

## Two-way RM ANOVA

| Figure | Time x Genotype     |          | Time                     |          | Genotype           |          | Subject             |          |
|--------|---------------------|----------|--------------------------|----------|--------------------|----------|---------------------|----------|
| 1C     | F (3, 54) = 8.068   | P=0.0002 | F (2.054, 36.97) = 30.86 | P<0.0001 | F (1, 18) = 14.08  | P=0.0015 | F (18, 54) = 5.946  | P<0.0001 |
| 1D     | F (12, 168) = 1.932 | P=0.0337 | F (4, 168) = 26.06       | P<0.0001 | F (3, 42) = 0.2072 | P=0.8908 | F (42, 168) = 181.1 | P<0.0001 |

## Two-way ANOVA

| Figure                 | Running x Genotype  |          | Running             |          | Genotype            |          |
|------------------------|---------------------|----------|---------------------|----------|---------------------|----------|
| 2A                     | F (1, 36) = 0.7865  | P=0.3810 | F (1, 36) = 6.342   | P=0.0164 | F (1, 36) = 11.22   | P=0.0019 |
| 2B                     | F (1, 36) = 1.557   | P=0.2202 | F (1, 36) = 10.43   | P=0.0027 | F (1, 36) = 14.81   | P=0.0005 |
| 2C                     | F (1, 36) = 5.755   | P=0.0217 | F (1, 36) = 1.626   | P=0.2104 | F (1, 36) = 3.457   | P=0.0712 |
| 2D                     | F (1, 36) = 0.01357 | P=0.9079 | F (1, 36) = 1.519   | P=0.2257 | F (1, 36) = 0.04194 | P=0.8389 |
| 2E                     | F (1, 44) = 4.188   | P=0.0467 | F (1, 44) = 4.820   | P=0.0334 | F (1, 44) = 152.2   | P<0.0001 |
| 2F                     | F (1, 51) = 1.077   | P=0.3042 | F (1, 51) = 2.915   | P=0.0938 | F (1, 51) = 12.50   | P=0.0009 |
| 3A                     | F (1, 24) = 0.1096  | P=0.7435 | F (1, 24) = 29.71   | P<0.0001 | F (1, 24) = 7.167   | P=0.0132 |
| 3C                     | F (1, 18) = 0.1978  | P=0.6618 | F (1, 18) = 10.53   | P=0.0045 | F (1, 18) = 0.6761  | P=0.4217 |
| 3D                     | F (1, 12) = 11.35   | P=0.0056 | F (1, 12) = 65.30   | P<0.0001 | F (1, 12) = 93.88   | P<0.0001 |
| 3E                     | F (1, 12) = 18.84   | P=0.0010 | F (1, 12) = 3.821   | P=0.0743 | F (1, 12) = 4.085   | P=0.0662 |
| 4A (left)              | F (1, 12) = 8.184   | P=0.0143 | F (1, 12) = 9.481   | P=0.0096 | F (1, 12) = 20.54   | P=0.0007 |
| 4A (right)             | F (1, 20) = 6.489   | P=0.0192 | F (1, 20) = 10.72   | P=0.0038 | F (1, 20) = 5.881   | P=0.0249 |
| 4B (left)              | F (1, 12) = 38.48   | P<0.0001 | F (1, 12) = 46.69   | P<0.0001 | F (1, 12) = 34.77   | P<0.0001 |
| 4B (right)             | F (1, 12) = 11.97   | P=0.0047 | F (1, 12) = 13.60   | P=0.0031 | F (1, 12) = 1.506   | P=0.2434 |
| 5A                     | F (1, 14) = 7.788   | P=0.0144 | F (1, 14) = 0.02021 | P=0.8890 | F (1, 14) = 0.07663 | P=0.7860 |
| 5C (filopodium + thin) | F (1, 14) = 15.75   | P=0.0014 | F (1, 14) = 18.53   | P=0.0007 | F (1, 14) = 22.88   | P=0.0003 |
| 5C (stubby)            | F (1, 14) = 0.2823  | P=0.6035 | F (1, 14) = 1.010   | P=0.3319 | F (1, 14) = 5.664   | P=0.0321 |
| 5C (mushroom)          | F (1, 14) = 28.71   | P=0.0001 | F (1, 14) = 31.58   | P<0.0001 | F (1, 14) = 55.71   | P<0.0001 |
| 5C (cup)               | F (1, 14) = 0.1728  | P=0.6840 | F (1, 14) = 3.909   | P=0.0681 | F (1, 14) = 6.903   | P=0.0199 |
| 5D                     | F (1, 14) = 67.07   | P<0.0001 | F (1, 14) = 149.0   | P<0.0001 | F (1, 14) = 262.9   | P<0.0001 |
| 6B                     | F (1, 12) = 1.389   | P=0.2614 | F (1, 12) = 64.27   | P<0.0001 | F (1, 12) = 8.001   | P=0.0152 |
| 6C                     | F (1, 47) = 0.4684  | P=0.4971 | F (1, 47) = 33.53   | P<0.0001 | F (1, 47) = 2.902   | P=0.0951 |

