

# Highlights of Analytical Sciences in Switzerland

## Division of Analytical Sciences

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### The Quest for Novel Cancer Biomarkers and Drug Targets in the Alternative Splicing Landscape

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Alternative splicing is a fundamental cellular process that enhances the functional diversity of genes. Under normal conditions, most genes predominantly express a canonical mRNA molecule upon activation. However, in complex diseases such as cancer and Alzheimer's, disruptions in the splicing machinery can lead to the overproduction of alternative isoforms with distinct biological functions. Understanding and mapping these changes provides critical insights into disease mechanisms and serves as a valuable resource for identifying novel biomarkers and therapeutic targets (Fig. 1).

Despite its significance, the role of alternative splicing in complex diseases remains understudied. To comprehensively identify and functionally assess disease-associated splicing alterations, a multidisciplinary approach is required. In our lab, we integrate bioinformatics, machine learning, sequencing, structural and systems biology with molecular pathology to unravel the full complexity of isoform changes in cancer and other diseases.

As an example, in our latest study, we leveraged a cutting-edge single-cell long-read sequencing technology to analyze the alternative splicing landscape in clear-cell renal cell carcinoma (ccRCC), the most prevalent subtype of kidney cancer. Our analysis identified over 30,000 previously uncharacterized mRNA transcripts, many of which were cell-type specific and associated with genes that drive ccRCC progression. More than half of these novel transcripts had the potential to encode functional proteins.

An interesting discovery was a previously unknown transcript of the NNMT gene. The NNMT gene is known to be part of ccRCC-related pathways. Our newly discovered isoform lacks the substrate-binding site, suggesting a loss of enzymatic activity. We were able to validate the novel mRNA sequence of NNMT using PCR. This finding underscores the importance of looking beyond DNA mutations in current standards of molecular diagnostics, as our samples revealed no functional loss at the DNA level. Functional disruptions of NNMT were only observed at the alternative splicing level. **Our research highlights the transformative potential of splicing-based diagnostics and therapeutics, which will pave the way for new strategies to combat cancer and other complex diseases at their molecular basis.**

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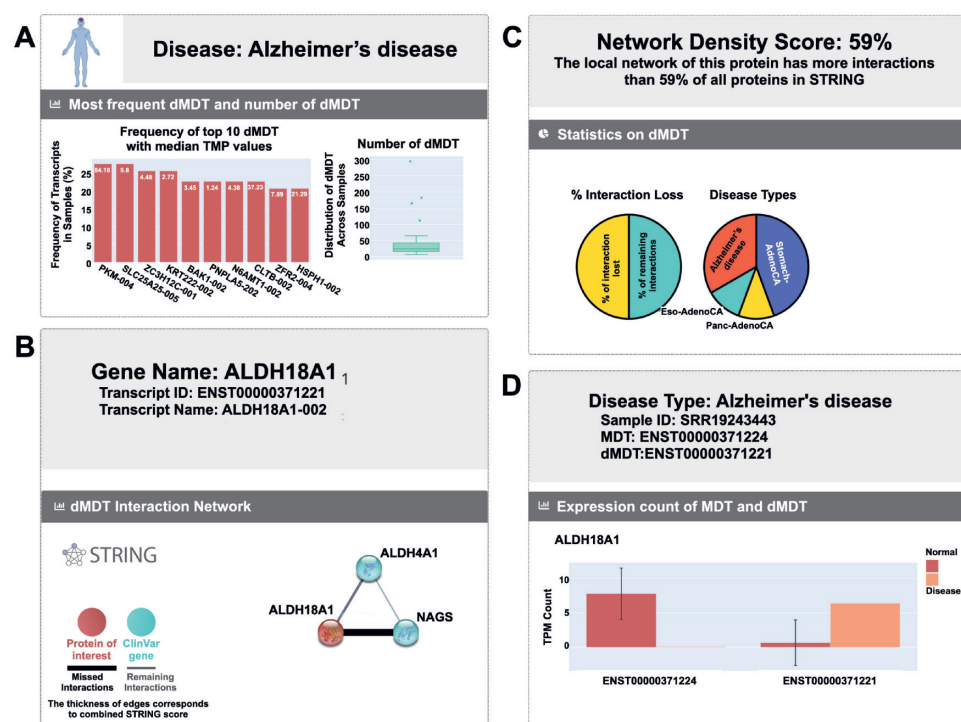


Fig. 1. Overview of functionalities of our disease-specific isoform database [www.caniso.net](http://www.caniso.net). The database provides users with various statistics to support the functional interpretation of disease-specific mRNA transcripts (dMDT). (A) *Disease page*: frequency of top 10 dMDT, most frequently observed in Alzheimer's Disease. (B) *Isoform page*: visualization of interaction losses due to the disease-specific protein isoform of the gene ALDH18A1, which is known to be mutated in neurodegenerative diseases. (C) *Network density score* and the percentage of interaction loss of the ALDH18A1 isoform. (D) *Sample page*: Median and sample-specific expression level of normal and disease-specific mRNA molecules.

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