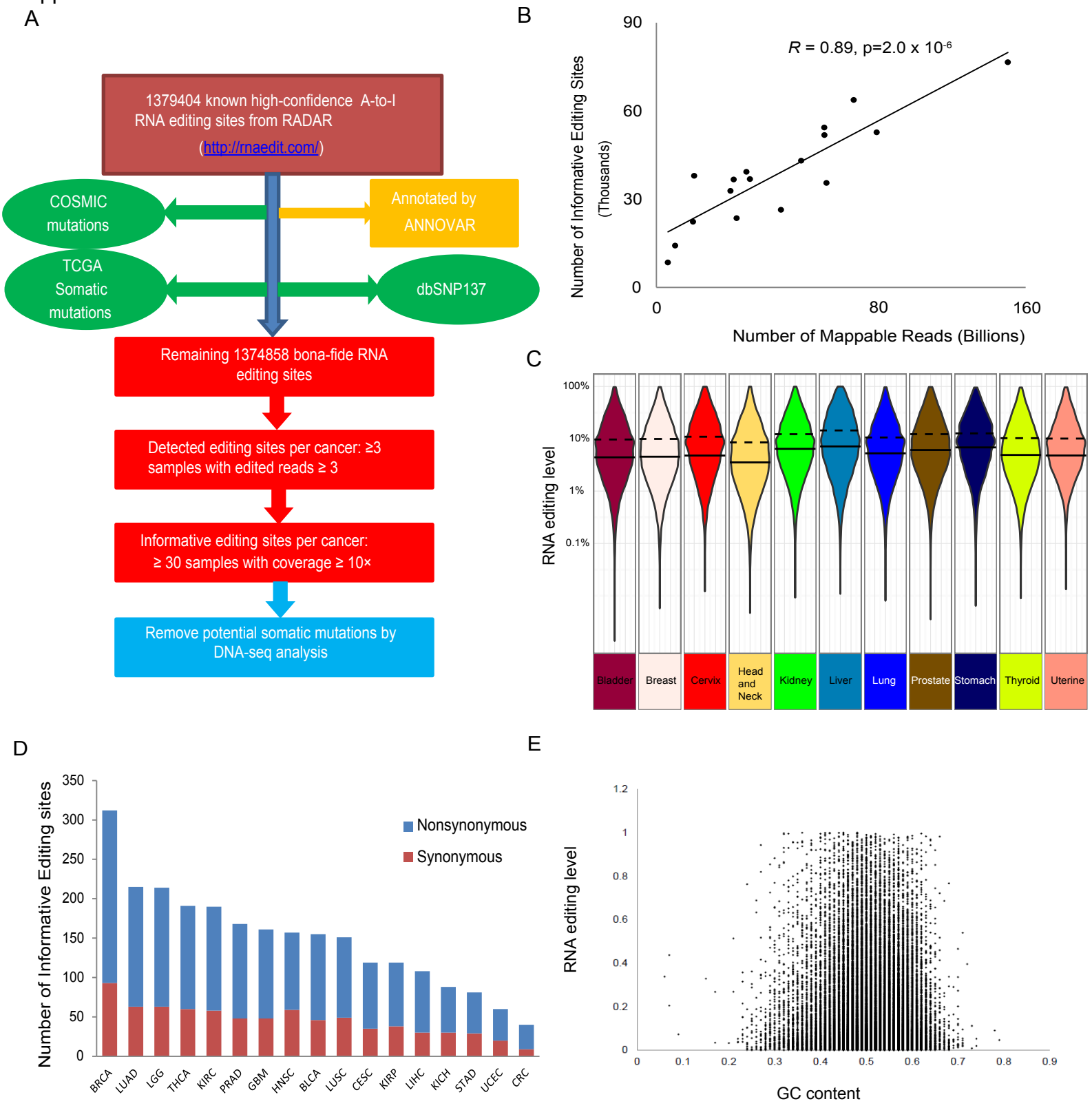


Figure S1 Overview of A-to-I RNA editing patterns in human cancer and normal tissues. Related to Figure 1.