## Uncorrected Fisher's LSD

**Figure 1C**

| Uncorrected Fisher's LSD                            | Mean Diff. | 95.00% CI of diff. | Significant | Summary | Individual P Value |
|---|------------|--------------------|-------------|---------|--------------------|
| Runner <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y |            |                    |             |         |                    |
| Day 7   | 4844       | 193.4 to 9495      | Yes         | *       | 0.0422             |
| Day 14  | 11271      | 716.6 to 21825     | Yes         | *       | 0.0386             |
| Day 21  | 26271      | 12477 to 40065     | Yes         | **      | 0.0013             |
| Day 28  | 15661      | 4884 to 26438      | Yes         | **      | 0.0069             |
| Runner <i>Cdkl5</i> +/Y                             |            |                    |             |         |                    |
| Day 7 vs. Day 14                                    | -13452     | -20608 to -6296    | Yes         | **      | 0.003              |
| Day 7 vs. Day 21                                    | -31110     | -41818 to -20401   | Yes         | ***     | 0.0002             |
| Day 7 vs. Day 28                                    | -21384     | -29482 to -13287   | Yes         | ***     | 0.0004             |
| Day 14 vs. Day 21                                   | -17658     | -23930 to -11385   | Yes         | ***     | 0.0003             |
| Day 14 vs. Day 28                                   | -7932      | -15794 to -70.42   | Yes         | *       | 0.0485             |
| Day 21 vs. Day 28                                   | 9726       | -833.4 to 20285    | No          | ns      | 0.0658             |
| Runner <i>Cdkl5</i> -/Y                             |            |                    |             |         |                    |
| Day 7 vs. Day 14                                    | -7026      | -11131 to -2920    | Yes         | **      | 0.0031             |
| Day 7 vs. Day 21                                    | -9683      | -17284 to -2082    | Yes         | *       | 0.0172             |
| Day 7 vs. Day 28                                    | -10567     | -19219 to -1916    | Yes         | *       | 0.0211             |
| Day 14 vs. Day 21                                   | -2658      | -8081 to 2765      | No          | ns      | 0.3038             |
| Day 14 vs. Day 28                                   | -3542      | -9446 to 2362      | No          | ns      | 0.2135             |
| Day 21 vs. Day 28                                   | -884.2     | -3320 to 1552      | No          | ns      | 0.4412             |

**Figure 1D**

| Uncorrected Fisher's LSD                                  | Predicted (LS) Mean Diff. | 95.00% CI of diff. | Significant | Summary | Individual P Value |
|---|---------------------------|--------------------|-------------|---------|--------------------|
| Day 1   |                           |                    |             |         |                    |
| Sedentary <i>Cdkl5</i> +/Y vs. Sedentary <i>Cdkl5</i> -/Y | 1.185                     | -1.515 to 3.886    | No          | ns      | 0.3878             |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y    | 0.05667                   | -2.578 to 2.691    | No          | ns      | 0.9662             |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> +/Y    | 0.69                      | -2.288 to 3.668    | No          | ns      | 0.6483             |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> -/Y    | -1.129                    | -3.968 to 1.711    | No          | ns      | 0.4341             |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> +/Y    | -0.4955                   | -3.656 to 2.665    | No          | ns      | 0.7576             |
| Runner <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> +/Y       | 0.6333                    | -2.472 to 3.738    | No          | ns      | 0.688              |

