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Indel mutational signatures reveal distinct subtypes of microsatellite instability

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Microsatellite instability (MSI), characterized by alterations in microsatellite sequences, plays a pivotal role in cancer development and therapy response. In this study, we analyzed whole-exome sequences of 528 colorectal cancer (CRC) and 525 uterine corpus endometrial carcinoma (UCEC) to identify indel (ID) signatures of MSI and to unveil distinct MSI-specific mutational feature that are distinct from DNA polymerase. A novel MSI subtype displaying an insertion-dominant pattern without concurrent POLE/POLD1 mutations, was identified. Through comprehensive genomic analysis of MLH1 methylation, transcriptome expression, we have confirmed that each subtype possesses distinct signatures with unique characteristics. Notably, we observed that the novel MSI subtype (novelsig) exhibited significantly higher immune infiltrate compared to other subtypes. In conclusion, this study can provide a comprehensive characterization of ID signature features and subtype classification in MSI-H tumors, offering valuable insights into the heterogeneity, immune microenvironment and clinical implications of these subtypes.