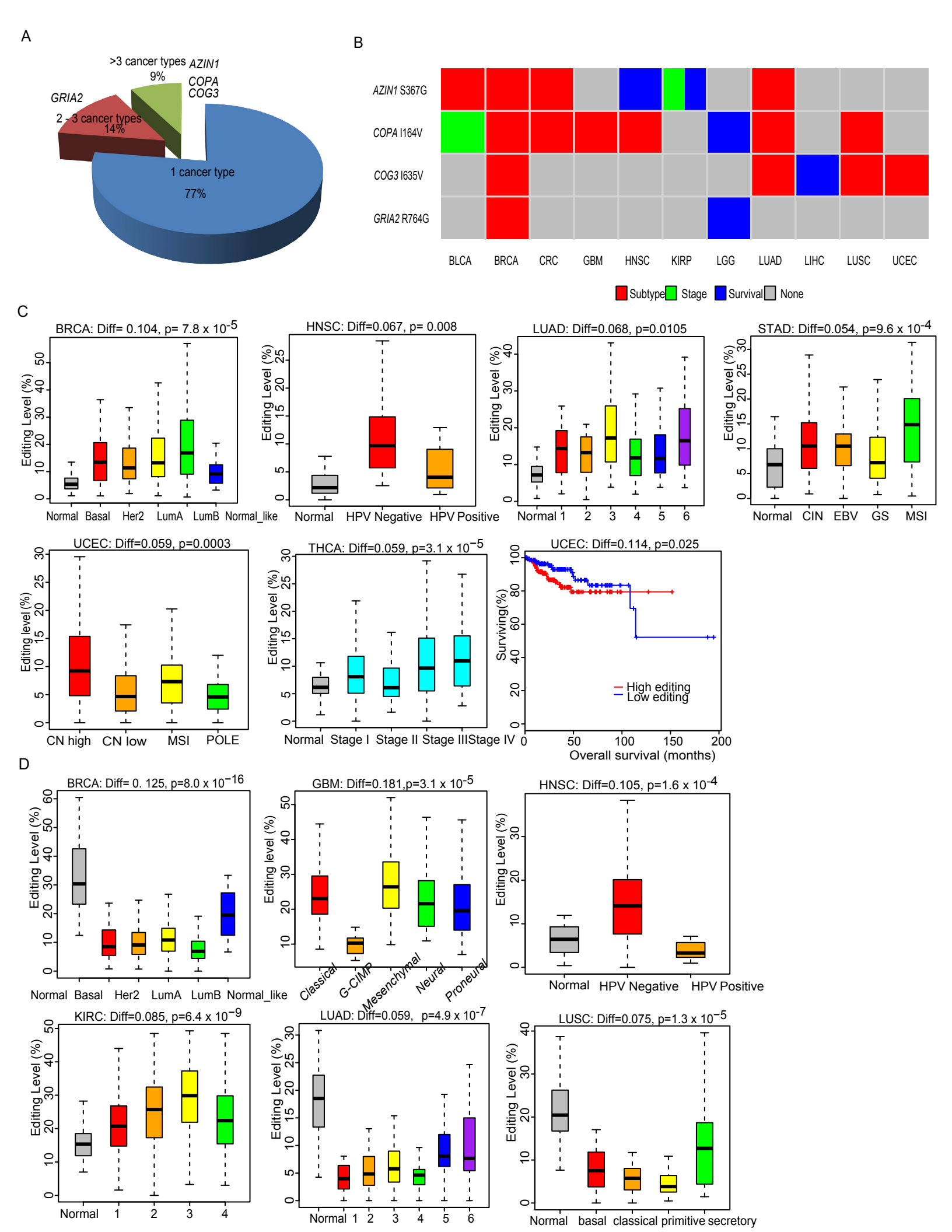
(A) The RNA editing analysis pipeline. (B) A correlation between the number of total mappable RNA-seq reads and the number of informative RNA editing sites across different cancer types. (C) The editing-level distributions across informative editing sites in different normal tissues. Dashed and solid lines denote average and median for each cancer type, respectively. (D) The numbers of nonsynonomous and synomous RNA editing sites in different cancer types.(E) No correlation between RNA editing level and the local GC content in BRCA (Pearson correlation R=-0.03).

Table S1, related to Figure 2

Correlations between the expression levels of ADAR enzymes and the number of RNA editing sites per sample

Cancer Type	# Samples	*ADAR1* Rs	*ADAR1* p	*ADAR2* Rs	*ADAR2* p	*ADAR3* Rs	*ADAR3* p
BLCA	252	0.395	7.43E-11	0.067	0.288	-0.074	0.242
BRCA	837	0.36	<2e-16	-0.054	0.121	0.095	0.006
CRC	228	0.42	3.58E-11	0.086	0.198	0.116	0.08
GBM	154	0.362	4.04E-06	0.158	0.051	0.05	0.538
HNSC	425	0.367	5.82E-15	-0.049	0.311	0.314	3.63E-11
KICH	66	0.34	5.00E-03	-0.107	0.393	-0.098	0.436
KIRC	448	0.3	8.71E-11	0.228	1.06E-06	0.096	0.043
KIRP	198	0.439	1.47E-10	0.206	0.004	-0.069	0.336
LGG	486	0.383	<2e-16	0.098	0.03	0.011	0.805
LIHC	200	0.341	7.52E-07	0.05	0.48	0.001	0.987
LUAD	488	0.205	5.14E-06	0.116	0.01	0.157	0.00049
PRAD	374	0.597	<2e-16	0.079	0.126	0.152	0.003
THCA	498	0.259	4.76E-09	0.091	0.041	0.076	0.091
UCEC	314	0.376	5.63E-12	0.053	0.348	-0.059	0.293

Table S2, related to Figure 3. Provided as an Excel file.


