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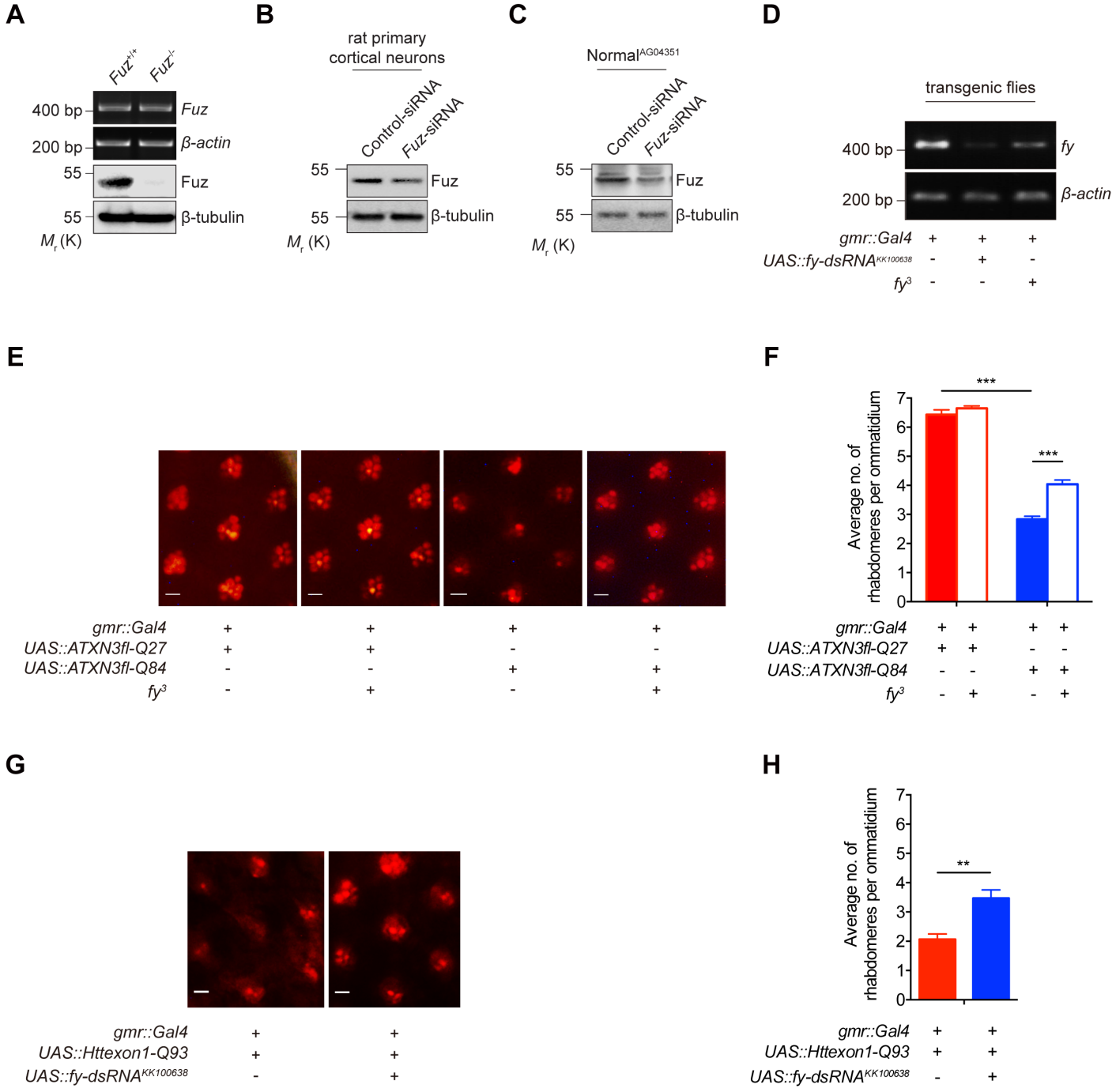
Appendix Figure S1.



Appendix Figure S1. Data related to Figure 3.

