

Driver

Cancers are caused by genomic alterations known as drivers. While hundreds of drivers in coding genes are known, only a handful of non-coding drivers have been discovered to date despite intensive searching.

Attention has recently shifted to the role of altered **RNA splicing** in cancer; driver **mutations** that lead to **transcriptome**-wide aberrant **splicing** have been identified in multiple cancer types, although they have only been found in protein-coding splicing factors like **SF3B1** (splicing factor 3b subunit 1). In contrast, cancer-related alterations in the non-coding component of the **spliceosome**, a series of small nuclear RNAs (snRNAs), have barely been studied due to the combined challenges of characterizing non-coding cancer drivers and the repetitive nature of snRNA genes.

Shuai et al. reported a highly recurrent A>C somatic mutation at the third base of U1 snRNA in several tumour types. The primary function of U1 is to recognize the 5' splice site (5'SS) via base-pairing. This mutation changes the preferential A-U base-pairing between U1 and 5'SS to C-G base-pairing, thereby creating novel splice junctions and altering the splicing pattern of multiple genes, including known cancer drivers. Clinically, the A>C mutation is associated with alcohol abuse in hepatocellular carcinoma (HCC) and the aggressive IGHV unmutated subtype of chronic lymphocytic leukaemia (CLL). The U1 mutation also confers an adverse prognosis to CLL patients independently. The study demonstrates one of the first non-coding drivers in spliceosomal RNAs, reveals a novel mechanism of aberrant splicing in cancer and may represent a new target for treatment. The findings also suggest that driver discovery should be extended to a wider range of genomic regions ¹⁾.

¹⁾

Shuai S, Suzuki H, Diaz-Navarro A, Nadeu F, Kumar SA, Gutierrez-Fernandez A, Delgado J, Pinyol M, López-Otín C, Puente XS, Taylor MD, Campo E, Stein LD. The U1 spliceosomal RNA is recurrently mutated in multiple cancers. *Nature*. 2019 Oct 9. doi: 10.1038/s41586-019-1651-z. [Epub ahead of print] PubMed PMID: 31597163.

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