A
>3 cancer types
9%
AZIN1
COPA
COG3
GRIA2
2 - 3 cancer types
14%
1 cancer type
77%
B
AZIN1 S367G
COPA I164V
COG3 I635V
GRIA2 R764G
BLCA BRCA CRC GBM HNSC KIRP LGG LUAD LIHC LUSC UCEC
Subtype Stage Survival None
C
BRCA: Diff= 0.104, p= 7.8 x 10-5
Editing Level (%)
Normal Basal Her2 LumA LumB Normal_like
HNSC: Diff=0.067, p= 0.008
Normal HPV Negative HPV Positive
LUAD: Diff=0.068, p=0.0105
Normal 1 2 3 4 5 6
STAD: Diff=0.054, p=9.6 x 10-4
Normal CIN EBV GS MSI
UCEC: Diff=0.059, p=0.0003
Editing level (%)
CN high CN low MSI POLE
THCA: Diff=0.059, p=3.1 x 10-5
Normal Stage I Stage II Stage III Stage IV
UCEC: Diff=0.114, p=0.025
Surviving(%)
High editing
Low editing
Overall survival (months)
D
BRCA: Diff= 0. 125, p=8.0 x 10-16
Normal Basal Her2 LumA LumB Normal_like
GBM: Diff=0.181,p=3.1 x 10-5
Classical G-CIMP Mesenchymal Neural Proneural
HNSC: Diff=0.105, p=1.6 x 10-4
Normal HPV Negative HPV Positive
KIRC: Diff=0.085, p=6.4 x 10-9
Normal 1 2 3 4
LUAD: Diff=0.059, p=4.9 x 10-7
Normal 1 2 3 4 5 6
LUSC: Diff=0.075, p=1.3 x 10-5
Normal basal classical primitive secretory