(A) The expression of *Fuz* transcript was not affected while Fuz protein expression was abolished in *Fuz*$^{-/-}$ HEK293 cells. The *Fuz*$^{-/-}$ HEK293 cell line was generated through CRISPR/Cas9 technique. The parental HEK293 cells were used as control. *n* = 3.

(B) Fuz protein expression was reduced in rat primary cortical neurons upon *Fuz*-siRNA treatment. *n* = 3.

(C) Knockdown of *Fuz* expression reduced the Fuz protein expression in normal fibroblasts. *n* = 3.

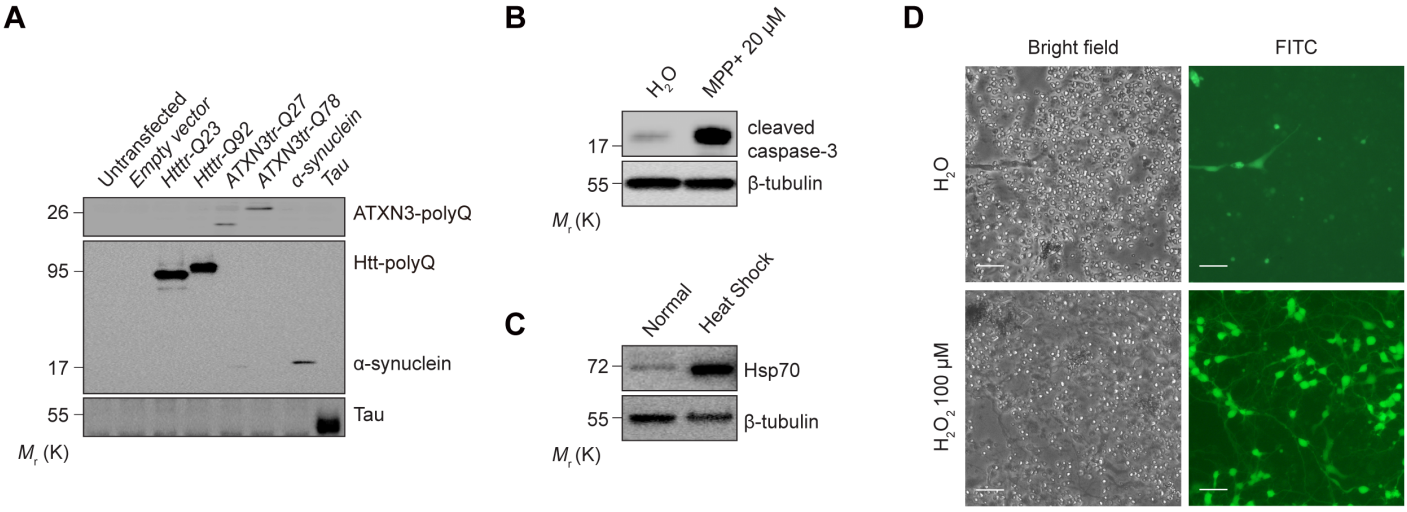
(D) The expression level of *fuzzy* transcript was reduced in both *fuzzy*-knockdown (*fy-dsRNA*^{KK100638}) and *fuzzy*-knockout (*fy*^{3}) *Drosophila* lines. *fy*^{3} is a null allele, it carries a 70 bp deletion in the *fy* coding region [1]. *n* = 3.

(E, F) (E) Neurodegenerative phenotype in SCA3 transgenic flies were suppressed in *fy*^{3} mutant background. The flies were of genotypes *w; gmr::Gal4 UAS::ATXN3fl-Q27/+; +/+*, *w; gmr::Gal4 UAS::ATXN3fl-Q27/fy*^{3}*; +/+*, *w; gmr::Gal4/+; UAS::ATXN3fl-Q84/+* and *w; gmr::Gal4/fy*^{3}*; UAS::ATXN3fl-Q84/+*. Scale bars: 5 μm. (F) is the quantification of (E). Error bars represent S.E.M., *n* = 3. For every control or experimental group, a total of 200 ommatidia collected from 20 fly eyes were examined in each replicate. Statistical analysis was performed using one-way ANOVA followed by post-hoc Tukey's test. *** $P < 0.001$.

