A

BRAF-like, RAI-treated (*n* = 137): ROC analysis

AP2A1 — AUC = 0.592, CUT-OFF = 10.88
AP2A2 — AUC = 0.618, CUT-OFF = 10.10
AP2B1 — AUC = 0.577, CUT-OFF = 12.72
AP2M1 — AUC = 0.515, CUT-OFF = 12.87
AP2S1 — AUC = 0.544, CUT-OFF = 9.68

B

THCA (*n* = 486); *AP2A1*: High *n* = 270, Low *n* = 216; *P* = 0.0323, *q* = 0.0339

THCA: RAI-treated (*n* = 256); *AP2A1*: High *n* = 113, Low *n* = 143; *P* = 0.0152, *q* = 0.0322

THCA: BRAF MUT (*n* = 228); *AP2A2*: High *n* = 144, Low *n* = 84; *P* = 0.0173, *q* = 0.0322

THCA: BRAF MUT RAI-treated (*n* = 125); *AP2A2*: High *n* = 72, Low *n* = 53; *P* = 0.0061, *q* = 0.0268

C

AP2A1 — HR ± 95% CI

	HR	
THCA	1.99	(*P* < 0.05)
BRAF-like	3.68	(*P* < 0.05)
RAI (BRAF-like)	3.05	(*P* = ns)
RAI (all)	2.57	(*P* < 0.05)
BRAF MUT	2.66	(*P* = ns)
RAI (BRAF MUT)	2.00	(*P* = ns)
RAS-like	1.28	(*P* = ns)
NON-RAI	0.42	(*P* = ns)

AP2A2 — HR ± 95% CI

	HR	
THCA	1.75	(*P* = ns)
BRAF-like	3.14	(*P* < 0.05)
RAI (BRAF-like)	4.58	(*P* < 0.05)
RAI (all)	2.06	(*P* = ns)
BRAF MUT	3.37	(*P* < 0.05)
RAI (BRAF MUT)	4.71	(*P* < 0.05)
RAS-like	0.67	(*P* = ns)
NON-RAI	1.91	(*P* = ns)

D

THCA: BRAF MUT RAI-treated

Nodal Status: N0 (*n* = 37), N1 (*n* = 75)
Disease Stage: I + II (*n* = 73), III + IV (*n* = 51)
Tumour Stage: T1 + T2 (*n* = 63), T3 + T4 (*n* = 62)

