## Supplementary Figures

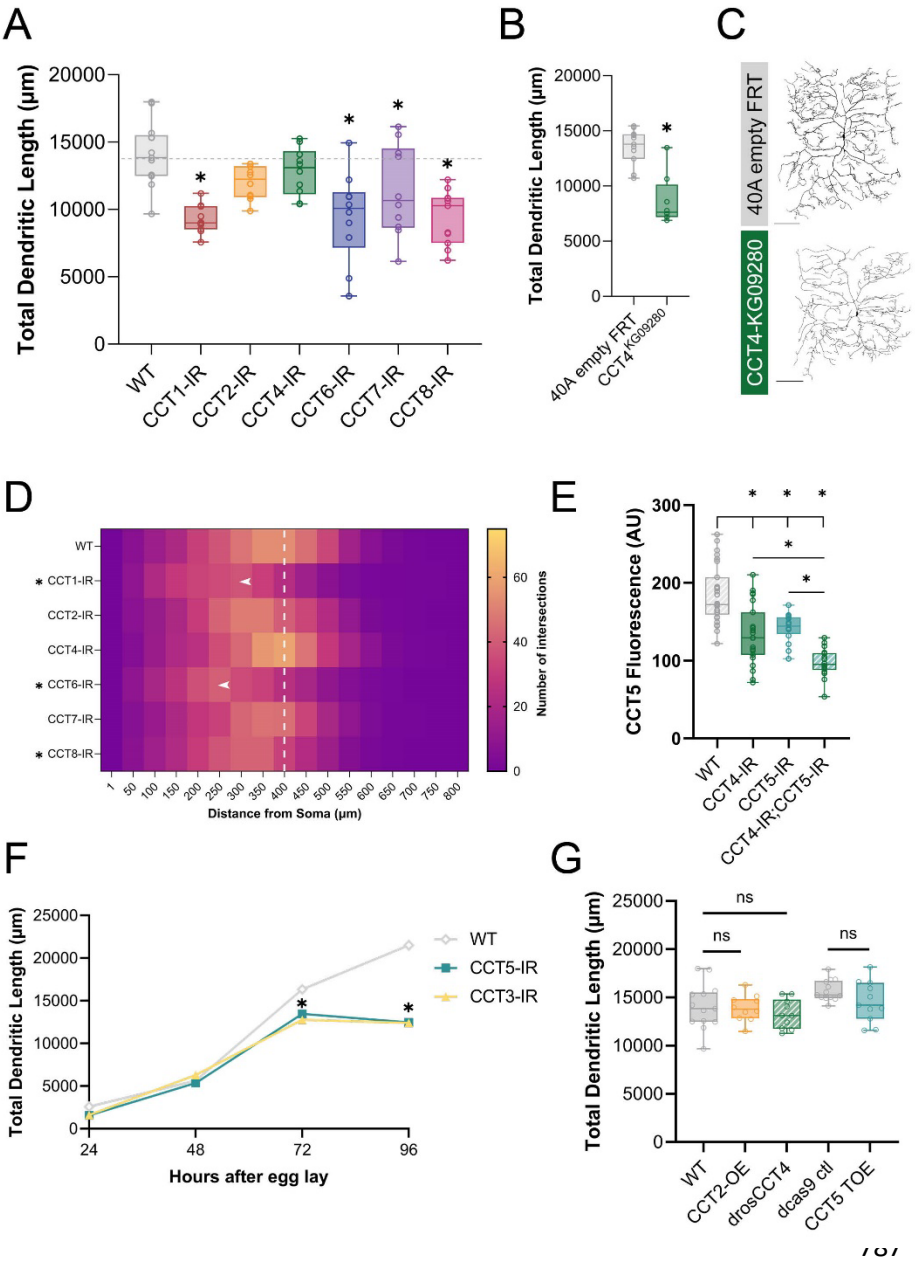


**Figure S1: CCT subunit LOF results in significant hypotrophy and underlying loss of stable MTs**. (**A**) Loss of individual CCT subunits results in significant decreases in TDL from WT controls. (**B**) Homozygous CCT4 MARCM mutant clones show significantly decreased TDL from control. (**C**) Representative images of CCT4 homozygous MARCM mutant CIV clones vs. control CIV MARCM clones (40A empty FRT). (**D**) Number of Sholl intersections mapped by color at increasing radial distances from soma (µm). White dashed line references the maximum Sholl intersections in WT neurons. Significant changes in Sholl maximum intersections are indicated by an asterisk. Arrows indicate genotypes where the radius of maximum intersections has shifted significantly from WT. (**E**) RNAi of *CCT4* or *CCT5* lead to a significant reduction in CCT5 fluorescence relative to WT as obtained through IHC. Combined knockdown of both *CCT4* and *CCT5* significantly reduces CCT5 expression from either knockdown alone. (**F**) TDL of neurons at 24, 48, 72, and 96 hours after egg lay (AEL) reveal significant decreases from WT in both *CCT5-IR* and *CCT3-IR* starting at 72 hours AEL. (**G**) Overexpression of individual CCT subunits (CCT2, CCT4, or CCT5) does not significantly alter TDL from their relevant control. In all panels * = $p < 0.05$, see **Supplementary Table S2** for detailed statistics.