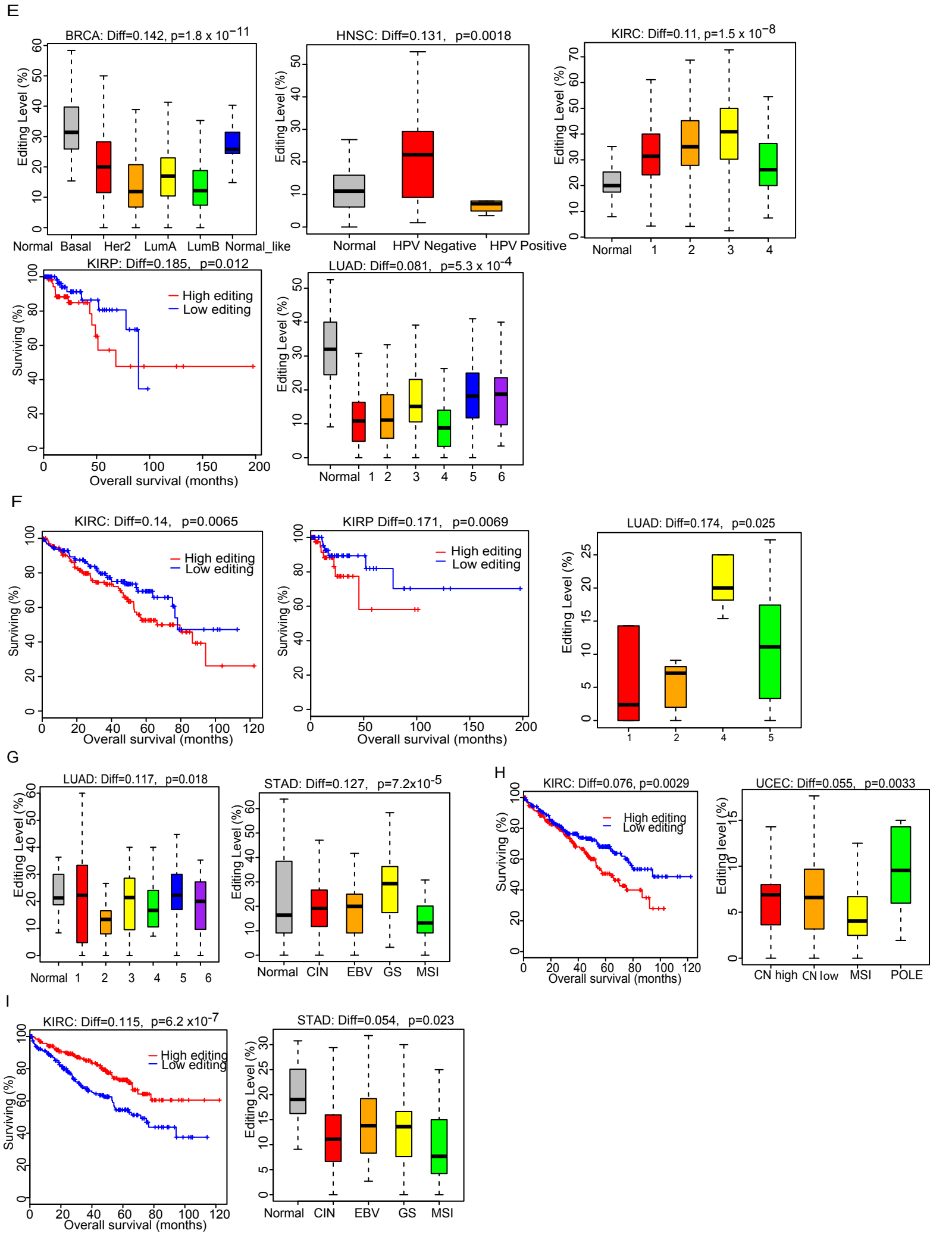

E
BRCA: Diff=0.142, p=1.8 x 10−11
Editing Level (%)
Normal Basal Her2 LumA LumB Normal_like
HNSC: Diff=0.131, p=0.0018
Normal HPV Negative HPV Positive
KIRC: Diff=0.11, p=1.5 x 10−8
Normal 1 2 3 4
KIRP: Diff=0.185, p=0.012
High editing
Low editing
Surviving (%)
Overall survival (months)
LUAD: Diff=0.081, p=5.3 x 10−4
Normal 1 2 3 4 5 6
F
KIRC: Diff=0.14, p=0.0065
KIRP Diff=0.171, p=0.0069
LUAD: Diff=0.174, p=0.025
G
LUAD: Diff=0.117, p=0.018
STAD: Diff=0.127, p=7.2x10-5
Normal CIN EBV GS MSI
H
KIRC: Diff=0.076, p=0.0029
UCEC: Diff=0.055, p=0.0033
CN high CN low MSI POLE
I
KIRC: Diff=0.115, p=6.2 x10-7
STAD: Diff=0.054, p=0.023

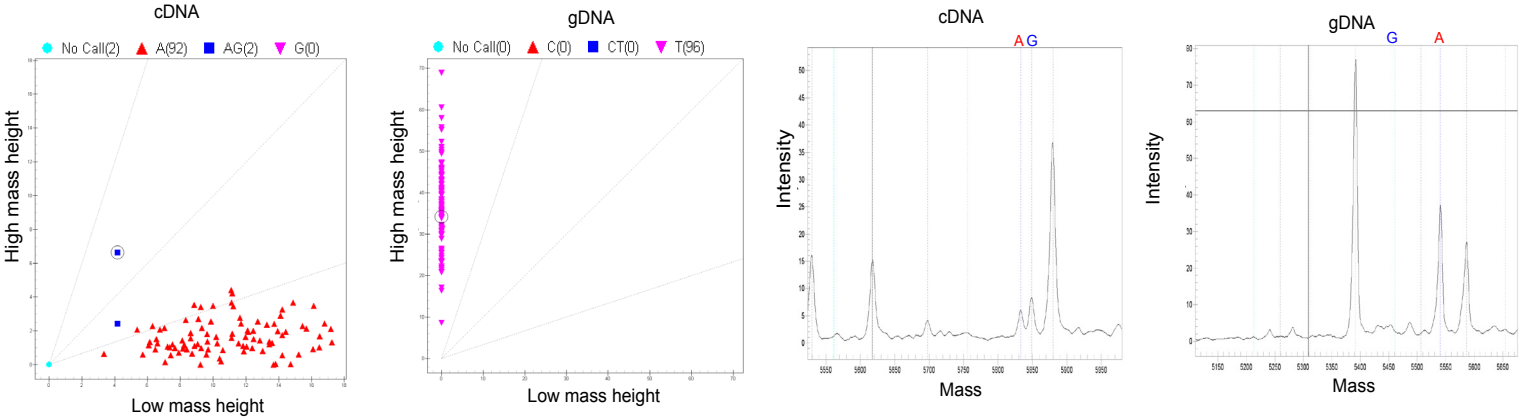
Figure S2 Nonsynonymous RNA editing sites with cross-tumor relevance. Related to Figure 4.

(A) A pie chart showing the distribution of nonsynomous RNA sites with cross-tumor clinical relevance. (B) The clinical relevance of the four top RNA editing canidates based on the analysis of the amount of edited transcripts. (C-I) Cross-tumor clinical relevance of nonsynonymous A-to-I RNA editing sites. *AZIN1* S367G (C), *COPA* I164V (D), *COG3* I635V (E), *ACBD4* T262A (F), *PPIL3* S59G (G), *BLCAP* Q5R (H) and *PODXL* H241R (I). The boxes show the median±1 quartile, with whiskers extending to the most extreme data point within 1.5 interquartile range from the box boundaries.

