Supplementary Figure Legend

Figure S1 mSigHdp extracted signatures highly similar to COSMIC signatures

Figure S2 mSigHdp extracted signatures and the genomes strongly supporting the presence of these signatures.

Figure S3 Detailed characterization of C\_ID5 and C\_ID8. (A) Mutational signature spectrum of C\_ID5 and C\_ID8; (B) Correlation between signature activity and age; (C) Length of deletions longer than 5bp characterized by C\_ID5 and C\_ID8; (D) The genomes strongly support the presence of C\_ID5 and C\_ID8; (E) Correlation between ID5 and ID8 activity in different tumor types reported in Alexandrov et al., 2020.

Figure S4 Comparison among COSMIC ID17, mSigHdp extracted C\_ID17 and ID\_TOP2A K743N reported by Boot et al., 2022

Figure S5 Example genomes supporting the presence of H\_ID27 and C\_ID14

Figure S6 MSI samples characterization. (A) Correlation between C\_ID2, H\_ID33 and H\_ID37; (B) Correlation between C\_ID1 and C\_ID2 in MSI tumors and non-MSI tumors; (C) AUROC in predicting MSI status provided by the literature.

Figure S7 C\_ID4, H\_ID29 and mutation spectra of TOP1-TAM in vitro models. (A) C\_ID4 and H\_ID29 mutational signature; (B) Mutational spectra of Rnaseh2b-KO mice model and their cosine similarities to H\_ID29 and C\_ID4 (excluding single C/T deletion/insertion); (C) Mutational spectra of RNASEH2A KO and RNASEH2B KO model and their cosine similarities to H\_ID29 and C\_ID4 (excluding single C/T deletion/insertion); (D) Mutational spectra of pol2-M644G rnh201Δ of yeast genomes from Williams et al., 2019 and Conover et al., 2015, and their cosine similarities to H\_ID29 and C\_ID4 (excluding single C/T deletion/insertion).

Figure S8 SigProfilterExtractor result in PCAWG and HMF indel analysis. (A) Optimal solution plot generated by SigProfilterExtractor. (B) SigProfilterExtractor extracted signatures.

Figure S9 Three indel signatures similar to the re-analysis of PCAWG genomes in Jin et al., 2024

Figure S10 MuSiCal result in PCAWG and HMF indel analysis. (A) Optimal solution plot generated by MuSiCal. (B) MuSiCal extracted signatures.