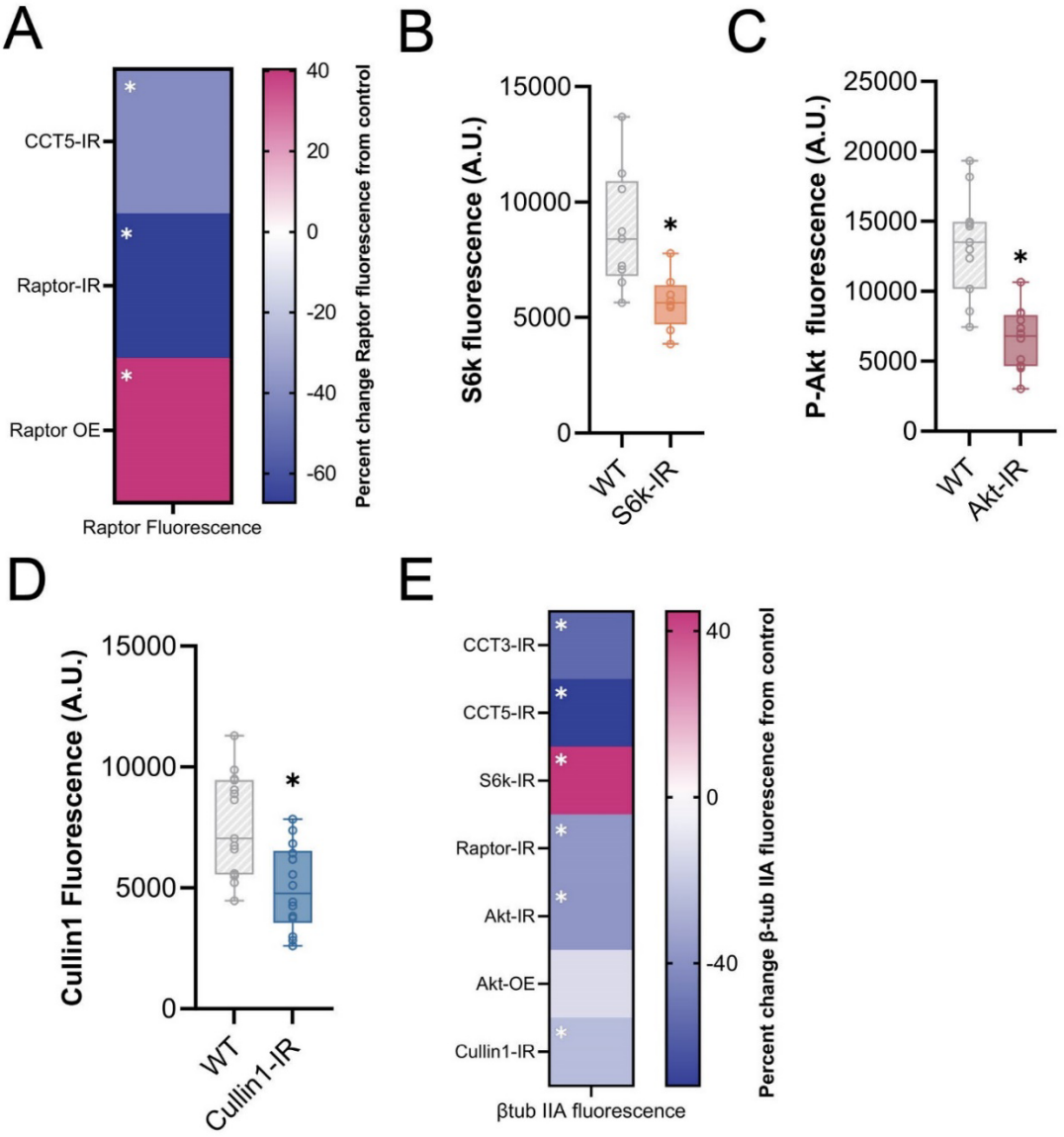


**Figure S2: Evidence for RNAi efficacy and CCT and Cullin1 regulate the TORC1 pathway *in vivo*.** (**A**) Heat map showing percent change in Raptor fluorescence of CCT5-IR or Raptor-IR knockdowns, as well as Raptor OE as compared to controls. (**B**) S6k fluorescence is significantly reduced in *S6k-IR* conditions as compared to WT. (**C**) P-Akt fluorescence is significantly reduced in *Akt-IR* conditions. (**D**) Cullin1 fluorescence is significantly reduced in *Cullin1-IR* conditions as compared to WT. (**E**) Heat map showing percent change in β -tubulin IIA for each genetic manipulation. Each experimental condition was compared to WT control and appropriate statistical comparisons were performed. In all panels * = $p < 0.05$, see **Supplementary Table S2** for detailed statistics.

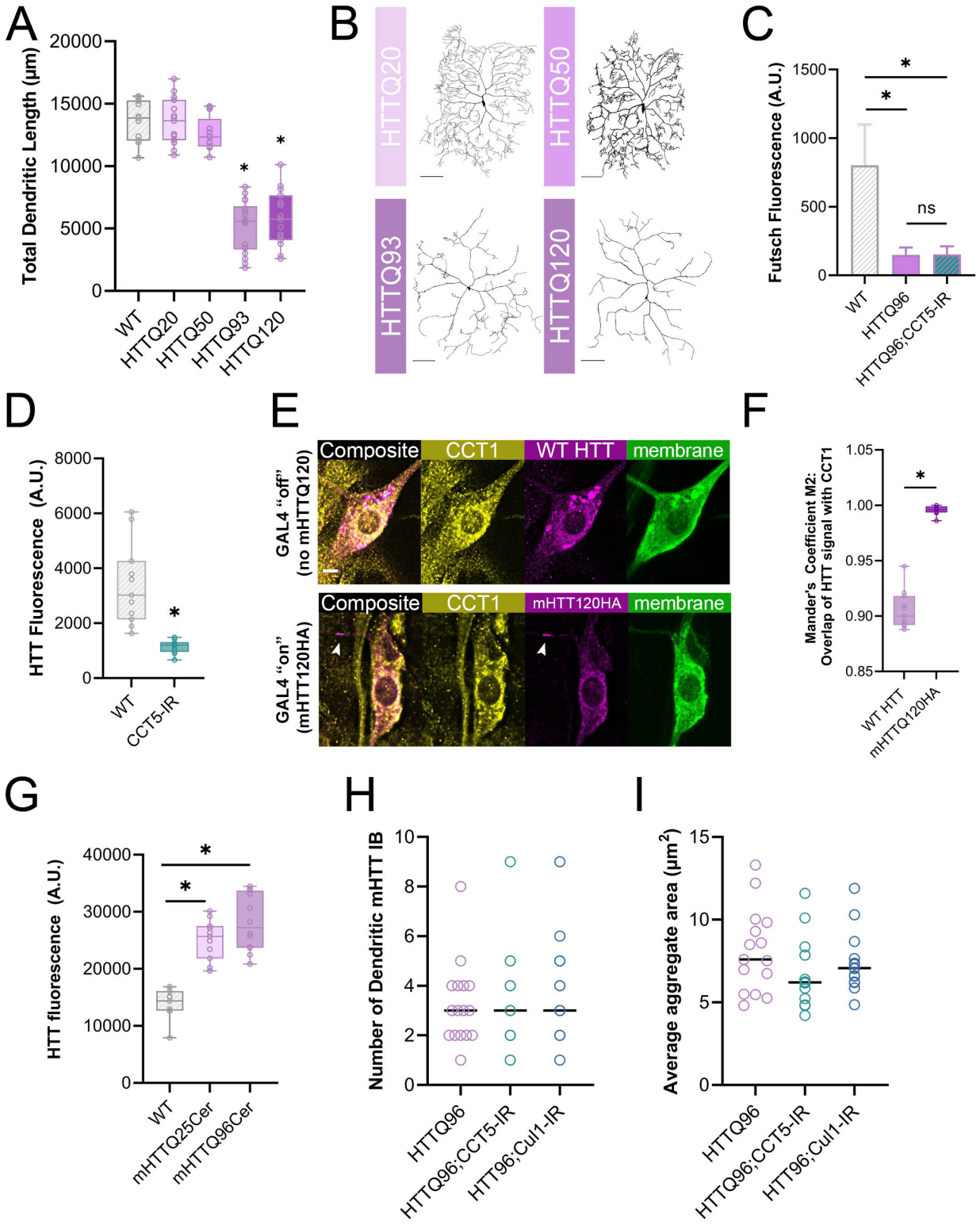


**Figure S3: mHTT aggregates are not affected by genetic combinations despite high co-expression of CCT1 and HTT.** (**A**) TDL is significantly reduced from control in neurons expressing mHTT93 or mHTT120 CAG repeats. (**B**) Representative images of CIV neurons expressing mHTT

809 polyQ repeat transgenes reveal repeat-length dependent dendritic hypotrophy. Scale bars =
810 100 µm. (**C**) Fluorescent levels of Futsch are significantly reduced in mHTTQ96 conditions and
811 are not significantly changed by additional *CCT5-IR* expression. (**D**) WT HTT fluorescence is
812 significantly reduced in *CCT5* LOF conditions. (**E**) Representative images of WT HTT distribution
813 in mHTT120HA suppressed (Gal4 "off") and mHTT120HA distribution in Gal4 "on" conditions.
814 Aggregate IB indicated by arrow in dendrite. Scale bar = 3 µm. (**F**) Mander's M2 coefficient is
815 significantly increased for co-expression of CCT1 and mHTT120HA as compared to CCT1 and WT
816 HTT in dendrites. (**G**) Expression of mHTT25-Cerulean or mHTT96-Cerulean both result in
817 significant increases in HTT fluorescence from WT. (**H**) Number of mHTT aggregate IBs does not
818 change due to *CCT5* or *Cullin1* LOF. (**I**) mHTT aggregates in mHTTQ96Cerulean conditions do not
819 change in average area due to *CCT5* or *Cullin1* LOF. In all panels * = $p < 0.05$, see
820 **Supplementary Table S2** for detailed statistics.