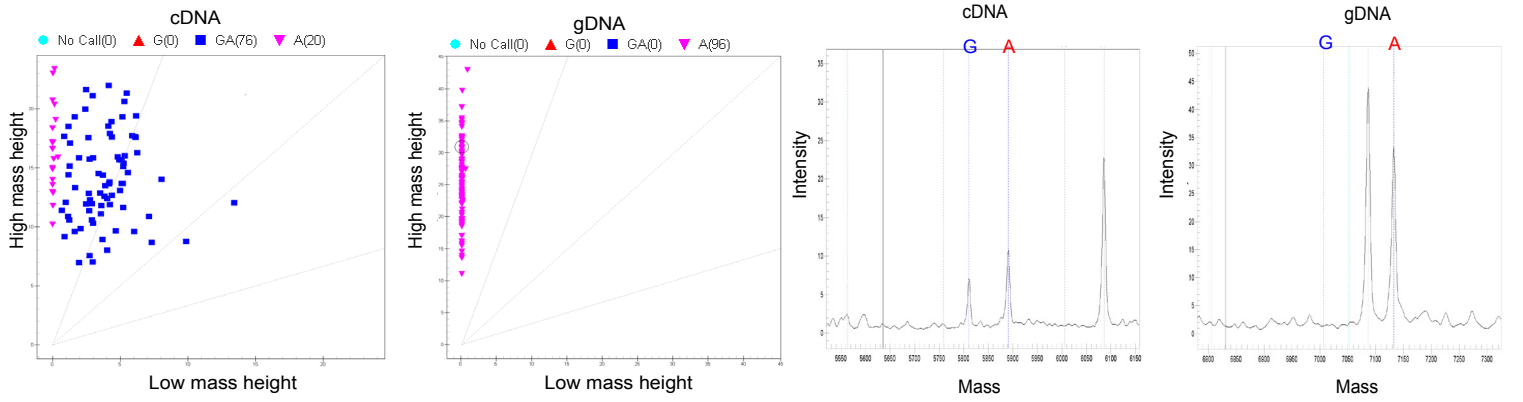
Table S3, related to Figure 4. Provided as an Excel file.