|   |         |                 |    |    |        |
|---|---------|-----------------|----|----|--------|
| Day 8   |         |                 |    |    |        |
| Sedentary <i>Cdkl5</i> +/Y vs. Sedentary <i>Cdkl5</i> -/Y | 0.36    | -2.340 to 3.060 | No | ns | 0.7929 |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y    | -0.54   | -3.175 to 2.095 | No | ns | 0.6866 |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> +/Y    | 0.3975  | -2.581 to 3.376 | No | ns | 0.7927 |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> -/Y    | -0.9    | -3.739 to 1.939 | No | ns | 0.5328 |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> +/Y    | 0.0375  | -3.123 to 3.198 | No | ns | 0.9814 |
| Runner <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> +/Y       | 0.9375  | -2.167 to 4.042 | No | ns | 0.5523 |
| Day 15  |         |                 |    |    |        |
| Sedentary <i>Cdkl5</i> +/Y vs. Sedentary <i>Cdkl5</i> -/Y | 0.02727 | -2.673 to 2.728 | No | ns | 0.9841 |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y    | -0.825  | -3.460 to 1.810 | No | ns | 0.5377 |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> +/Y    | 0.275   | -2.703 to 3.253 | No | ns | 0.8557 |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> -/Y    | -0.8523 | -3.692 to 1.987 | No | ns | 0.5547 |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> +/Y    | 0.2477  | -2.913 to 3.409 | No | ns | 0.8774 |
| Runner <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> +/Y       | 1.1     | -2.005 to 4.205 | No | ns | 0.4857 |
| Day 22  |         |                 |    |    |        |
| Sedentary <i>Cdkl5</i> +/Y vs. Sedentary <i>Cdkl5</i> -/Y | 0.5158  | -2.184 to 3.216 | No | ns | 0.7069 |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y    | -0.6683 | -3.303 to 1.966 | No | ns | 0.6175 |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> +/Y    | 0.1942  | -2.784 to 3.172 | No | ns | 0.8979 |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> -/Y    | -1.184  | -4.024 to 1.655 | No | ns | 0.412  |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> +/Y    | -0.3216 | -3.482 to 2.839 | No | ns | 0.8412 |
| Runner <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> +/Y       | 0.8625  | -2.242 to 3.967 | No | ns | 0.5845 |
| Day 30  |         |                 |    |    |        |
| Sedentary <i>Cdkl5</i> +/Y vs. Sedentary <i>Cdkl5</i> -/Y | 0.3558  | -2.344 to 3.056 | No | ns | 0.7953 |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y    | -0.9117 | -3.546 to 1.723 | No | ns | 0.4959 |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> +/Y    | -0.1658 | -3.144 to 2.812 | No | ns | 0.9127 |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> -/Y    | -1.267  | -4.107 to 1.572 | No | ns | 0.3799 |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> +/Y    | -0.5216 | -3.682 to 2.639 | No | ns | 0.7453 |
| Runner <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> +/Y       | 0.7458  | -2.359 to 3.851 | No | ns | 0.6363 |

## Figure 2A

| Uncorrected Fisher's LSD                                  | Mean Diff. | 95.00% CI of diff. | Significant | Summary | Individual P Value |
|---|------------|--------------------|-------------|---------|--------------------|
| Sedentary <i>Cdkl5</i> +/Y vs. Sedentary <i>Cdkl5</i> -/Y | -1418      | -2248 to -587.2    | Yes         | **      | 0.0014             |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> +/Y    | 546.1      | -386.3 to 1478     | No          | ns      | 0.2427             |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y    | -278       | -1251 to 694.6     | No          | ns      | 0.5657             |

|  |        |                |     |     |        |
|--|--------|----------------|-----|-----|--------|
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> +/Y | 1964   | 1017 to 2911   | Yes | *** | 0.0002 |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> -/Y | 1140   | 152.9 to 2126  | Yes | *   | 0.0248 |
| Runner <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y    | -824.1 | -1898 to 249.7 | No  | ns  | 0.1283 |

