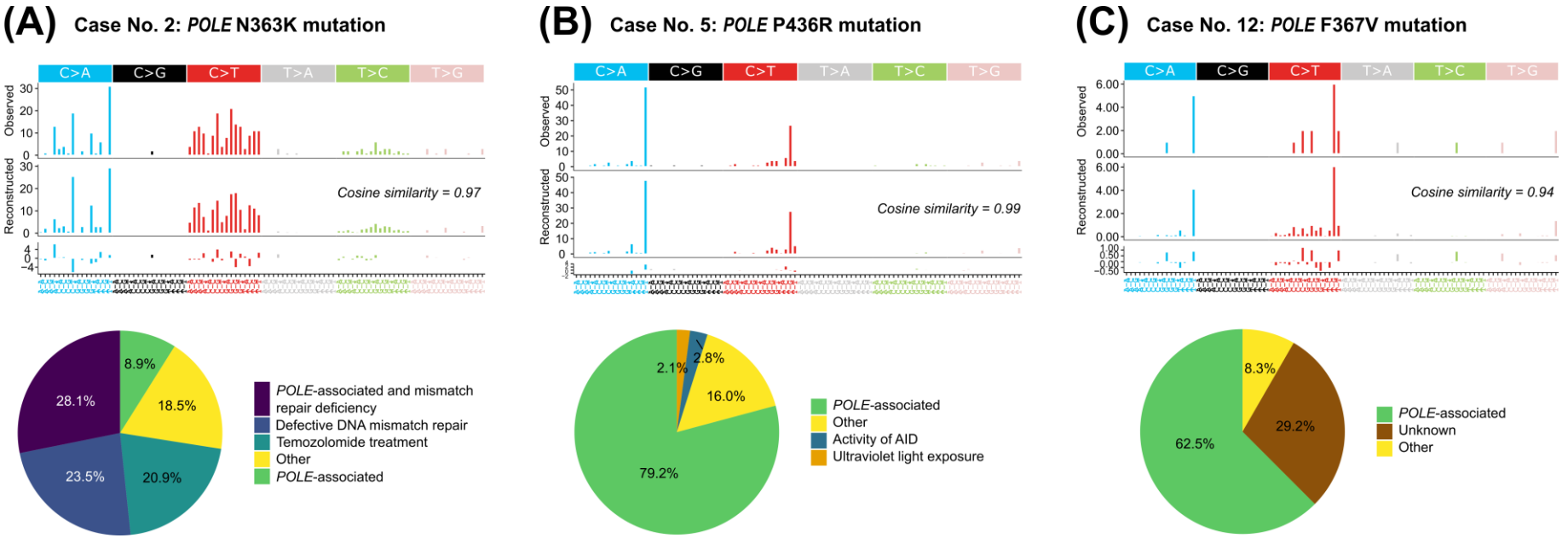



**Supplementary Fig. S2.** Mutational signature profiles in tumors with non-hotspot *POLE* exonuclease domain variants. (A–C) For each case, the upper panel displays the observed (top), reconstructed (middle), and residual difference (bottom) SBS spectra across 96 trinucleotide contexts, grouped by six substitution classes. Cosine similarity between the observed and reconstructed profiles is indicated. The pie charts show the relative contributions of refitted COSMIC SBS signatures grouped according to their proposed etiologies. Etiologic labels reproduce the COSMIC-associated annotations of computationally attributed signatures and do not indicate documented clinical exposure in an individual patient. Cosine similarity quantifies reconstruction of the observed spectrum and does not by itself establish the biological accuracy of each attributed signature. SBS, single base substitution; COSMIC, Catalogue of Somatic Mutations in Cancer.