A

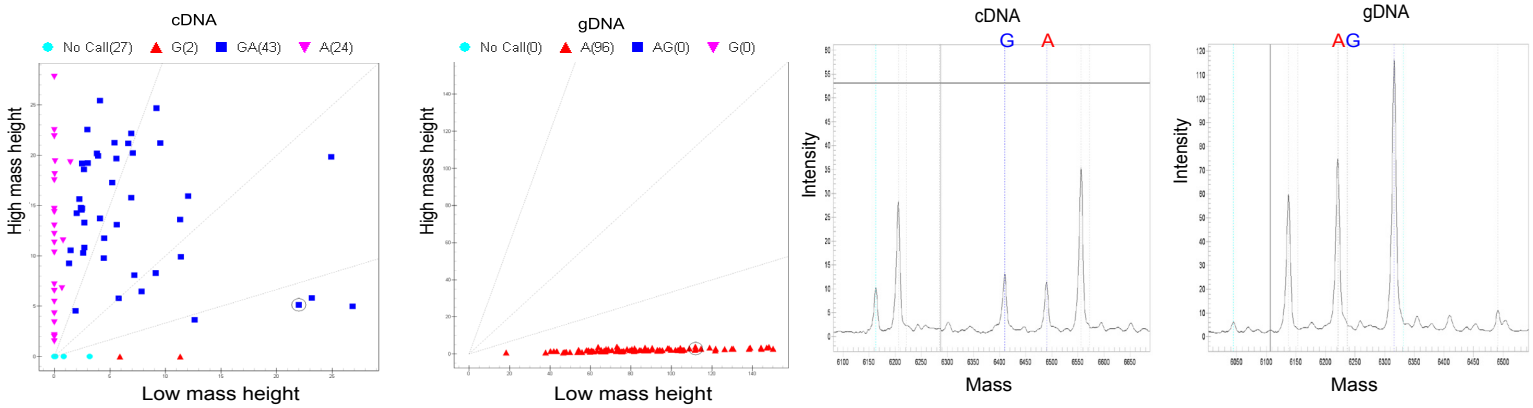
COPA I164V



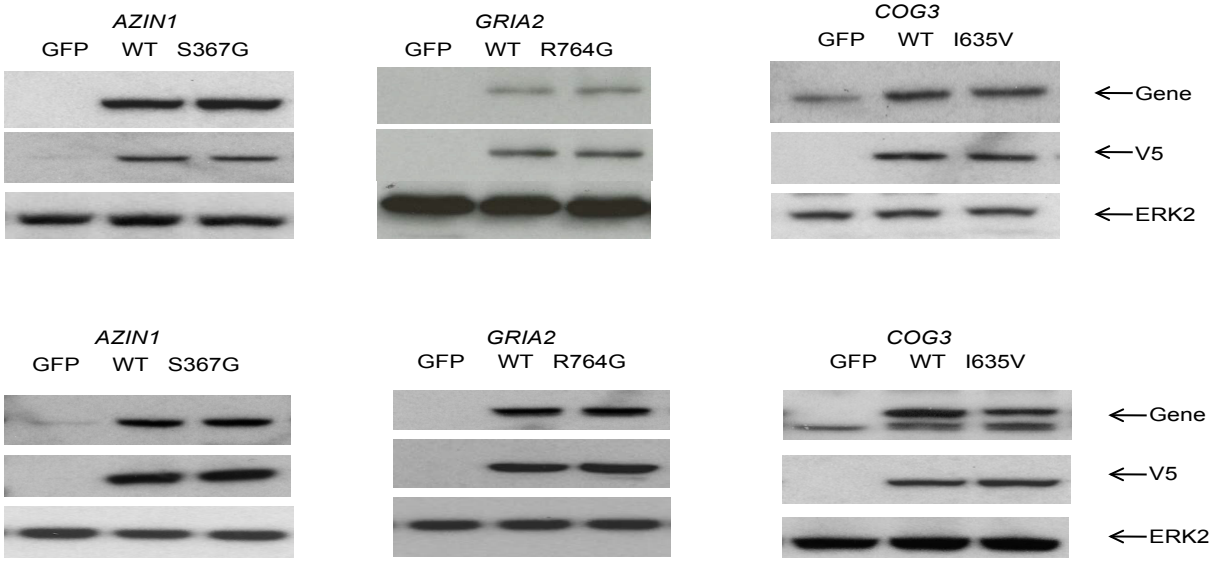
COG3 I635V



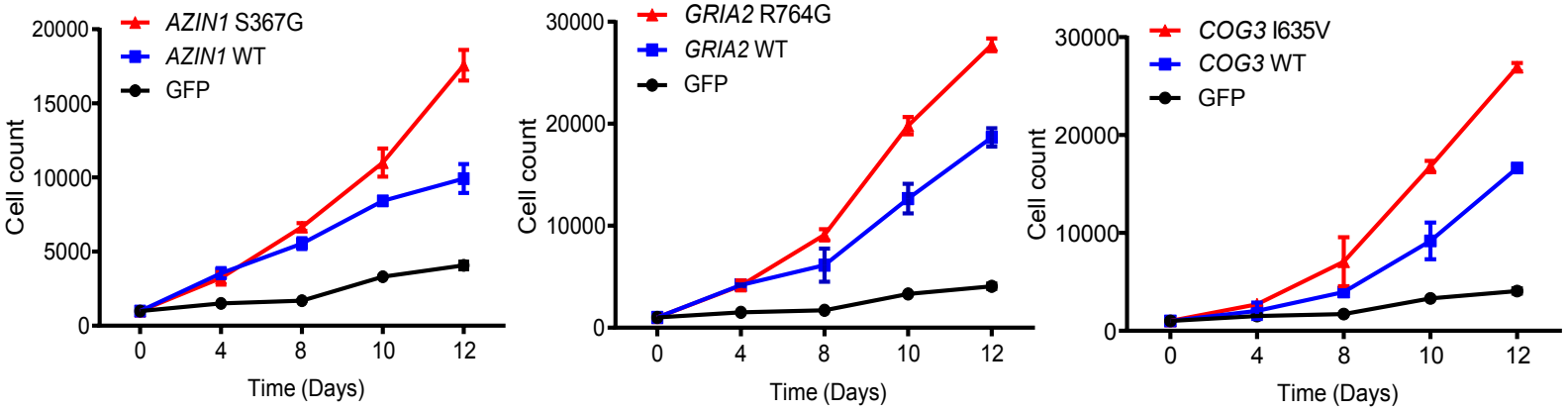
GRIA2 R764G



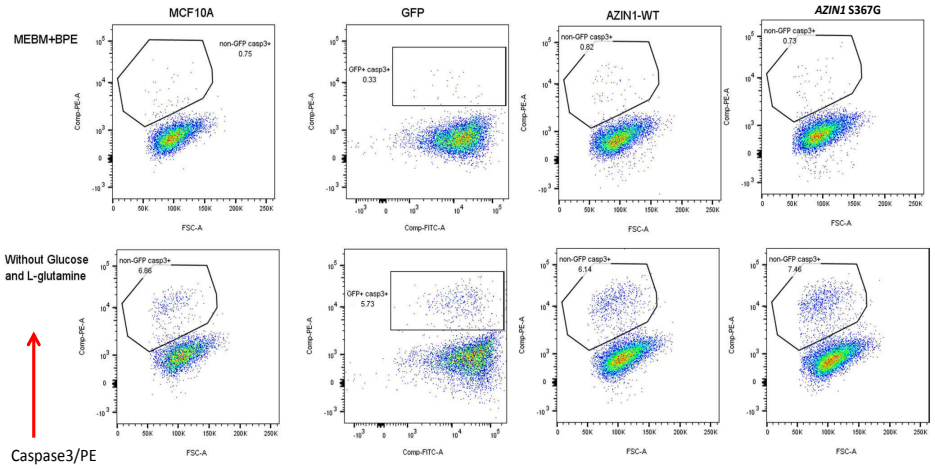
B

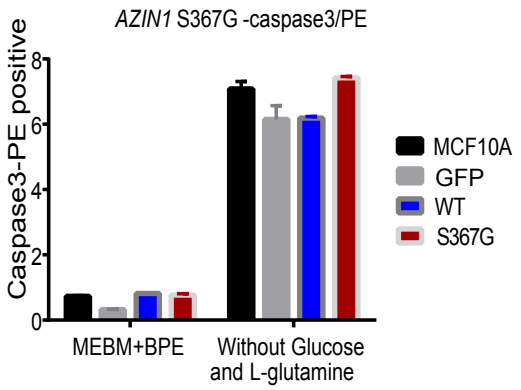


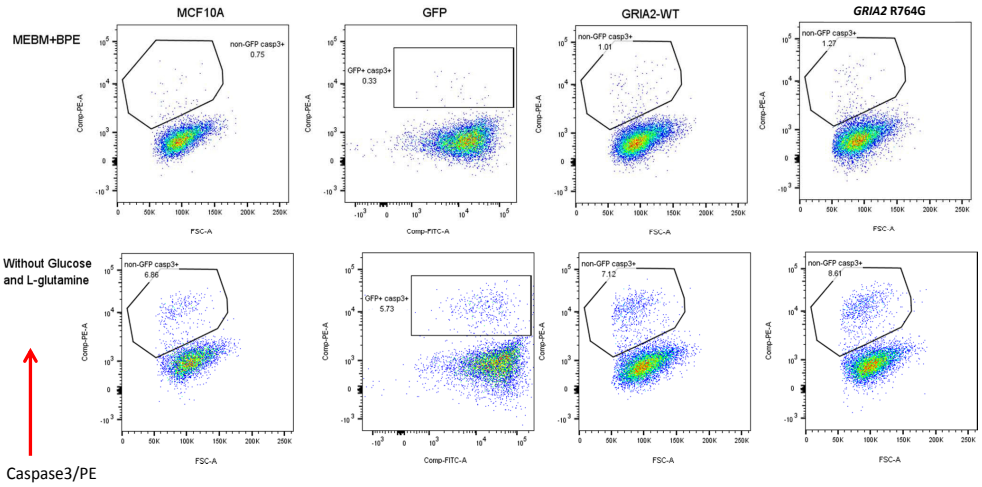
C

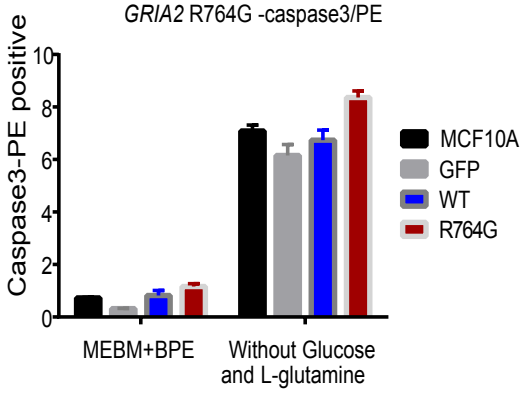