#### Figure 2B

| Uncorrected Fisher's LSD                                  | Mean Diff. | 95.00% CI of diff. | Significant | Summary | Individual P Value |
|---|------------|--------------------|-------------|---------|--------------------|
| Sedentary <i>Cdkl5</i> +/Y vs. Sedentary <i>Cdkl5</i> -/Y | -2.832     | -4.211 to -1.453   | Yes         | ***     | 0.0002             |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> +/Y    | 1.101      | -0.4469 to 2.649   | No          | ns      | 0.1578             |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y    | -0.3443    | -1.959 to 1.271    | No          | ns      | 0.668              |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> +/Y    | 3.933      | 2.361 to 5.505     | Yes         | ****    | <0.0001            |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> -/Y    | 2.488      | 0.8494 to 4.126    | Yes         | **      | 0.004              |
| Runner <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y       | -1.445     | -3.228 to 0.3374   | No          | ns      | 0.1088             |

#### Figure 2C

| Uncorrected Fisher's LSD                                  | Mean Diff. | 95.00% CI of diff. | Significant | Summary | Individual P Value |
|---|------------|--------------------|-------------|---------|--------------------|
| Sedentary <i>Cdkl5</i> +/Y vs. Sedentary <i>Cdkl5</i> -/Y | -57.73     | -91.38 to -24.09   | Yes         | **      | 0.0013             |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> +/Y    | -15.23     | -53.00 to 22.53    | No          | ns      | 0.4187             |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y    | -7.919     | -47.32 to 31.48    | No          | ns      | 0.686              |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> +/Y    | 42.5       | 4.137 to 80.86     | Yes         | *       | 0.0309             |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> -/Y    | 49.81      | 9.841 to 89.78     | Yes         | *       | 0.016              |
| Runner <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y       | 7.314      | -36.18 to 50.81    | No          | ns      | 0.7351             |

#### Figure 2D

| Uncorrected Fisher's LSD                                  | Mean Diff. | 95.00% CI of diff. | Significant | Summary | Individual P Value |
|---|------------|--------------------|-------------|---------|--------------------|
| Sedentary <i>Cdkl5</i> +/Y vs. Sedentary <i>Cdkl5</i> -/Y | -2.077     | -60.45 to 56.29    | No          | ns      | 0.9429             |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> +/Y    | -26.25     | -91.77 to 39.27    | No          | ns      | 0.4218             |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y    | -33.81     | -102.2 to 34.55    | No          | ns      | 0.3225             |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> +/Y    | -24.18     | -90.73 to 42.38    | No          | ns      | 0.4661             |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> -/Y    | -31.73     | -101.1 to 37.61    | No          | ns      | 0.3596             |
| Runner <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y       | -7.556     | -83.02 to 67.91    | No          | ns      | 0.8402             |

#### Figure 2E

| Uncorrected Fisher's LSD                                  | Mean Diff. | 95.00% CI of diff. | Significant | Summary | Individual P Value |
|---|------------|--------------------|-------------|---------|--------------------|
| Sedentary <i>Cdkl5</i> +/Y vs. Sedentary <i>Cdkl5</i> -/Y | -65.27     | -81.30 to -49.25   | Yes         | ****    | <0.0001            |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> +/Y    | -0.946     | -19.60 to 17.71    | No          | ns      | 0.919              |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y    | -92.17     | -107.8 to -76.57   | Yes         | ****    | <0.0001            |

|  |        |                  |     |      |         |
|--|--------|------------------|-----|------|---------|
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> +/Y | 64.32  | 44.08 to 84.57   | Yes | **** | <0.0001 |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> -/Y | -26.9  | -44.38 to -9.422 | Yes | **   | 0.0034  |
| Runner <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y    | -91.23 | -111.1 to -71.31 | Yes | **** | <0.0001 |