E

AP2A1, *AP2A2*, *AP2B1*, *AP2M1*, *AP2S1* — Relative expression by RISK (LOW, INTERM, HIGH)
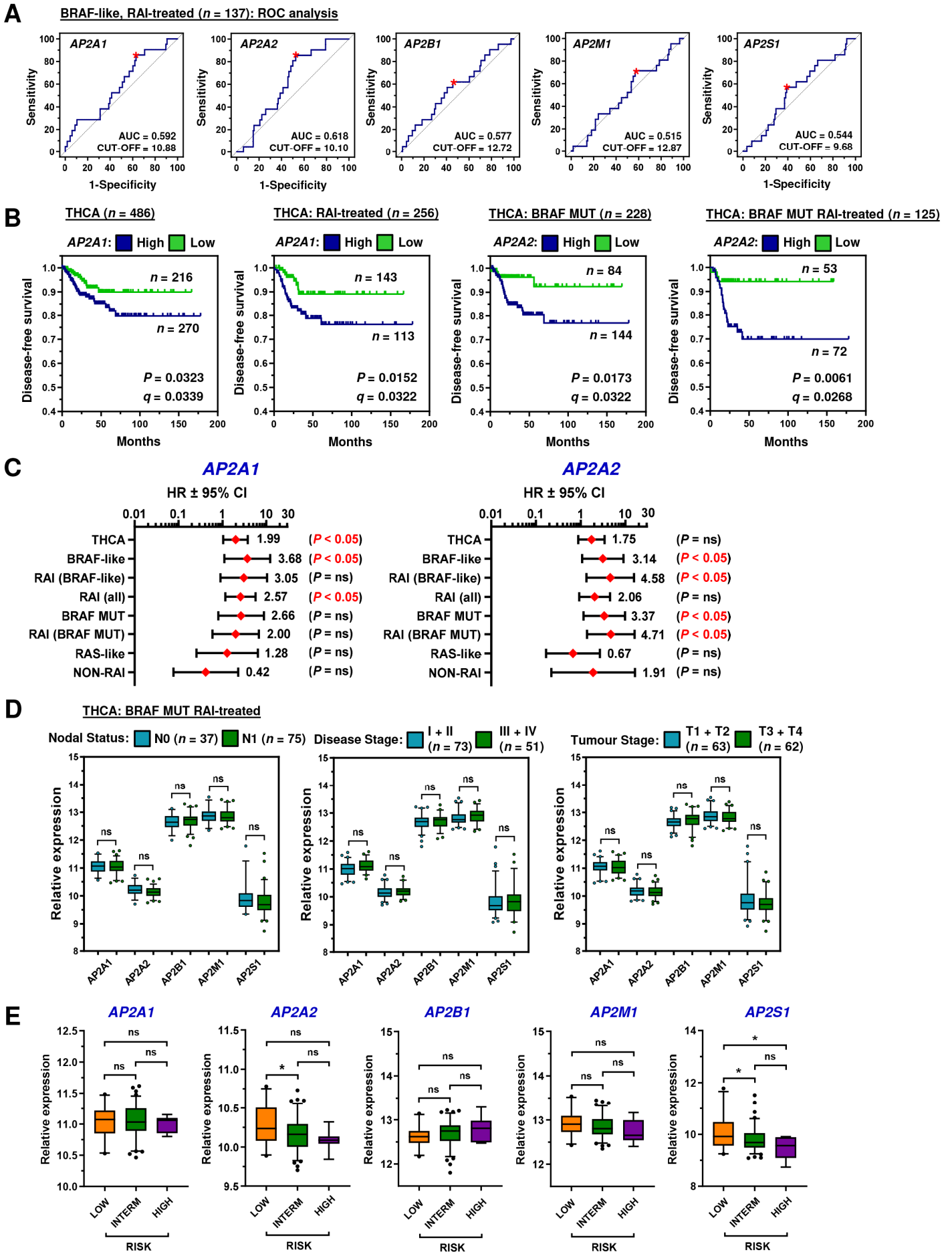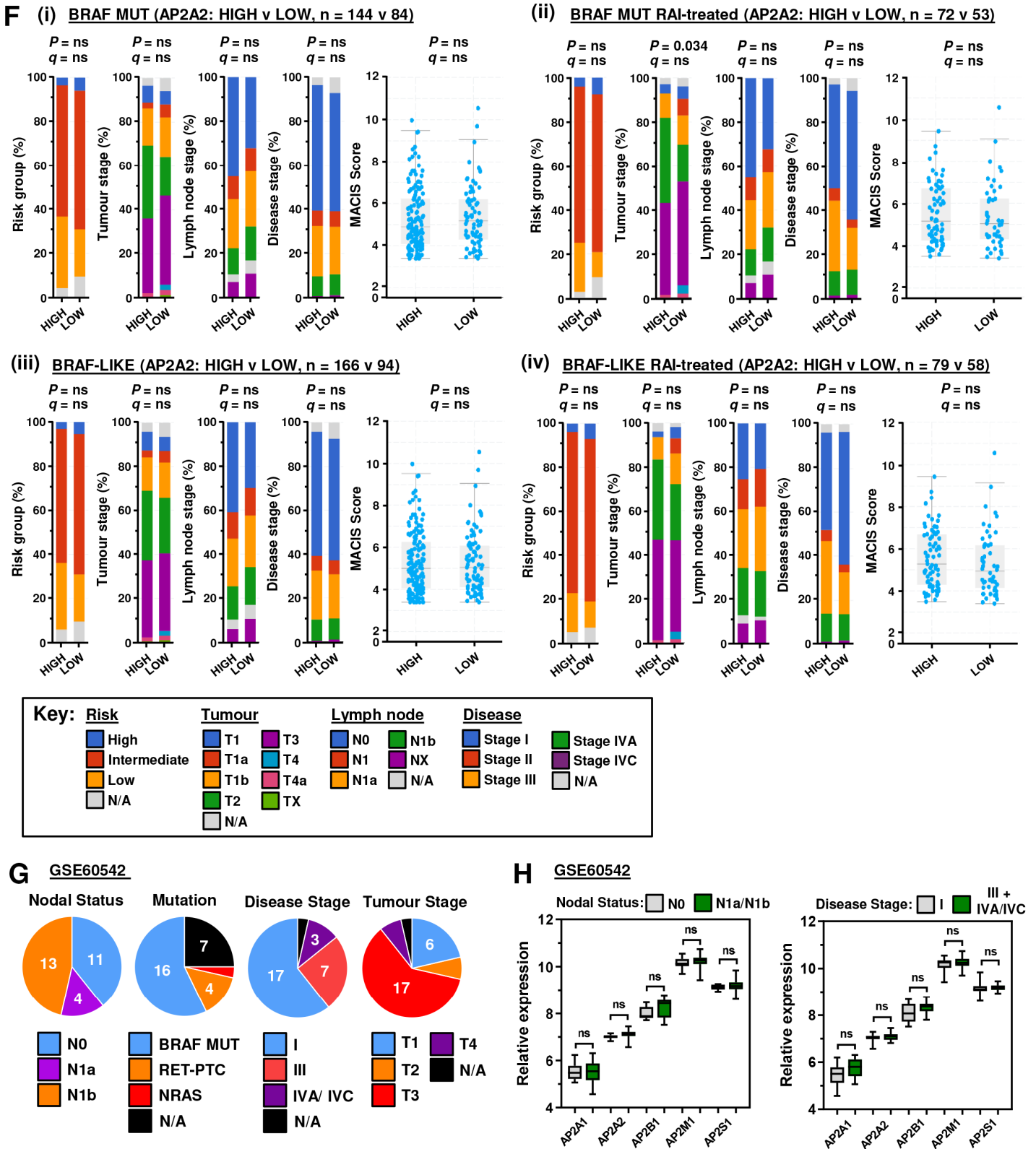
Figure S5. High AP2A1 and AP2A2 expression associated with increased risk of recurrence. **A,** Representative ROC curves of AP2 genes in the BRAF-like, RAI-treated THCA cohort (*n* = 137). **B,** Representative Kaplan-Meier analysis of DFS for indicated THCA TCGA cohorts stratified on high versus low tumoral expression for either *AP2A1* or *AP2A2*; log-rank test. Number (*n*) of patients per expression sub-group (high/low), *P*-values and *q*-values are shown. **C,** Hazard ratio (HR) ± 95% CI for patients stratified on AP2A1 and AP2A2 expression in THCA with the indicated treatment and genetic signature or alteration. **D,** Box and whisker plots showing expression (log₂) of indicated AP2 genes in the BRAF MUT, RAI-treated THCA cohort stratified on nodal status (*left*), disease stage (*middle*) and tumour stage (*right*); *P*-values determined by Mann-Whitney test and adjusted using the Benjamini-Hochberg FDR correction procedure (ns, not significant). **E,** Same as **D** but showing expression (log2) of indicated AP2 genes in the BRAF MUT, RAI-treated THCA cohort stratified according to risk criteria [i.e. low, intermediate (INTERM) and high]. (ns, not significant; *P* < 0.05). **F,** Stacked bar charts showing clinical characteristics of THCA cohorts (i) BRAF MUT (n = 228), (ii) BRAF

MUT RAI-treated (n = 125), (iii) BRAF-like (n = 260) and (iv) BRAF-like RAI-treated (n = 137) stratified by AP2A2 expression (high versus low). Cut-off expression value used was 10.10. Clinical staging attributes include risk group, tumour staging, lymph node staging, disease staging and MACIS score. P-values derived using Chi-Squared test and adjusted using the Benjamini-Hochberg FDR correction procedure. **G,** Pie charts showing cancer staging and tumour mutational characteristics of patients in the GSE60542 cohort (n = 28). **H,** Box and whisker plots showing expression ($\log_2$) of indicated AP2 genes in the GSE60542 cohort stratified on nodal status (*left*) and disease stage (*right*); P-values determined by Mann-Whitney test and adjusted using the Benjamini-Hochberg FDR correction procedure (ns, not significant).