Table EV1. Characterization of AASs. The table summarizes the five distinct AAS signatures (AAS1 to AAS5) based on specific nucleotide mutations, single base substitutions (SBS), associated mutagens or biological processes, gene knockouts (KO), amino acid substitutions, and cancer types. Of note, nucleotide substitutions are represented relative to the pyrimidine bases to avoid redundancy and simplify interpretation (see Figure 2A for details). ROS: reactive oxygen species. MMR: mismatch repair. HR: homologous recombination. ENU: N-ethyl-N-nitrosourea.

	AAS1	AAS2	AAS3	AAS4	AAS5
Nucleotide mutations	5' C/G **C > A** A/C/T 3'	5' C/T **C > T** C/T 3'	5' A/C/G **C > T** G 3'	5' C **T > C** G / T **T > G** T 3'	5' T **C > G** A/T 3'
SBS	4, 8, 18, 24, 29, 35, 36	2, 7a, 7b, 11, 30	1, 6, 15	3, 5, 9, 12, 25, 26, 37, 40, 41 44, 46	13
Associated mutagens/ processes	Cigarette smoke Aflatoxin A1 Cisplatin, ROS (KBr03)	UV light APOBEC3 Temozolomide	MMR deficiency Clock-like sign.	MMR deficiency HR deficiency Alkilating agents (ENU) Glycidamide Clock-like sign.	APOBEC3
Gene KO	OGG1 MUTYH	NTHL1 UNG	PMS1	MLH1, MSH2, PMS2, MSH6 EXO1, RNF168	-
AA substitutions Hydrophobic, polar, negative, positive, special	Gly > Val Ala > Ser	Glu > Lys, Pro > Ser Asp > Asn, Gly > Glu Ser > Phe, Pro > Leu	Arg > His, Arg > Cys Arg > Gln, Arg > Trp Ala > Val, Ala > Thr	Heterogeneous	Glu > Lys Glu > Gln
Cancer types	LUAD LUSC LIHC	SKCM	COAD, READ PAAD, STAD UCEC, PRAD	KIRC KIRP LIHC THCA	BLCA CESC