#### Figure 2F

| Uncorrected Fisher's LSD                                  | Mean Diff. | 95.00% CI of diff. | Significant | Summary | Individual P Value |
|---|------------|--------------------|-------------|---------|--------------------|
| Sedentary <i>Cdkl5</i> +/Y vs. Sedentary <i>Cdkl5</i> -/Y | 168        | 88.41 to 247.5     | Yes         | ****    | <0.0001            |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> +/Y    | -24.59     | -131.5 to 82.32    | No          | ns      | 0.6463             |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y    | 67.14      | -30.33 to 164.6    | No          | ns      | 0.1727             |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> +/Y    | -192.6     | -303.2 to -81.92   | Yes         | ***     | 0.001              |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> -/Y    | -100.8     | -202.4 to 0.7349   | No          | ns      | 0.0516             |
| Runner <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y       | 91.73      | -32.42 to 215.9    | No          | ns      | 0.1441             |

#### Figure 3A

| Uncorrected Fisher's LSD                                  | Mean Diff. | 95.00% CI of diff. | Significant | Summary | Individual P Value |
|---|------------|--------------------|-------------|---------|--------------------|
| Sedentary <i>Cdkl5</i> +/Y vs. Sedentary <i>Cdkl5</i> -/Y | 0.7363     | -0.2430 to 1.716   | No          | ns      | 0.1338             |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> +/Y    | -1.815     | -2.731 to -0.8987  | Yes         | ***     | 0.0004             |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y    | -0.8706    | -1.787 to 0.04545  | No          | ns      | 0.0615             |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> +/Y    | -2.551     | -3.467 to -1.635   | Yes         | ****    | <0.0001            |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> -/Y    | -1.607     | -2.523 to -0.6909  | Yes         | **      | 0.0014             |
| Runner <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y       | 0.9441     | 0.09600 to 1.792   | Yes         | *       | 0.0306             |

#### Figure 3C

| Uncorrected Fisher's LSD                                  | Mean Diff. | 95.00% CI of diff.  | Significant | Summary | Individual P Value |
|---|------------|---------------------|-------------|---------|--------------------|
| Sedentary <i>Cdkl5</i> +/Y vs. Sedentary <i>Cdkl5</i> -/Y | 0.01149    | -0.09016 to 0.1131  | No          | ns      | 0.8149             |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> +/Y    | -0.1123    | -0.2051 to -0.01951 | Yes         | *       | 0.0204             |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y    | -0.07375   | -0.1618 to 0.01429  | No          | ns      | 0.0954             |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> +/Y    | -0.1238    | -0.2166 to -0.03101 | Yes         | *       | 0.0118             |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> -/Y    | -0.08524   | -0.1733 to 0.002800 | No          | ns      | 0.0569             |
| Runner <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y       | 0.03857    | -0.03907 to 0.1162  | No          | ns      | 0.3105             |

#### Figure 3D

| Uncorrected Fisher's LSD                                  | Mean Diff. | 95.00% CI of diff. | Significant | Summary | Individual P Value |
|---|------------|--------------------|-------------|---------|--------------------|
| Sedentary <i>Cdkl5</i> +/Y vs. Sedentary <i>Cdkl5</i> -/Y | 0.8745     | 0.6682 to 1.081    | Yes         | ****    | <0.0001            |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> +/Y    | -0.3155    | -0.5219 to -0.1092 | Yes         | **      | 0.006              |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y    | 0.1077     | -0.09866 to 0.3140 | No          | ns      | 0.2777             |

|  |         |                    |     |      |         |
|--|---------|--------------------|-----|------|---------|
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> +/Y | -1.19   | -1.396 to -0.9837  | Yes | **** | <0.0001 |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> -/Y | -0.7668 | -0.9732 to -0.5605 | Yes | **** | <0.0001 |
| Runner <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y    | 0.4232  | 0.2169 to 0.6296   | Yes | ***  | 0.0008  |