AZIN1 S367G
AZIN1 WT
GFP
Cell count
Time (Days)
GRIA2 R764G
GRIA2 WT
GFP
Cell count
Time (Days)
COG3 I635V
COG3 WT
GFP
Cell count
Time (Days)

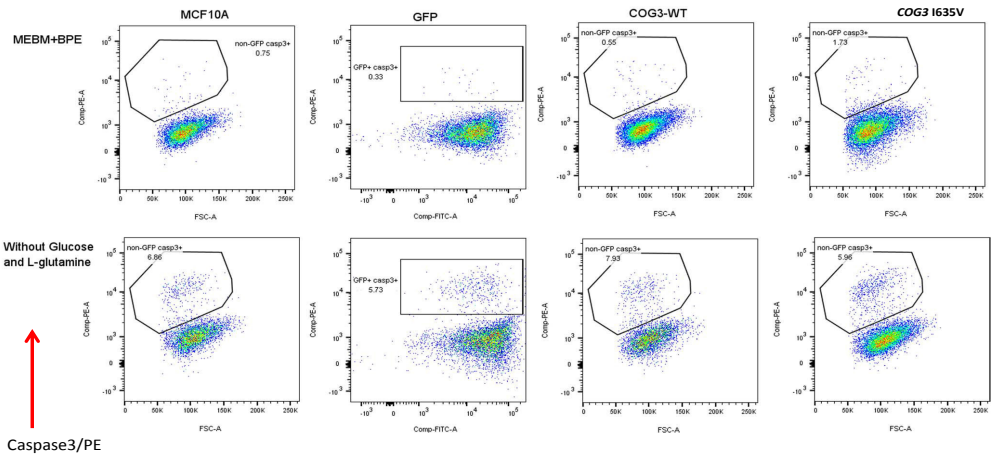
D

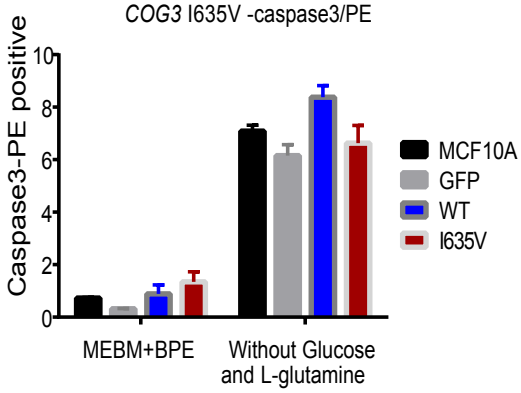

MCF10A
GFP
AZIN1-WT
AZIN1 S367G
MEBM+BPE
Without Glucose and L-glutamine
Caspase3/PE


