</sup> ,without Cre (n = 4) | 0.08351375  | 795.4505    | 7.433           | 10.91675           | 143.957725                 | 419.75                      | 563.707725             | 56.506           | 0.6291             | 4.1115              | 4.7405          | 104.9              | 156.47                | 38254                | 149203            | 3.0808        | 2.2898           | 18.269          |  |
| Trisomic, <i>Dyrk1a</i> <sup>wt/wt</sup> ,with Cre (n = 4)    | 0.058926    | 697.7579    | 3.19225         | 7.62925            | 92.350325                  | 768.25                      | 860.600325             | 38.87            | 0.1611             | 4.5282              | 4.6893          | 58.695             | 139.68                | 21530                | 199393            | 3.0381        | 0.7002           | 20.531          |  |
| TTEST   | 0.037449058 | 0.037449058 | 4.16381E-05     | 0.009270851        | 0.002598123                | 0.117142111                 | 0.10892131             | 0.1309           | 0.0238             | 0.0989              | 0.6898          | 0.9539             | 0.0081                | 0.2356               | 0.0715            | 0.2343        | 0.9167           | 0.079           |  |