### Figure 3E

| Uncorrected Fisher's LSD                                  | Mean Diff. | 95.00% CI of diff.  | Significant | Summary | Individual P Value |
|---|------------|---------------------|-------------|---------|--------------------|
| Sedentary <i>Cdkl5</i> +/Y vs. Sedentary <i>Cdkl5</i> -/Y | 0.24       | 0.1237 to 0.3563    | Yes         | ***     | 0.0007             |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> +/Y    | 0.09       | -0.02625 to 0.2063  | No          | ns      | 0.1174             |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y    | 0.0025     | -0.1138 to 0.1188   | No          | ns      | 0.9634             |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> +/Y    | -0.15      | -0.2663 to -0.03375 | Yes         | *       | 0.0157             |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> -/Y    | -0.2375    | -0.3538 to -0.1212  | Yes         | ***     | 0.0008             |
| Runner <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y       | -0.0875    | -0.2038 to 0.02875  | No          | ns      | 0.127              |

### Figure 4A (left)

| Uncorrected Fisher's LSD                                  | Mean Diff. | 95.00% CI of diff. | Significant | Summary | Individual P Value |
|---|------------|--------------------|-------------|---------|--------------------|
| Sedentary <i>Cdkl5</i> +/Y vs. Sedentary <i>Cdkl5</i> -/Y | -6.348     | -8.993 to -3.702   | Yes         | ***     | 0.0002             |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> +/Y    | 0.1875     | -2.458 to 2.833    | No          | ns      | 0.8798             |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y    | -1.248     | -3.893 to 1.398    | No          | ns      | 0.3245             |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> +/Y    | 6.535      | 3.889 to 9.181     | Yes         | ***     | 0.0002             |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> -/Y    | 5.1        | 2.454 to 7.746     | Yes         | **      | 0.0012             |
| Runner <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y       | -1.435     | -4.081 to 1.211    | No          | ns      | 0.2602             |

### Figure 4A (right)

| Uncorrected Fisher's LSD                                  | Mean Diff. | 95.00% CI of diff. | Significant | Summary | Individual P Value |
|---|------------|--------------------|-------------|---------|--------------------|
| Sedentary <i>Cdkl5</i> +/Y vs. Sedentary <i>Cdkl5</i> -/Y | -1.286     | -1.909 to -0.6630  | Yes         | ***     | 0.0003             |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> +/Y    | 0.1881     | -0.5748 to 0.9510  | No          | ns      | 0.6126             |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y    | 0.2198     | -0.5431 to 0.9827  | No          | ns      | 0.5546             |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> +/Y    | 1.474      | 0.7111 to 2.237    | Yes         | ***     | 0.0007             |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> -/Y    | 1.506      | 0.7428 to 2.269    | Yes         | ***     | 0.0005             |
| Runner <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y       | 0.03166    | -0.8492 to 0.9126  | No          | ns      | 0.941              |

### Figure 4B (left)

| Uncorrected Fisher's LSD                                  | Mean Diff. | 95.00% CI of diff. | Significant | Summary | Individual P Value |
|---|------------|--------------------|-------------|---------|--------------------|
| Sedentary <i>Cdkl5</i> +/Y vs. Sedentary <i>Cdkl5</i> -/Y | -7.593     | -9.526 to -5.659   | Yes         | ****    | <0.0001            |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> +/Y    | 0.395      | -1.538 to 2.328    | No          | ns      | 0.6641             |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y    | 0.5875     | -1.346 to 2.521    | No          | ns      | 0.5204             |

|  |        |                 |     |      |         |
|--|--------|-----------------|-----|------|---------|
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> +/Y | 7.988  | 6.054 to 9.921  | Yes | **** | <0.0001 |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> -/Y | 8.18   | 6.247 to 10.11  | Yes | **** | <0.0001 |
| Runner <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y    | 0.1925 | -1.741 to 2.126 | No  | ns   | 0.8319  |

#### Figure 4B (right)

| Uncorrected Fisher's LSD                                  | Mean Diff. | 95.00% CI of diff. | Significant | Summary | Individual P Value |
|---|------------|--------------------|-------------|---------|--------------------|
| Sedentary <i>Cdkl5</i> +/Y vs. Sedentary <i>Cdkl5</i> -/Y | -0.7583    | -1.257 to -0.2598  | Yes         | **      | 0.0062             |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> +/Y    | 0.03694    | -0.4616 to 0.5355  | No          | ns      | 0.8744             |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y    | 0.3982     | -0.1004 to 0.8967  | No          | ns      | 0.1074             |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> +/Y    | 0.7953     | 0.2967 to 1.294    | Yes         | **      | 0.0046             |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> -/Y    | 1.157      | 0.6579 to 1.655    | Yes         | ***     | 0.0003             |
| Runner <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y       | 0.3613     | -0.1373 to 0.8598  | No          | ns      | 0.1404             |