821

## Supplementary Genetics Table S1

| Shorthand | Full Genotype |
|---|---|
| WT | *Oregon R (ORR) (B5)* |
| CCT3-IR | *UAS-CCT3-IR (v106093)* |
| CCT5-IR | *UAS-CCT5-IR (B41818)* |
| Raptor-IR | *UAS-Raptor-IR (B34814)* |
| S6k-IR | *UAS-S6k-IR (B57016) and (B41702)* |
| Akt-IR | *UAS-Akt-IR (B8191)* |
| Cullin1-IR | *UAS-Cullin1-IR (B36601)* |
| S6k-OE | *UAS-S6k (B6910)* |
| Akt-OE | *UAS-Akt1 (B8191)* |
| Raptor OE | *UAS-Raptor-HA (B53726)* |
| Raptor-OE;CCT5-IR | *UAS-Raptor-HA;UAS-CCT5-IR* |
| S6k-OE;CCT5-IR | *UAS-S6k;UAS-CCT5-IR* |
| CCT3-IR;Cul1-IR | *UAS-CCT3-IR;UAS-Cullin1-IR* |
| HTTQ20 | *UAS-human HTTQ20 (B68412)* |
| HTTQ50 | *UAS-human HTTQ50 (B68413)* |
| HTTQ93 | *UAS-human HTTQ93 (B68418)* |
| HTTQ120 | *UAS-human HTTQ120 (B76352)* |
| HTTQ25/HTTQ25Cer | *UAS-human HTTQ25-Cerulean (B58360)* |
| HTTQ96/HTTQ96Cer | *UAS-human HTTQ96-Cerulean (B56771)* |
| HTTQ25;Cul1-IR | *UAS-human HTTQ25-Cerulean;UAS-Cullin1-IR* |
| HTTQ96;CCT5-IR | *UAS-human HTTQ96-Cerulean;UAS-CCT5-IR* |
| HTTQ25;CCT5-IR | *UAS-human HTTQ25-Cerulean; UAS-CCT5-IR* |
| mHTTQ120HA | *UAS-HTTQ120-HA (B68431)* |
| CCT1-IR | *UAS-CCT1-IR (B32854)* |
| CCT2-IR | *UAS-CCT2-IR (B34711)* |
| CCT4-IR | *UAS-CCT4-IR (v22154)* |
| CCT6-IR | *UAS-CCT6-IR (B43146)* |
| CCT7-IR | *UAS-CCT7-IR (B34931)* |
| CCT8-IR | *UAS-CCT8-IR (v103905)* |
| 40A empty FRT | *P{Car20y}25F;P{neoFRT}40A (B1816)* |
| $CCT4^{KG09280}$ | *ey-FLP1 $FRT^{40A}$ $CG5525^{KG09280}$, (DGRC 111690)* |
| CCT4-IR;CCT5-IR | *UAS-CCT4-IR (v106099);UAS-CCT5-IR* |
| CCT2-OE | *UAS-CCT2-EGFP (B53755)* |
| *drosCCT4 | *UAS-Drosophila CCT4 (k10379)* |
| CCT5 TOE | *CCT5 (guide RNA) snRNA;U6:96Aa, snRNA:U6:96Ac (B78122)* |
| | |
| **Source Abbreviations** | **Full Center Name** |
| B | Bloomington Drosophila Stock Center |
| v | Vienna Drosophila Resource Center |
| DRGC | Kyoto Drosophila Stock Center |

*Gift of Dr. Kwang-Wook Choi, KAIST, South Korea

825 Fly lines were crossed to *GAL4$^{477}$;ppk-GAL4::GFP*, with the following exceptions:

826 In *mCherry:Jupiter* experiments (Figs 3B-C, 4C-D) lines were crossed to *UAS-GMA::GFP;GAL4$^{477}$;UAS-*
827 *mCherry::Jupiter*.

828 In *tsG80* experiments (Figs 4E-F, S3E-F), as described in Methods, ORR and mHTTQ120HA were crossed
829 to *ppk::EGFP;tsGAL80;GAL4$^{ppk}$*

830 For MARCM analysis (Fig S1B-C), *CCT4$^{KG09280}$* and the 40A empty FRT control were crossed to MARCM
831 40A FLP (*GAL$^{5-40}$UAS-Venus:pm SOP-FLP#42;tubP-GAL80FRT40A [2L MARCM] DRGC 109947)* as described
832 in the Methods.

833 For developmental morphological analysis (Fig S1F), *UAS-CCT3-IR;ppk-GAL4* and *GAL4$^{477}$;UAS-CCT5-IR*
834 were crossed to *nanos-GAL4;ppk-hCD4-tdTOMATO* and compared to *+;ppk-GAL4* and *GAL4$^{477}$;+* crossed
835 to *nanos-GAL4;ppk-hCD4-tdTOMATO* as controls, respectively.

836 CRISPR-mediated overexpression line *UAS-CCT5-TOE* was crossed to *dcas9;ppk-GAL4::GFP* and
837 compared to *ORR* crossed to *dcas9;ppk-GAL4::GFP* as control (Fig S1G)

838

839 **Supplementary Statistics Table S2**

| Comparison | Passed Shapiro-Wilk Normality Test | Statistical test used | Sig | p-value | Number of neurons (N) |
|---|---|---|---|---|---|
| **Fig 1C (TDL)** | | One-way ANOVA & Dunnett's | | | |
| WT vs. CCT3-IR | Yes | | **** | <0.0001 | 13, 11 |
| WT vs. CCT5-IR | Yes | | **** | <0.0001 | 13, 12 |
| WT vs. Raptor-IR | Yes | | *** | 0.0002 | 13, 10 |
| WT vs. S6k-IR | Yes | | **** | <0.0001 | 13, 13 |
| WT vs. Akt-IR | Yes | | **** | <0.0001 | 13, 10 |
| WT vs. Cul1-IR | Yes | | *** | 0.0003 | 13, 13 |
| WT vs. S6k-OE | Yes | | **** | <0.0001 | 13, 10 |
| WT vs. Akt-OE | Yes | | **** | <0.0001 | 13, 11 |
| | | | | | |
| **Fig ID (Sholl Maximum)** | | One-way ANOVA & Dunnett's | | | |
| WT vs. CCT3-IR | Yes | | * | 0.0219 | 9, 11 |
| WT vs. CCT5-IR | Yes | | ns | >0.9999 | 9, 14 |
| WT vs. S6k-IR | Yes | | ns | 0.2517 | 9, 14 |
| WT vs. Akt-IR | Yes | | **** | <0.0001 | 9, 10 |
| WT vs. Akt-OE | Yes | | ** | 0.0012 | 9, 11 |
| WT vs. S6k-OE | Yes | | **** | <0.0001 | 9,10 |
| WT vs. Cul1-IR | Yes | | ** | 0.0027 | 9,12 |
| | | | | | |
| **Fig 1D (Sholl Radius)** | | One-way ANOVA & Dunnett's | | | |
| WT vs. CCT3-IR | Yes | | ns | 0.0522 | 9, 11 |
| WT vs. CCT5-IR | Yes | | **** | <0.0001 | 9, 14 |
| WT vs. S6k-IR | Yes | | ns | 0.9261 | 9, 14 |
| WT vs. Akt-IR | Yes | | ns | 0.7088 | 9, 10 |
| WT vs. Akt-OE | Yes | | * | 0.0126 | 9, 11 |
| WT vs. S6k-OE | Yes | | **** | <0.0001 | 9,10 |
| WT vs. Cul1-IR | Yes | | ns | 0.9965 | 9,12 |
| | | | | | |
| **Fig 2A (P-S6k IHC)** | | | | | |
| WT vs. S6k-IR | No | Mann-Whitney test | **** | <0.0001 | 14, 12 |
| WT vs. CCT5-IR | Yes | One-way ANOVA & Tukey's | *** | 0.0008 | 9, 9 |
| WT vs. Raptor-IR | Yes | One-way ANOVA & Dunnett's | ** | 0.0099 | 14, 9 |
| WT vs. Raptor-OE | Yes | One-way ANOVA & Dunnett's | ns | 0.9612 | 14, 16 |
| WT vs. Cullin1-IR | Yes | Unpaired t-test | * | 0.0454 | 14, 13 |