(G, H) (G) Knockdown of *fy* expression suppressed the neurodegeneration in HD transgenic flies. The flies were of genotypes *UAS::Httexon1-Q93; gmr::Gal4/+* and *UAS::Httexon1-Q93; gmr::Gal4/UAS::fy-dsRNA*^{KK100638}. Scale bars: 5 μm. (H) is the quantification of (G). Error bars represent S.E.M., *n* = 3. For every control or experimental

group, a total of 200 ommatidia collected from 20 fly eyes were examined in each replicate. Statistical analysis was performed using two-tailed unpaired Student's *t*-test. ** $P < 0.01$. Data information: *beta-actin* or beta-tubulin was used as loading control. *n* represents the number of biological replicates. Only representative images, gels and blots are shown.

Appendix Figure S2.



Appendix Figure S2. Data related to Figure 7.

(A) Western blot analysis showing the overexpression of ATXN3tr-Q27/Q78, Htttr-Q23/Q92, α-synuclein and Tau proteins in rat primary cortical neurons. *n* = 3.

(B) Treatment of MPP+ induced capsase-3 cleavage in rat primary cortical neurons. *n* = 3.

(C) Heat shock treatment increased the expression of heat shock protein 70 (Hsp70) in rat primary cortical neurons. *n* = 3.

(D) H_2O_2 treatment increased the reactive oxygen species (ROS) production in rat primary cortical neurons. Scale bars: 50 μm. *n* = 3.

Data information: Beta-tubulin was used as loading control. *n* represents the number of biological replicates. Only representative images and blots are shown.

Appendix Table S1. Summary of the *Fuz* promoter methylation in different disease models.

Disease model	*Fuz* promoter region	Methylation change	Hypomethylation restored by YY1 overexpression
expanded polyQ	+117/+347CpG	hypomethylation	Yes
$A\beta_{1-42}$	+117/+347CpG	hypomethylation	Yes
Tau	+117/+347CpG	hypomethylation	Yes
α-synuclein	-1962/-1861CpG	hypomethylation	No

Appendix Table S2. SCA3 patient and control brain sample description.

Sample ID	Case ID	Dx	Age	Gender	PMI (minutes)	Brain Weight (grams)
SCA3-1	UMB1687	SCA3	50	Male	1,500	1,410
SCA3-2	UMB4626	SCA3	64	Male	720	1,550
SCA3-3	UMB5749	SCA3	45	Male	1,680	1,537
SCA3-4	UMB5777	SCA3	52	Male	1,320	n/a
SCA3-5	UMB5856	SCA3	61	Female	300	1,046
SCA3-6	T5147	SCA3	39	Female	1,265	1,000
CTL-1	T206	Control	49	Male	905	1,325
CTL-2	T274	Control	65	Female	1,422	1,066
CTL-3	T99	Control	44	Male	2,955	1,817
CTL-4	T145	Control	57	Female	554	1,050
CTL-5	T343	Control	62	Male	496	1,301
CTL-6	T4812	Control	36	Male	517	1,225

Dx: diagnosis, SCA3: spinocerebellar ataxia type 3, PMI: post-mortem interval, n/a: not available

Appendix Table S3. Clinical features of SCA3 cases and control individuals described in this study.

Variable	Control	SCA3
n	6	6
Age at death (years)	52.2 ± 11.1	51.8 ± 9.5
Male	4 (66.7%)	4 (66.7%)
Female	2 (33.3%)	2 (33.3%)
Brain Weight (grams)	1,297 ± 279	1,308 ± 266
Post Mortem Interval (minutes)	1,142 ± 957	1,131 ± 520

Appendix Reference

1. Collier S, Gubb D (1997) Drosophila tissue polarity requires the cell-autonomous activity of the fuzzy gene, which encodes a novel transmembrane protein. *Development* **124:** 4029-4037