#### Figure 5A

| Uncorrected Fisher's LSD                                  | Mean Diff. | 95.00% CI of diff.  | Significant | Summary | Individual P Value |
|---|------------|---------------------|-------------|---------|--------------------|
| Sedentary <i>Cdkl5</i> +/Y vs. Sedentary <i>Cdkl5</i> -/Y | 0.084      | -0.01156 to 0.1796  | No          | ns      | 0.0803             |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> +/Y    | 0.0885     | -0.01285 to 0.1899  | No          | ns      | 0.0821             |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y    | -0.014     | -0.1154 to 0.08735  | No          | ns      | 0.7714             |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> +/Y    | 0.0045     | -0.09685 to 0.1059  | No          | ns      | 0.9255             |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> -/Y    | -0.098     | -0.1994 to 0.003354 | No          | ns      | 0.057              |
| Runner <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y       | -0.1025    | -0.2093 to 0.004336 | No          | ns      | 0.0587             |

#### Figure 5C (filopodium + thin)

| Uncorrected Fisher's LSD                                  | Mean Diff. | 95.00% CI of diff. | Significant | Summary | Individual P Value |
|---|------------|--------------------|-------------|---------|--------------------|
| Sedentary <i>Cdkl5</i> +/Y vs. Sedentary <i>Cdkl5</i> -/Y | -14.26     | -18.92 to -9.599   | Yes         | ****    | <0.0001            |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> +/Y    | 0.548      | -4.393 to 5.489    | No          | ns      | 0.8154             |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y    | -0.7795    | -5.721 to 4.162    | No          | ns      | 0.7401             |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> +/Y    | 14.81      | 9.865 to 19.75     | Yes         | ****    | <0.0001            |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> -/Y    | 13.48      | 8.537 to 18.42     | Yes         | ****    | <0.0001            |
| Runner <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y       | -1.328     | -6.536 to 3.881    | No          | ns      | 0.5932             |

#### Figure 5C (stubby)

| Uncorrected Fisher's LSD                                  | Mean Diff. | 95.00% CI of diff. | Significant | Summary | Individual P Value |
|---|------------|--------------------|-------------|---------|--------------------|
| Sedentary <i>Cdkl5</i> +/Y vs. Sedentary <i>Cdkl5</i> -/Y | -2.694     | -6.861 to 1.473    | No          | ns      | 0.1873             |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> +/Y    | 2.239      | -2.181 to 6.659    | No          | ns      | 0.2957             |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y    | -2.004     | -6.424 to 2.417    | No          | ns      | 0.3475             |

|  |        |                  |     |    |        |
|--|--------|------------------|-----|----|--------|
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> +/Y | 4.933  | 0.5127 to 9.353  | Yes | *  | 0.0313 |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> -/Y | 0.6905 | -3.730 to 5.111  | No  | ns | 0.7426 |
| Runner <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y    | -4.243 | -8.902 to 0.4169 | No  | ns | 0.0711 |

#### Figure 5C (mushroom)

| Uncorrected Fisher's LSD                                  | Mean Diff. | 95.00% CI of diff. | Significant | Summary | Individual P Value |
|---|------------|--------------------|-------------|---------|--------------------|
| Sedentary <i>Cdkl5</i> +/Y vs. Sedentary <i>Cdkl5</i> -/Y | 14.64      | 11.38 to 17.91     | Yes         | ****    | <0.0001            |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> +/Y    | -0.2985    | -3.763 to 3.166    | No          | ns      | 0.856              |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y    | 2.106      | -1.358 to 5.571    | No          | ns      | 0.2132             |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> +/Y    | -14.94     | -18.41 to -11.48   | Yes         | ****    | <0.0001            |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> -/Y    | -12.54     | -16.00 to -9.073   | Yes         | ****    | <0.0001            |
| Runner <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y       | 2.405      | -1.247 to 6.057    | No          | ns      | 0.1796             |