| | | | | | |
|---|---|---|---|---|---|
| **Fig 2B (Raptor IHC)** | | Kruskal-Wallis & Dunn's | | | |
| Raptor-OE vs. CCT5-IR | Yes | | **** | <0.0001 | 17, 13 |
| Raptor-OE vs. Raptor-OE;CCT5-IR | Yes | | *** | 0.0002 | 17, 10 |
| CCT5-IR vs. Raptor-OE;CCT5-IR | No | | ns | >0.9999 | 15, 10 |
| WT vs. CCT5-IR | Yes | | * | 0.0355 | 15, 13 |
| WT vs. Raptor-OE;CCT5-IR | Yes | | ns | 0.2341 | 15, 10 |
| | | | | | |
| **Fig 2C (P-S6k IHC)** | | Kruskal-Wallis & Dunn's | | | |
| WT vs. CCT5-IR | No | | **** | <0.0001 | 13, 10 |
| WT vs. S6k-OE;CCT5-IR | Yes | | **** | <0.0001 | 13, 11 |
| CCT5-IR vs. S6k-OE;CCT5-IR | No | | ns | 0.9773 | 10, 11 |
| | | | | | |
| **Fig 2E (TDL)** | | One-way ANOVA & Šídák's | | | |
| CCT3-IR vs. CCT3-IR;Cul1-IR | Yes | | ns | 0.9534 | 10, 10 |
| Cullin1-IR vs. S6k-OE;Cul1-IR | Yes | | ns | 0.7985 | 13, 7 |
| S6k-OE;Cul1-IR vs. S6k-OE | Yes | | ns | 0.3506 | 7, 10 |
| S6k-OE;CCT5-IR vs. CCT5-IR | Yes | | ns | 0.0608 | 10, 12 |
| | | | | | |
| **Fig 3A (IHC acet tub)** | | | | | |
| WT vs. CCT3-IR | Yes | One-way ANOVA & Dunnett's | **** | <0.0001 | 14, 11 |
| WT vs. CCT5-IR | Yes | One-way ANOVA & Dunnett's | ** | <0.0001 | 14, 13 |
| WT vs. Raptor-IR | No | One-way ANOVA & Dunnett's | *** | 0.0006 | 14, 9 |
| WT vs. S6k-IR | No | Mann-Whitney | *** | 0.0008 | 14, 12 |
| WT vs. Akt-IR | Yes | One-way ANOVA & Dunnett's | * | 0.0148 | 16, 14 |
| WT vs. Cullin1-IR | Yes | Unpaired t-test | ns | 0.2324 | 14, 13 |
| WT vs. S6k-OE | Yes | One-way ANOVA & Dunnett's | ns | 0.9584 | 10, 9 |
| WT vs. Akt-OE | Yes | One-way ANOVA & Dunnett's | ns | 0.6653 | 16, 12 |
| | | | | | |
| **Fig 3A (IHC Futsch)** | | | | | |
| WT vs. CCT3-IR | Yes | Unpaired t-test | *** | 0.0002 | 13, 12 |
| WT vs. CCT5-IR | Yes | Unpaired t-test | * | 0.0398 | 9, 5 |
| WT vs. Raptor-IR | Yes | Unpaired t-test | ** | 0.0089 | 14, 11 |
| WT vs. S6k-IR | Yes | Unpaired t-test | * | 0.0427 | 13, 13 |

| | | | | | |
|---|---|---|---|---|---|
| WT vs. Akt-IR | Yes | One-way ANOVA & Dunnett's | *** | 0.0002 | 14, 13 |
| WT vs. Cullin1-IR | Yes | Unpaired t-test | ns | 0.0767 | 10, 13 |
| WT vs. S6k-OE | Yes | One-way ANOVA & Dunnett's | *** | 0.0004 | 16, 15 |
| WT vs. Akt-OE | Yes | Unpaired t-test | ** | 0.0013 | 10, 13 |
| | | | | | |
| | | | | | |
| **Fig 3C (*mCherry::Jupiter*)** | | Two-Way ANOVA & Tukey's | | | |
| 20 µm: WT vs. CCT3-IR | | | **** | <0.0001 | 12, 10 |
| 20 µm: WT vs. CCT5-IR | | | **** | <0.0001 | 12, 10 |
| 20 µm: WT vs. Raptor-IR | | | **** | <0.0001 | 12, 10 |
| 20 µm: WT vs. S6k-IR | | | ** | 0.0035 | 12, 11 |
| 20 µm: WT vs. Akt-IR | | | ** | 0.0040 | 12, 10 |
| 20 µm: WT vs. Cullin1-IR | | | **** | <0.0001 | 12, 11 |
| 20 µm: WT vs. S6k-OE | | | ns | 0.8037 | 12, 10 |
| 20 µm: WT vs. Akt-OE | | | ns | >0.9999 | 12, 10 |
| 40 µm: WT vs. CCT3-IR | | | **** | <0.0001 | 12, 10 |
| 40 µm: WT vs. CCT5-IR | | | **** | <0.0001 | 12, 10 |
| 40 µm: WT vs. Raptor-IR | | | **** | <0.0001 | 12, 10 |
| 40 µm: WT vs. S6k-IR | | | ** | 0.0035 | 12, 11 |
| 40 µm: WT vs. Akt-IR | | | ** | 0.0040 | 12, 10 |
| 40 µm: WT vs. Cullin1-IR | | | **** | <0.0001 | 12, 11 |
| 40 µm: WT vs. S6k-OE | | | ns | 0.8037 | 12, 10 |
| 40 µm: WT vs. Akt-OE | | | ns | >0.9999 | 12, 10 |
| 60 µm: WT vs. CCT3-IR | | | **** | <0.0001 | 12, 10 |
| 60 µm: WT vs. CCT5-IR | | | **** | <0.0001 | 12, 10 |
| 60 µm: WT vs. Raptor-IR | | | **** | <0.0001 | 12, 10 |
| 60 µm: WT vs. S6k-IR | | | ** | 0.0035 | 12, 11 |
| 60 µm: WT vs. Akt-IR | | | ** | 0.0040 | 12, 10 |
| 60 µm: WT vs. Cullin1-IR | | | **** | <0.0001 | 12, 11 |
| 60 µm: WT vs. S6k-OE | | | ns | 0.8037 | 12, 10 |
| 60 µm: WT vs. Akt-OE | | | ns | >0.9999 | 12, 10 |
| 80 µm: WT vs. CCT3-IR | | | **** | <0.0001 | 12, 10 |
| 80 µm: WT vs. CCT5-IR | | | **** | <0.0001 | 12, 10 |
| 80 µm: WT vs. Raptor-IR | | | **** | <0.0001 | 12, 10 |
| 80 µm: WT vs. S6k-IR | | | ** | 0.0035 | 12, 11 |
| 80 µm: WT vs. Akt-IR | | | ** | 0.0040 | 12, 10 |
| 80 µm: WT vs. Cullin1-IR | | | **** | <0.0001 | 12, 11 |
| 80 µm: WT vs. S6k-OE | | | ns | 0.8037 | 12, 10 |
| 80 µm: WT vs. Akt-OE | | | ns | >0.9999 | 12, 10 |
| 100 µm: WT vs. CCT3-IR | | | **** | <0.0001 | 12, 10 |
| 100 µm: WT vs.CCT5-IR | | | **** | <0.0001 | 12, 10 |
| 100 µm: WT vs. Raptor-IR | | | **** | <0.0001 | 12, 10 |
| 100 µm: WT vs. S6k-IR | | | ** | 0.0035 | 12, 11 |

