A P301S S305N MAPTKI (heatmap with z score legend, z score range −2 to 2)

B PCA with 95% Confidence Ellipses
Genotype: MAPT KI, S305N, P301S
PC1, PC2

C
Metabolism, Mitochondria, and Energy:
Aldoa *
Gapdh
Glul *
Gpi *
Fasn *
Ampd2
Pfkl *
Hk1 *
Sgpp1
Sult4a1

Chromatin remodelling:
Atrx *
Hdac5 *
Hmgn1
Ncor2 *
Smarcad1 *
Trim28 **

RNA splicing and processing:
Rbm15b
Rbm39 *
Sf3a1
Srrm2
U2af2
Thrap3 *
Tfip11
Tra2a *

Epigenetic and Transcriptional Regulators

MAPT KI   S305N   P301S
(z-score legend −2.0 to 2.0)

D S-adenosylmethionine pathway
Dnmt1 *
Dnmt3a
Mat2a *
Mat2b **
Amdhd1
Amdhd2
Shmt2 *
Shmt1 *
Ehmt1 *
Mettl14
Mettl3
Nsun2 *
Mtr *
Ahcy *
Mthfr
Cbs *
Cth
Mocs1

MAPT KI   S305N   P301S
(z-score legend −2 to 2)

Fig. S1. (**A**) Cluster heatmap of total proteomics dataset comparing 15M posterior cortex from MAPT KI (N=3; N=1 male; N=2 female); S305N (N=4; sex matched) and P301S (N=4; sex matched) and (**B**) PCA showing data distribution across dataset from (A). Ellipses represent 95% confidence intervals (**C**) Heatmap showing protein level abundance of the proteins in the P301S-specific cluster (named metabolism and epigenetic regulators). * indicate proteins that show a $p<0.05$ with FDR correction between *MAPT* KI and P301S. (**D**) Heatmap showing protein level abundance of SAM (S-adenosylmethionine)–pathway. * indicate proteins that show a $p<0.05$ with FDR correction between *MAPT* KI and P301S.