#### Figure 5C (cup)

| Uncorrected Fisher's LSD                                  | Mean Diff. | 95.00% CI of diff. | Significant | Summary | Individual P Value |
|---|------------|--------------------|-------------|---------|--------------------|
| Sedentary <i>Cdkl5</i> +/Y vs. Sedentary <i>Cdkl5</i> -/Y | 2.304      | -0.6750 to 5.283   | No          | ns      | 0.1194             |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> +/Y    | -2.493     | -5.652 to 0.6672   | No          | ns      | 0.1128             |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y    | 0.6775     | -2.482 to 3.837    | No          | ns      | 0.6527             |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> +/Y    | -4.797     | -7.956 to -1.637   | Yes         | **      | 0.0057             |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> -/Y    | -1.627     | -4.786 to 1.533    | No          | ns      | 0.2882             |
| Runner <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y       | 3.17       | -0.1606 to 6.501   | No          | ns      | 0.0605             |

#### Figure 5D

| Uncorrected Fisher's LSD                                  | Mean Diff. | 95.00% CI of diff. | Significant | Summary | Individual P Value |
|---|------------|--------------------|-------------|---------|--------------------|
| Sedentary <i>Cdkl5</i> +/Y vs. Sedentary <i>Cdkl5</i> -/Y | 16.95      | 14.96 to 18.93     | Yes         | ****    | <0.0001            |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> +/Y    | -2.789     | -4.896 to -0.6824  | Yes         | *       | 0.0131             |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y    | 2.784      | 0.6769 to 4.890    | Yes         | *       | 0.0133             |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> +/Y    | -19.74     | -21.84 to -17.63   | Yes         | ****    | <0.0001            |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> -/Y    | -14.16     | -16.27 to -12.06   | Yes         | ****    | <0.0001            |
| Runner <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y       | 5.573      | 3.352 to 7.793     | Yes         | ****    | <0.0001            |

#### Figure 6B

| Uncorrected Fisher's LSD                                  | Mean Diff. | 95.00% CI of diff. | Significant | Summary | Individual P Value |
|---|------------|--------------------|-------------|---------|--------------------|
| Sedentary <i>Cdkl5</i> +/Y vs. Sedentary <i>Cdkl5</i> -/Y | -6.041     | -17.32 to 5.241    | No          | ns      | 0.266              |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> +/Y    | -25.04     | -36.32 to -13.76   | Yes         | ***     | 0.0004             |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y    | -39.71     | -50.99 to -28.43   | Yes         | ****    | <0.0001            |



|  |        |                  |     |      |         |
|--|--------|------------------|-----|------|---------|
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> +/Y | -19    | -30.28 to -7.714 | Yes | **   | 0.0032  |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> -/Y | -33.67 | -44.95 to -22.39 | Yes | **** | <0.0001 |
| Runner <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y    | -14.67 | -25.96 to -3.390 | Yes | *    | 0.0151  |

#### Figure 6C

| Uncorrected Fisher's LSD                                  | Mean Diff. | 95.00% CI of diff. | Significant | Summary | Individual P Value |
|---|------------|--------------------|-------------|---------|--------------------|
| Sedentary <i>Cdkl5</i> +/Y vs. Sedentary <i>Cdkl5</i> -/Y | -39.78     | -81.24 to 1.684    | No          | ns      | 0.0596             |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> +/Y    | -107.8     | -158.3 to -57.34   | Yes         | ****    | <0.0001            |
| Sedentary <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y    | -124.8     | -169.5 to -80.14   | Yes         | ****    | <0.0001            |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> +/Y    | -68.07     | -118.0 to -18.11   | Yes         | **      | 0.0086             |
| Sedentary <i>Cdkl5</i> -/Y vs. Runner <i>Cdkl5</i> -/Y    | -85.04     | -129.1 to -40.99   | Yes         | ***     | 0.0003             |
| Runner <i>Cdkl5</i> +/Y vs. Runner <i>Cdkl5</i> -/Y       | -16.98     | -69.63 to 35.68    | No          | ns      | 0.5197             |

**Table S3.** Descriptive statistics.