**Figure S1. ID83 mutational signatures asymmetries in DNA regions, replication strands and transcription strands across cancer types.**

(A) Enrichment of mutations in genic and intergenic regions for ID83 signatures. Each row represents one ID83 signature, and each column displays a cancer type. Signatures enriched in genic and intergenic regions are shown in circles with yellow and light blue colors, respectively. Significance of enrichment was shown as stars (Fisher’s exact test, \* p < 0.05, \*\* p < 0.01, \*\*\* p < 0.001).Color intensities and Circle sizes represent the odds ratio between the ratio of real mutations and the ratio of simulated mutations (See Methods).

(B) Replication strand asymmetries of ID83 signatures. Data are presented in a format similar to the one in panel (A), with green and orange colors indicating replication strand asymmetries on the lagging and leading strands, respectively.

(C) Transcription strand asymmetries of ID83 signatures. Data are presented in a format similar to the one in panel (A), with red and dark blue colors indicating transcription strand asymmetries on the transcribed and untranscribed strands, respectively.

**Figure S2. Interplay between ID83 signatures and replication time.**

Mutation densities of ID83 signatures per decile (y axes) are presented for early (left) to late (right) replication domains. Real mutations for signatures are shown as bars, and simulated mutations are shown as red dashed lines. As the numbers shown on top of each plot, green bars indicate signatures consistently associated with late replication timing across cancer types; yellow bars indicate signatures consistently associated with early replication timing across cancer types; purple bars indicate signatures not affected by replication timing; blue bars indicate signatures showing inconsistent trend across cancer types.