AZIN1 S367G -caspase3/PE
Caspase3-PE positive
MEBM+BPE
Without Glucose and L-glutamine
MCF10A
GFP
WT
S367G


MCF10A
GFP
GRIA2-WT
GRIA2 R764G
MEBM+BPE
Without Glucose and L-glutamine
Caspase3/PE


GRIA2 R764G -caspase3/PE
Caspase3-PE positive
MEBM+BPE
Without Glucose and L-glutamine
MCF10A
GFP
WT
R764G


MCF10A
GFP
COG3-WT
COG3 I635V
MEBM+BPE
Without Glucose and L-glutamine
Caspase3/PE


COG3 I635V -caspase3/PE
Caspase3-PE positive
MEBM+BPE
Without Glucose and L-glutamine
MCF10A
GFP
WT
I635V

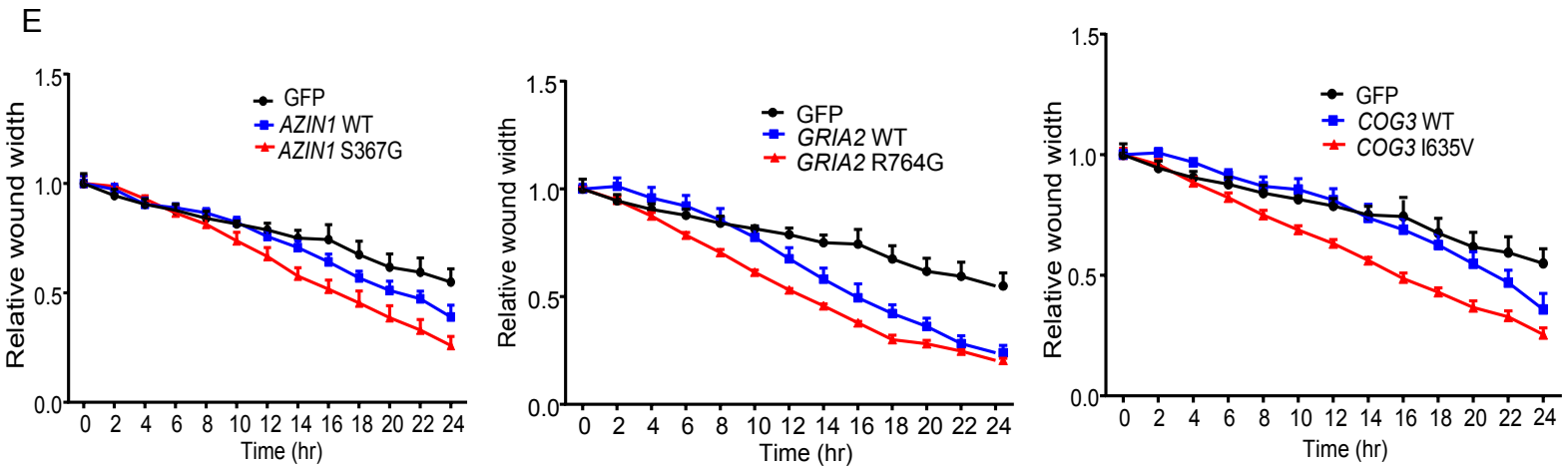


Figure S3 Experimental assays for selected nonsynoymous RNA editing sites. Related to Figure 5.

(A) Sequenom validation of *GRIA2* R764G, *COG3* I635V, and *COPA* I164V. For each gene, the upper panels show the results of a group of samples at cDNA and gDNA, respectively, where each blue symbol represents the AG genotype of a sample; while the bottom panels show the results of an individual sample in cDNA and gDNA, respectively, where there are one "A" peak and one "G" peak in cDNA but only one "A" peak in gDNA. (B) Western blots of the wild-type and the mutants of *AZIN1* S367G, *GRIA2* R764G and *COG3* I635V in stable MCF10A cell line and stable BaF3 cell line. (C) The effects of *AZIN1* S367G, *GRIA2* R764G and *COG3* I635V in MCF10A cell viability assays based on cell counts. Error bars denote +/-SEM. (D) The effects of *AZIN1* S367G, *GRIA2* R764G and *COG3* I635V in MCF10A apoptosis assays. MCF10A cells with different transfections (GFP, WT, and edited form) were subjected to serum starvation (MEGM and BPE) or serum starvation without Glucose and L-glutamine for 24 h to induce apoptosis. Apoptotic cells were assessed via flow cytometric analysis using PE-conjugated active caspase 3 antibody. PE active caspase 3 positive cells were gated for flow cytometry analysis. The percentage of cells exhibiting active caspase 3 is indicated on each histogram as the mean +/- SEM of three replicated experiments. (E) The effects of *AZIN1* S367G, *GRIA2* R764G and *COG3* I635V in MCF10A wound healing assays. Error bars denote +/- SEM.