

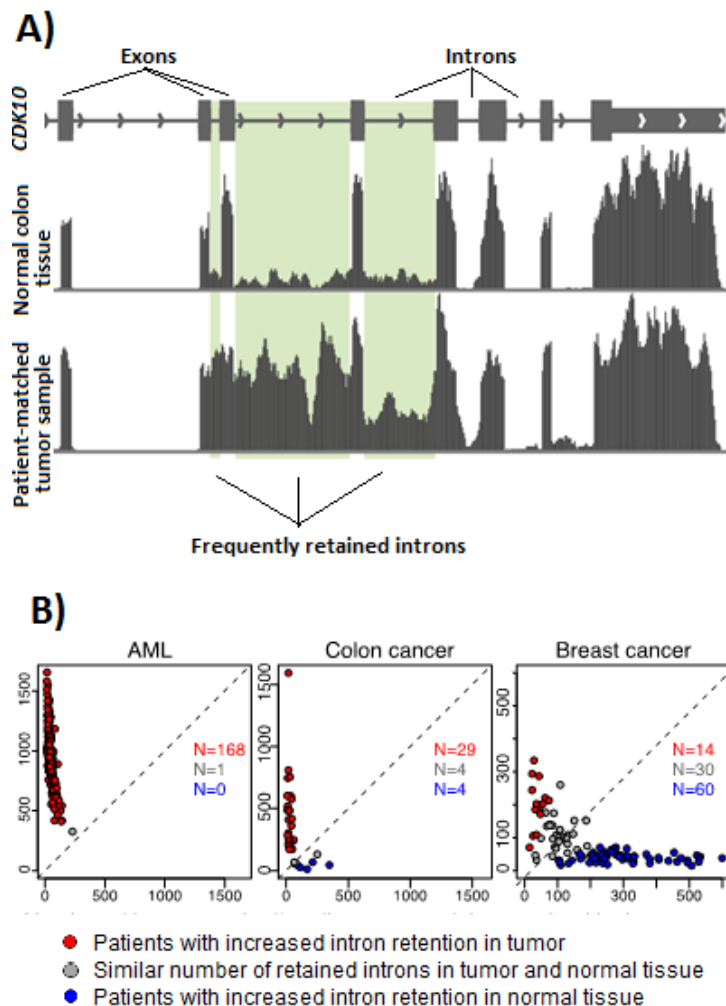
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SCIENCE SPOTLIGHT

Most cancer transcriptomes are bloated by widespread intron retention

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A) Comparing RNA-seq read coverage for a portion of the CDK10 gene shows that some introns are more frequently retained in the tumor sample than the adjacent normal tissue. B) For each individual, the number of introns retained in the tumor sample (y-axis) is plotted against the number of introns retained in the matched normal sample (x-axis). Aggregating patients, most tumors showed much more frequent intron retention (left, middle), while breast cancer was the exception where normal tissue exhibited more common intron retention (right).

Image provided by Dr. Heidi Dvinge

Alternative splicing of specific genes can contribute to cancer initiation, progression, and metastasis. With the advent of cancer genome sequencing, it was discovered that many tumor types contain high frequencies of somatic mutations affecting components of the RNA splicing machinery. Additional evidence suggested that common RNA processing differences might distinguish between cancer and normal cells, but had not been systematically tested. To evaluate this question, Drs. Heidi Dvinge and Robert Bradley in the Public Health Sciences and Basic Sciences Divisions performed a genome-wide search for signals of abnormal cancer-associated

splicing. As recently reported in *Genome Medicine*, the authors found that abnormal RNA splicing is a common characteristic of most cancers, even when the RNA splicing machinery appears unaltered.

Genes are made up of protein-encoding exons interspersed with introns. Normally, DNA is transcribed into RNA and then modified through a process that only retains the genetic information from the exons. In this process, the cellular splicing machinery excises the introns out of the RNA copy and joins the ends of exons together. "One of the surprising findings from the large-scale cancer genomics effort in the last few years has been the high frequency of mutations in the RNA processing machinery," said lead author Dr. Dvinge. Errors in this process can result in the retention of introns, potentially leading to abnormal protein products with unknown consequences.

To evaluate for systematic differences in RNA splicing, the authors utilized the comprehensive transcriptome data available from The Cancer Genome Atlas (TCGA). This involved comparing patterns of RNA splicing between 800 tumor and patient-matched normal control samples, and across 16 distinct cancer types. These cancers included 15 solid tumors as well as one liquid tumor (acute myeloid leukemia). Using RNA-seq data from TCGA, for each tumor-normal pair the authors identified introns that were differentially retained between the samples (see figure). These differences in intron retention were quantified and then compared among and across cancer types. Said Dr. Dvinge, "we found that abnormal RNA splicing is a common feature of a wide range of primary tumors, even in the absence of DNA mutations or other obvious changes to the RNA processing machinery."

Notably, 15 of the 16 cancer types showed a strong enrichment for increased retention of alternative introns within the tumor compared to the adjacent normal control tissue. The one exception was breast cancer, which actually showed the opposite pattern. The authors found that the majority of these retained introns were either specific to a particular cancer, or were found at low frequencies in multiple cancers. At the same time, a handful of retained introns were shared across most cancer types, mostly within genes encoding RNA splicing and export factors. These results suggest that the RNA splicing process may be commonly dysregulated in cancer, which may be useful for differentiating normal versus cancerous cells.

While this study demonstrates that intron retention is a common occurrence in many tumor types, the functional consequences of this phenomenon remain to be explored. "It remains to be seen whether the intron-containing transcripts are dead-end cellular products, or whether they contribute to the cancer proteome," said Dr. Dvinge. "Regardless, analyzing the dysregulated RNA splicing

events may help us to unravel why small molecules that inhibit splicing also have anti-tumor activity, or help design novel therapies targeting tumor cells."

Citation:

[Dvinge H, Bradley RK](#). 2015. Widespread intron retention diversifies most cancer transcriptomes. *Genome Med.* 7(1):45. doi: 10.1186/s13073-015-0168-9.

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