| | | | | | |
|---|---|---|---|---|---|
| 100 µm: WT vs. Akt-IR | | | ** | 0.0040 | 12, 10 |
| 100 µm: WT vs. Cullin1-IR | | | **** | <0.0001 | 12, 11 |
| 100 µm: WT vs. S6k-OE | | | ns | 0.8037 | 12, 10 |
| 100 µm: WT vs. Akt-OE | | | ns | >0.9999 | 12, 10 |
| 120 µm: WT vs. CCT3-IR | | | **** | <0.0001 | 12, 10 |
| 120 µm: WT vs. CCT5-IR | | | **** | <0.0001 | 12, 10 |
| 120 µm: WT vs. Raptor-IR | | | **** | <0.0001 | 12, 10 |
| 120 µm: WT vs. S6k-IR | | | ** | 0.0035 | 12, 11 |
| 120 µm: WT vs. Akt-IR | | | ** | 0.0040 | 12, 10 |
| 120 µm: WT vs. Cullin1-IR | | | **** | <0.0001 | 12, 11 |
| 120 µm: WT vs. S6k-OE | | | ns | 0.8037 | 12, 10 |
| 120 µm: WT vs. Akt-OE | | | ns | >0.9999 | 12, 10 |
| 140 µm: WT vs. CCT3-IR | | | **** | <0.0001 | 12, 10 |
| 140 µm: WT vs. CCT5-IR | | | **** | <0.0001 | 12, 10 |
| 140 µm: WT vs. Raptor-IR | | | **** | <0.0001 | 12, 10 |
| 140 µm: WT vs. S6k-IR | | | ** | 0.0035 | 12, 11 |
| 140 µm: WT vs. Akt-IR | | | ** | 0.0040 | 12, 10 |
| 140 µm: WT vs. Cullin1-IR | | | **** | <0.0001 | 12, 11 |
| 140 µm: WT vs. S6k-OE | | | ns | 0.8037 | 12, 10 |
| 140 µm: WT vs. Akt-OE | | | ns | >0.9999 | 12, 10 |
| 160 µm: WT vs. CCT3-IR | | | **** | <0.0001 | 12, 10 |
| 160 µm: WT vs. CCT5-IR | | | **** | <0.0001 | 12, 10 |
| 160 µm: WT vs. Raptor-IR | | | **** | <0.0001 | 12, 10 |
| 160 µm: WT vs. S6k-IR | | | ** | 0.0035 | 12, 11 |
| 160 µm: WT vs. Akt-IR | | | ** | 0.0040 | 12, 10 |
| 160 µm: WT vs. Cullin1-IR | | | **** | <0.0001 | 12, 11 |
| 160 µm: WT vs. S6k-OE | | | ns | 0.8037 | 12, 10 |
| 160 µm: WT vs. Akt-OE | | | ns | >0.9999 | 12, 10 |
| 180 µm: WT vs. CCT3-IR | | | **** | <0.0001 | 12, 10 |
| 180 µm: WT vs. CCT5-IR | | | **** | <0.0001 | 12, 10 |
| 180 µm: WT vs. Raptor-IR | | | **** | <0.0001 | 12, 10 |
| 180 µm: WT vs. S6k-IR | | | ** | 0.0035 | 12, 11 |
| 180 µm: WT vs. Akt-IR | | | ** | 0.0040 | 12, 10 |
| 180 µm: WT vs. Cullin1-IR | | | **** | <0.0001 | 12, 11 |
| 180 µm: WT vs. S6k-OE | | | ns | 0.8037 | 12, 10 |
| 180 µm: WT vs. Akt-OE | | | ns | >0.9999 | 12, 10 |
| 200 µm: WT vs. CCT3-IR | | | **** | <0.0001 | 12, 10 |
| 200 µm: WT vs. CCT5-IR | | | **** | <0.0001 | 12, 10 |
| 200 µm: WT vs. Raptor-IR | | | **** | <0.0001 | 12, 10 |
| 200 µm: WT vs. S6k-IR | | | ** | 0.0035 | 12, 11 |
| 200 µm: WT vs. Akt-IR | | | ** | 0.0040 | 12, 10 |
| 200 µm: WT vs. Cullin1-IR | | | **** | <0.0001 | 12, 11 |
| 200 µm: WT vs. S6k-OE | | | ns | 0.8037 | 12, 10 |
| 200 µm: WT vs. Akt-OE | | | ns | >0.9999 | 12, 10 |
| 220 µm: WT vs. CCT3-IR | | | **** | <0.0001 | 12, 10 |
| 220 µm: WT vs. CCT5-IR | | | **** | <0.0001 | 12, 10 |

| | | | | | |
|---|---|---|---|---|---|
| 220 µm: WT vs. Raptor-IR | | | **** | <0.0001 | 12, 10 |
| 220 µm: WT vs. S6k-IR | | | ** | 0.0035 | 12, 11 |
| 220 µm: WT vs. Akt-IR | | | ** | 0.0040 | 12, 10 |
| 220 µm: WT vs. Cullin1-IR | | | **** | <0.0001 | 12, 11 |
| 220 µm: WT vs. S6k-OE | | | ns | 0.8037 | 12, 10 |
| 220 µm: WT vs. Akt-OE | | | ns | >0.9999 | 12, 10 |
| 240 µm: WT vs. CCT3-IR | | | **** | <0.0001 | 12, 10 |
| 240 µm: WT vs. CCT5-IR | | | **** | <0.0001 | 12, 10 |
| 240 µm: WT vs. Raptor-IR | | | **** | <0.0001 | 12, 10 |
| 240 µm: WT vs. S6k-IR | | | ** | 0.0035 | 12, 11 |
| 240 µm: WT vs. Akt-IR | | | ** | 0.0040 | 12, 10 |
| 240 µm: WT vs. Cullin1-IR | | | **** | <0.0001 | 12, 11 |
| 240 µm: WT vs. S6k-OE | | | ns | 0.8037 | 12, 10 |
| 240 µm: WT vs. Akt-OE | | | ns | >0.9999 | 12, 10 |
| 260 µm: WT vs. CCT3-IR | | | **** | <0.0001 | 12, 10 |
| 260 µm: WT vs. CCT5-IR | | | **** | <0.0001 | 12, 10 |
| 260 µm: WT vs. Raptor-IR | | | **** | <0.0001 | 12, 10 |
| 260 µm: WT vs. S6k-IR | | | ** | 0.0035 | 12, 11 |
| 260 µm: WT vs. Akt-IR | | | ** | 0.0040 | 12, 10 |
| 260 µm: WT vs. Cullin1-IR | | | **** | <0.0001 | 12, 11 |
| 260 µm: WT vs. S6k-OE | | | ns | 0.8037 | 12, 10 |
| 260 µm: WT vs. Akt-OE | | | ns | >0.9999 | 12, 10 |
| 280 µm: WT vs. CCT3-IR | | | **** | <0.0001 | 12, 10 |
| 280 µm: WT vs. CCT5-IR | | | **** | <0.0001 | 12, 10 |
| 280 µm: WT vs. Raptor-IR | | | **** | <0.0001 | 12, 10 |
| 280 µm: WT vs. S6k-IR | | | ** | 0.0035 | 12, 11 |
| 280 µm: WT vs. Akt-IR | | | ** | 0.0040 | 12, 10 |
| 280 µm: WT vs. Cullin1-IR | | | **** | <0.0001 | 12, 11 |
| 280 µm: WT vs. S6k-OE | | | ns | 0.8037 | 12, 10 |
| 280 µm: WT vs. Akt-OE | | | ns | >0.9999 | 12, 10 |
| 300 µm: WT vs. CCT3-IR | | | **** | <0.0001 | 12, 10 |
| 300 µm: WT vs. CCT5-IR | | | **** | <0.0001 | 12, 10 |
| 300 µm: WT vs. Raptor-IR | | | **** | <0.0001 | 12, 10 |
| 300 µm: WT vs. S6k-IR | | | ** | 0.0035 | 12, 11 |
| 300 µm: WT vs. Akt-IR | | | ** | 0.0040 | 12, 10 |
| 300 µm: WT vs. Cullin1-IR | | | **** | <0.0001 | 12, 11 |
| 300 µm: WT vs. S6k-OE | | | ns | 0.8037 | 12, 10 |
| 300 µm: WT vs. Akt-OE | | | ns | >0.9999 | 12, 10 |
| 320 µm: WT vs. CCT3-IR | | | **** | <0.0001 | 12, 10 |
| 320 µm: WT vs. CCT5-IR | | | **** | <0.0001 | 12, 10 |
| 320 µm: WT vs. Raptor-IR | | | **** | <0.0001 | 12, 10 |
| 320 µm: WT vs. S6k-IR | | | ** | 0.0035 | 12, 11 |
| 320 µm: WT vs. Akt-IR | | | ** | 0.0040 | 12, 10 |
| 320 µm: WT vs. Cullin1-IR | | | **** | <0.0001 | 12, 11 |
| 320 µm: WT vs. S6k-OE | | | ns | 0.8037 | 12, 10 |
| 320 µm: WT vs. Akt-OE | | | ns | >0.9999 | 12, 10 |

| | | | | | |
|---|---|---|---|---|---|
| 340 µm: WT vs. CCT3-IR | | | **** | <0.0001 | 12, 10 |
| 340 µm: WT vs. CCT5-IR | | | **** | <0.0001 | 12, 10 |
| 340 µm: WT vs. Raptor-IR | | | **** | <0.0001 | 12, 10 |
| 340 µm: WT vs. S6k-IR | | | ** | 0.0035 | 12, 11 |
| 340 µm: WT vs. Akt-IR | | | ** | 0.0040 | 12, 10 |
| 340 µm: WT vs. Cullin1-IR | | | **** | <0.0001 | 12, 11 |
| 340 µm: WT vs. S6k-OE | | | ns | 0.8037 | 12, 10 |
| 340 µm: WT vs. Akt-OE | | | ns | >0.9999 | 12, 10 |
| 360 µm: WT vs. CCT3-IR | | | **** | <0.0001 | 12, 10 |
| 360 µm: WT vs. CCT5-IR | | | **** | <0.0001 | 12, 10 |
| 360 µm: WT vs. Raptor-IR | | | **** | <0.0001 | 12, 10 |
| 360 µm: WT vs. S6k-IR | | | ** | 0.0035 | 12, 11 |
| 360 µm: WT vs. Akt-IR | | | ** | 0.0040 | 12, 10 |
| 360 µm: WT vs. Cullin1-IR | | | **** | <0.0001 | 12, 11 |
| 360 µm: WT vs. S6k-OE | | | ns | 0.8037 | 12, 10 |
| 360 µm: WT vs. Akt-OE | | | ns | >0.9999 | 12, 10 |
| 380 µm: WT vs. CCT3-IR | | | **** | <0.0001 | 12, 10 |
| 380 µm: WT vs. CCT5-IR | | | **** | <0.0001 | 12, 10 |
| 380 µm: WT vs. Raptor-IR | | | **** | <0.0001 | 12, 10 |
| 380 µm: WT vs. S6k-IR | | | ** | 0.0035 | 12, 11 |
| 380 µm: WT vs. Akt-IR | | | ** | 0.0040 | 12, 10 |
| 380 µm: WT vs. Cullin1-IR | | | **** | <0.0001 | 12, 11 |
| 380 µm: WT vs. S6k-OE | | | ns | 0.8037 | 12, 10 |
| 380 µm: WT vs. Akt-OE | | | ns | >0.9999 | 12, 10 |
| 400 µm: WT vs. CCT3-IR | | | **** | <0.0001 | 12, 10 |
| 400 µm: WT vs. CCT5-IR | | | **** | <0.0001 | 12, 10 |
| 400 µm: WT vs. Raptor-IR | | | **** | <0.0001 | 12, 10 |
| 400 µm: WT vs. S6k-IR | | | ** | 0.0035 | 12, 11 |
| 400 µm: WT vs. Akt-IR | | | ** | 0.0040 | 12, 10 |
| 400 µm: WT vs. Cullin1-IR | | | **** | <0.0001 | 12, 11 |
| 400 µm: WT vs. S6k-OE | | | ns | 0.8037 | 12, 10 |
| 400 µm: WT vs. Akt-OE | | | ns | >0.9999 | 12, 10 |
| 420 µm: WT vs. CCT3-IR | | | **** | <0.0001 | 12, 10 |
| 420 µm: WT vs. CCT5-IR | | | **** | <0.0001 | 12, 10 |
| 420 µm: WT vs. Raptor-IR | | | **** | <0.0001 | 12, 10 |
| 420 µm: WT vs. S6k-IR | | | ** | 0.0035 | 12, 11 |
| 420 µm: WT vs. Akt-IR | | | ** | 0.0040 | 12, 10 |
| 420 µm: WT vs. Cullin1-IR | | | **** | <0.0001 | 12, 11 |
| 420 µm: WT vs. S6k-OE | | | ns | 0.8037 | 12, 10 |
| 420 µm: WT vs. Akt-OE | | | ns | >0.9999 | 12, 10 |
| 440 µm: WT vs. CCT3-IR | | | **** | <0.0001 | 12, 10 |
| 440 µm: WT vs. CCT5-IR | | | **** | <0.0001 | 12, 10 |
| 440 µm: WT vs. Raptor-IR | | | **** | <0.0001 | 12, 10 |
| 440 µm: WT vs. S6k-IR | | | ** | 0.0035 | 12, 11 |
| 440 µm: WT vs. Akt-IR | | | ** | 0.0040 | 12, 10 |
| 440 µm: WT vs. Cullin1-IR | | | **** | <0.0001 | 12, 11 |

| | | | | | |
|---|---|---|---|---|---|
| 440 µm: WT vs. S6k-OE | | | ns | 0.8037 | 12, 10 |
| 440 µm: WT vs. Akt-OE | | | ns | >0.9999 | 12, 10 |
| 460 µm: WT vs. CCT3-IR | | | **** | <0.0001 | 12, 10 |
| 460 µm: WT vs. Raptor-IR | | | **** | <0.0001 | 12, 10 |
| 460 µm: WT vs. Akt-IR | | | ** | 0.0040 | 12, 10 |
| 460 µm: WT vs. Cullin1-IR | | | **** | <0.0001 | 12, 11 |
| 460 µm: WT vs. S6k-OE | | | ns | 0.8037 | 12, 11 |
| 460 µm: WT vs. Akt-OE | | | ns | >0.9999 | 12, 10 |
| 480 µm: WT vs. Akt-IR | | | ** | 0.0040 | 12, 10 |
| 480 µm: WT vs. Cullin1-IR | | | **** | <0.0001 | 12, 11 |
| 480 µm: WT vs. S6k-OE | | | ns | 0.8037 | 12, 11 |
| 480 µm: WT vs. Akt-OE | | | ns | >0.9999 | 12, 10 |
| 500 µm: WT vs. Akt-IR | | | ** | 0.0040 | 12, 10 |
| 500 µm: WT vs. Cullin1-IR | | | **** | <0.0001 | 12, 11 |
| 500 µm: WT vs. S6k-OE | | | ns | 0.8037 | 12, 11 |
| 500 µm: WT vs. Akt-OE | | | ns | >0.9999 | 12, 10 |
| | | | | | |
| **Fig 4D (HTT *mCherry::Jupiter*)** | | Two-Way ANOVA & Tukey's | | | |
| 40 µm: HTT20 vs. HTT50 | | | ns | 0.9996 | 10,9 |
| 40 µm: HTT20 vs. HTT93 | | | **** | <0.0001 | 10,11 |
| 80 µm: HTT20 vs. HTT50 | | | ns | 0.9996 | 10,9 |
| 80 µm: HTT20 vs. HTT93 | | | **** | <0.0001 | 10,11 |
| 120 µm: HTT20 vs. HTT50 | | | ns | 0.9996 | 10,9 |
| 120 µm: HTT20 vs. HTT93 | | | **** | <0.0001 | 10,11 |
| 160 µm: HTT20 vs. HTT50 | | | ns | 0.9996 | 10,9 |
| 160 µm: HTT20 vs. HTT93 | | | **** | <0.0001 | 10,11 |
| 200 µm: HTT20 vs. HTT50 | | | ns | 0.9996 | 10,9 |
| 200 µm: HTT20 vs. HTT93 | | | **** | <0.0001 | 10,11 |
| 240 µm: HTT20 vs. HTT50 | | | ns | 0.9996 | 10,9 |
| 240 µm: HTT20 vs. HTT93 | | | **** | <0.0001 | 10,11 |
| 280 µm: HTT20 vs. HTT50 | | | ns | 0.9996 | 10,9 |
| 280 µm: HTT20 vs. HTT93 | | | **** | <0.0001 | 10,11 |
| 320 µm: HTT20 vs. HTT50 | | | ns | 0.9996 | 10,9 |
| 320 µm: HTT20 vs. HTT93 | | | **** | <0.0001 | 10,11 |
| 360 µm: HTT20 vs. HTT50 | | | ns | 0.9996 | 10,9 |
| 360 µm: HTT20 vs. HTT93 | | | **** | <0.0001 | 10,11 |
| 400 µm: HTT20 vs. HTT50 | | | ns | 0.9996 | 10,9 |
| 400 µm: HTT20 vs. HTT93 | | | **** | <0.0001 | 10,11 |
| 440 µm: HTT20 vs. HTT50 | | | ns | 0.9996 | 10,9 |
| 440 µm: HTT20 vs. HTT93 | | | **** | <0.0001 | 10,11 |
| | | | | | |
| **Fig 4E (Pearson's)** | | One-way ANOVA & Šídák's | | | |
| WT (HA) GAL4 "off" vs. HTT120 (HA) GAL4 "off" | Yes | | ns | 0.9965 | 11, 9 |

| | | | | | |
|---|---|---|---|---|---|
| WT control (HA) GAL4 “off” vs. HTT120 WT HTT GAL4 “off” | Yes | | ns | 0.4664 | 11, 10 |
| HTT120 (HA) GAL4 “off” vs. HTT120 (HA) GAL4 “on” | Yes | | ** | 0.0045 | 9, 11 |
| HTT120 WT HTT GAL4 “off” vs. HTT120 (HA) GAL4 “on” | Yes | | ns | 0.5580 | 10, 11 |
| | | | | | |
| **Fig 4F (Manders Soma)** | | | | | |
| WT HTT v HTT120HA 48 hr | No | Mann-Whitney | *** | 0.0007 | 10, 11 |
| | | | | | |
| **Fig 4G (HTT TDL)** | | One-way ANOVA & Šídák’s | | | |
| WT vs. HTTQ25 | Yes | | ** | 0.0042 | 11, 11 |
| WT vs. HTT96 | Yes | | * | 0.0211 | 11, 16 |
| WT vs. HTTQ96;CCT5-iR | Yes | | **** | <0.0001 | 11, 16 |
| WT vs. HTTQ96;Cul1-IR | Yes | | ns | 0.8400 | 11, 9 |
| WT vs. HTT25;CCT5-IR | Yes | | **** | <0.0001 | 11, 9 |
| WT vs. HTTQ25;Cul1-IR | Yes | | * | 0.0383 | 11, 9 |
| HTTQ25 vs. HTTQ25;CCT5-IR | Yes | | **** | <0.0001 | 11, 9 |
| HTTQ25 vs. HTTQ25;Cul1-IR | Yes | | ns | >0.9999 | 11, 9 |
| HTTQ96 vs. HTTQ96;CCT5-IR | Yes | | *** | 0.0004 | 16, 16 |
| HTTQ96 vs. HTTQ96;Cul1-IR | Yes | | *** | 0.0002 | 16, 9 |
| HTTQ96;CCT5-IR vs. HTTQ25;CCT5-IR | Yes | | ns | 0.9993 | 16, 9 |
| HTTQ96;Cul1-IR vs. HTTQ25;Cul1-IR | Yes | | ns | 0.8662 | 9, 9 |
| | | | | | |
| **Fig S1A (CCT TDL)** | | One-way ANOVA & Dunnett’s | | | |
| WT vs. CCT1-IR | Yes | | **** | <0.0001 | 13, 10 |
| WT vs. CCT2-IR | Yes | | ns | 0.1586 | 13, 10 |
| WT vs. CCT4-IR | Yes | | ns | 0.6527 | 13, 10 |
| WT vs. CCT6-IR | Yes | | **** | <0.0001 | 13, 10 |
| WT vs. CCT7-IR | Yes | | * | 0.0388 | 13, 10 |
| WT vs. CCT8-IR | Yes | | **** | <0.0001 | 13, 11 |
| | | | | | |
| **Fig S1B (CCT4 TDL)** | | | | | |
| 40A FRT vs. CCT4$^{KG09280}$ | No | Mann-Whitney Test | *** | 0.0003 | 11, 8 |
| | | | | | |
| **Fig S1D (CCT Sholl Max)** | | One-way ANOVA & Dunnett’s | | | |
| WT vs. CCT1-IR | Yes | | ** | 0.0025 | 9, 10 |
| WT vs. CCT2-IR | Yes | | ns | 0.9665 | 9, 10 |
| WT vs. CCT4-IR | Yes | | ns | 0.5974 | 9, 11 |
| WT vs. CCT6-IR | Yes | | * | 0.0153 | 9, 10 |
| WT vs. CCT7-IR | Yes | | ns | 0.3998 | 9, 10 |

| | | | | | |
|---|---|---|---|---|---|
| WT vs. CCT8-IR | Yes | | * | 0.0471 | 9, 11 |
| | | | | | |
| **Fig S1D (CCT Sholl Radius)** | | One-way ANOVA & Dunnett's | | | |
| WT vs. CCT1-IR | Yes | | *** | 0.0001 | 9, 10 |
| WT vs. CCT2-IR | Yes | | ns | 0.2714 | 9, 10 |
| WT vs. CCT4-IR | Yes | | ns | 0.3769 | 9, 11 |
| WT vs. CCT6-IR | Yes | | *** | 0.0007 | 9, 10 |
| WT vs. CCT7-IR | Yes | | ns | >0.9999 | 9, 10 |
| WT vs. CCT8-IR | Yes | | ns | 0.1483 | 9, 11 |
| | | | | | |
| **Fig S1E (CCT5 IHC)** | | One-way ANOVA & Šídák's | | | |
| WT vs. CCT4-IR | Yes | | **** | <0.0001 | 29, 23 |
| WT vs. CCT5-IR | Yes | | *** | 0.0002 | 29, 16 |
| WT vs. CCT4-IR;CCT5-IR | Yes | | **** | <0.0001 | 29, 18 |
| CCT4-IR vs. CCT4-IR;CCT5-IR | Yes | | ** | 0.0021 | 23, 18 |
| CCT5-IR vs. CCT4-IR;CCT5-IR | Yes | | *** | 0.0004 | 16, 18 |
| | | | | | |
| **Fig S1F (AEL TDL)** | | One-way ANOVA & Šídák's | | | |
| 24 hr: mean of genetic controls vs. CCT3-IR | Yes | | ns | 0.4890 | 17, 15 |
| 24 hr: mean of genetic controls vs. CCT5-IR | Yes | | ns | 0.4424 | 12, 13 |
| 48 hr: mean of genetic controls vs. CCT3-IR | Yes | | ns | 0.1891 | 18, 12 |
| 48 hr: mean of genetic controls vs. CCT5-IR | Yes | | ns | 0.6169 | 10, 12 |
| 72 hr: mean of genetic controls vs. CCT3-IR | Yes | | *** | 0.0004 | 11, 14 |
| 72 hr: mean of genetic controls vs. CCT5-IR | Yes | | * | 0.0104 | 10, 12 |
| 96 hr: mean of genetic controls vs. CCT3-IR | Yes | | **** | <0.0001 | 10, 10 |
| 96 hr: mean of genetic controls vs. CCT5-IR | Yes | | **** | <0.0001 | 12, 12 |
| 72 hr CCT3-IR vs. 96 hr CCT3-IR | Yes | | ns | 0.6523 | 14, 10 |
| 72 hr CCT5-IR vs. 96 hr CCT5-IR | Yes | | ns | 0.5468 | 12, 12 |
| | | | | | |
| **Fig S1G (CCT OE TDL)** | | One-way ANOVA & Šídák's | | | |
| WT vs. CCT2-OE | Yes | | ns | 0.9917 | 13, 10 |
| WT vs. drosCCT4 | Yes | | ns | 0.6067 | 13, 10 |
| dcas9 vs. CCT5 TOE | Yes | | ns | 0.2882 | 13, 11 |
| | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| **Fig S2A (Raptor fluorescence IHC)** | | | | | |
| WT vs. CCT5-IR | Yes | One-way ANOVA & Dunnett's | **** | <0.0001 | 11, 14 |
| WT vs. Raptor-IR | Yes | One-way ANOVA & Dunnett's | **** | <0.0001 | 16, 16 |
| WT vs. Raptor-OE | Yes | One-way ANOVA & Dunnett's | *** | 0.0005 | 16, 14 |
| | | | | | |
| **Fig S2B (S6k IHC)** | | Unpaired t-test | | | |
| WT vs. S6k-IR | Yes | | ** | 0.0071 | 9, 8 |
| | | | | | |
| **Fig S2C (P-Akt IHC)** | | Unpaired t-test | | | |
| WT vs. Akt-IR | Yes | | **** | <0.0001 | 11, 12 |
| | | | | | |
| **Fig S2D (Cullin1 IHC)** | | Unpaired t-test | | | |
| WT vs. Cullin1-IR | Yes | | ** | 0.0013 | 15, 14 |
| | | | | | |
| **Fig S2E (BtubIIA fluorescence)** | | | | | |
| WT vs. CCT3-IR | Yes | One-way ANOVA & Dunnett's | **** | <0.0001 | 14, 11 |
| WT vs. CCT5-IR | Yes | One-way ANOVA & Dunnett's | **** | <0.0001 | 14, 15 |
| WT vs. S6k-IR | Yes | Unpaired t-test | * | 0.0339 | 13, 13 |
| WT vs. Raptor-IR | Yes | Unpaired t-test | ** | 0.0078 | 14, 11 |
| WT vs. Akt-IR | Yes | One-way ANOVA & Dunnett's | ** | 0.0055 | 16, 14 |
| WT vs. Akt-OE | Yes | One-way ANOVA & Dunnett's | ns | 0.4915 | 16, 12 |
| WT vs. Cullin1-IR | Yes | Unpaired t-test | * | 0.0105 | 10, 13 |
| | | | | | |
| **Fig S3A (HTT TDL)** | | One-way ANOVA & Šídák's | | | |
| WT vs. HTTQ20 | Yes | | ns | >0.9999 | 11, 15 |
| WT vs. HTTQ50 | Yes | | ns | 0.8793 | 11, 13 |
| WT vs. HTTQ93 | Yes | | **** | <0.0001 | 11, 18 |
| WT vs. HTTQ120 | Yes | | **** | <0.0001 | 11, 15 |
| | | | | | |
| **Fig S3C (HTT Futsch)** | | One-way ANOVA & Tukey's | | | |
| WT vs. HTT96 | Yes | | **** | <0.0001 | 11, 11 |
| WT vs. HTT96;CCT5-IR | Yes | | **** | <0.0001 | 11, 9 |
| HTT96 vs. HTT96;CCT5-IR | Yes | | ns | >0.9999 | 11, 9 |
| | | | | | |
| **Fig S3D (WT HTT)** | | | | | |
| WT vs. CCT5-IR | Yes | Unpaired t-test | *** | 0.0002 | 11, 10 |

| | | | | | |
|---|---|---|---|---|---|
| **Fig S3F (M2 Dendrites)** | | | | | |
| WT HTT v HTT120HA 48 hr | Yes | Unpaired t-test | **** | <0.0001 | 11, 9 |
| | | | | | |
| **Fig S3G (WT HTT IHC)** | | One-way ANOVA & Tukey's | | | |
| WT vs. HTT25-Cer | Yes | | * | 0.0117 | 11, 11 |
| WT vs. HTT96-Cer | Yes | | **** | <0.0001 | 11, 11 |
| | | | | | |
| **Fig S3H (# mHTT IB)** | | Kruskal-Wallis & Dunn's | | | |
| HTT96 vs. HTT96;CCT5-IR | No | | ns | >0.9999 | 15, 14 |
| HTT96 vs. HTT96;Cul1-IR | No | | ns | 0.7909 | 15, 14 |
| | | | | | |
| **Fig S3I (area mHTT IB)** | | Kruskal-Wallis & Dunn's | | | |
| HTT96 vs. HTT96;CCT5-IR | No | | ns | 0.1699 | 16, 16 |
| HTT96 vs. HTT96;Cul1-IR | No | | ns | >0.9999 | 16, 15 |

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