DANSKE KRÆFTFORSKNINGSDAGE 2025

Whole genome sequencing reveals germline structural rearrangements, highly polymorphic in Danes, with major impact on the colorectal cancer transcriptome and patient prognosis (#52)

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Research Question

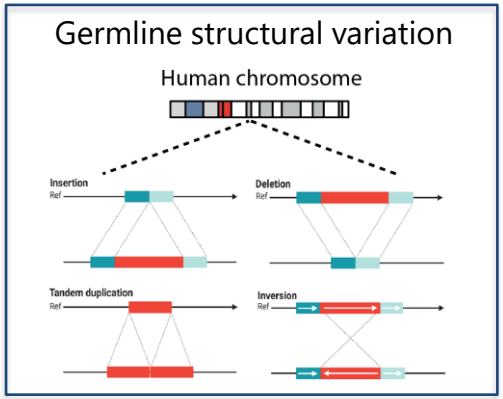
- Does structural variation (SV) in the germline influence gene expression, tumor biology, and clinical outcomes in colorectal cancer (CRC)?

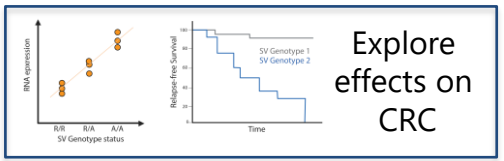
Motivation

- Until recently, the presence and polymorphic diversity of germline SVs in humans were poorly characterized.
- The impact of germline SVs in cancer remains largely unexplored.

Methods

- Profiling: Whole-genome and total RNA sequencing of 347 CRC patients with long-term follow-up
- Genotyping: Germline SVs genotyped using a pangenome reference
- Associations: Tested associations between SV genotypes, tumor RNA expression, and relapse-free survival (RFS)





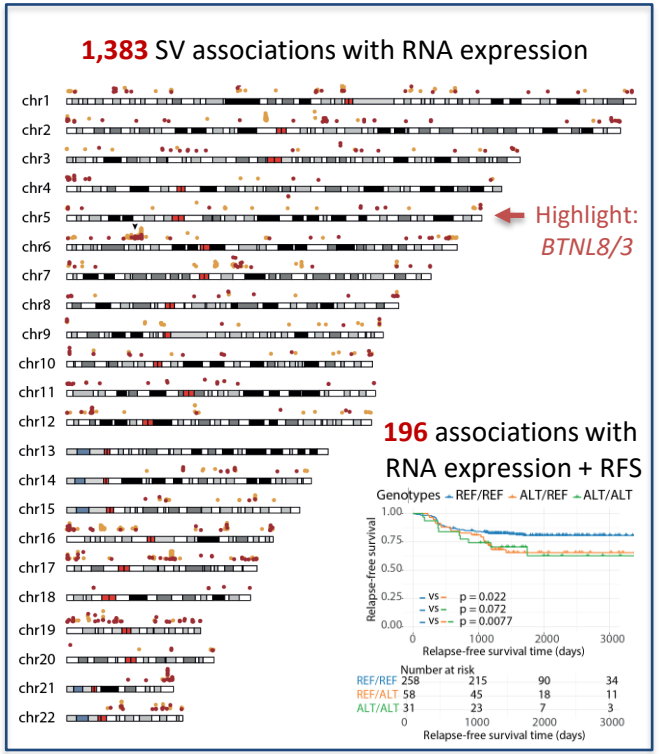
Results Overview

Germline SVs identified

- 152,192 SVs identified
- 75,254 SVs classified as “common” (AF > 0.05)
- **25,545 SVs per patient** (56% validated by Nanopore WGS)

SV associations identified

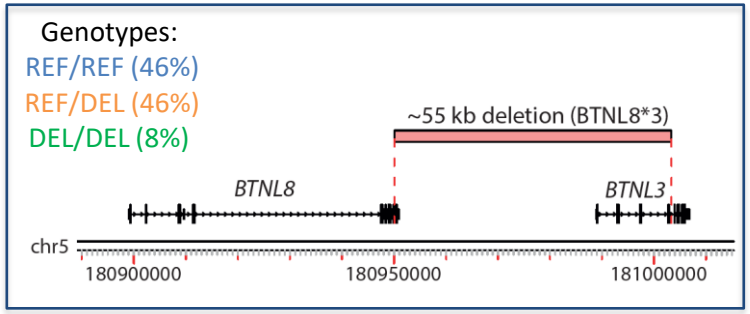
- SVs intersected 3,771 exons within 1,537 genes and >4,000 gene regulatory regions
- **1,383** SV associations with RNA expression (1,050 SVs / 586 genes)
- **196** SV associations with RNA expression and patient relapse-free survival (153 SVs / 184 genes)



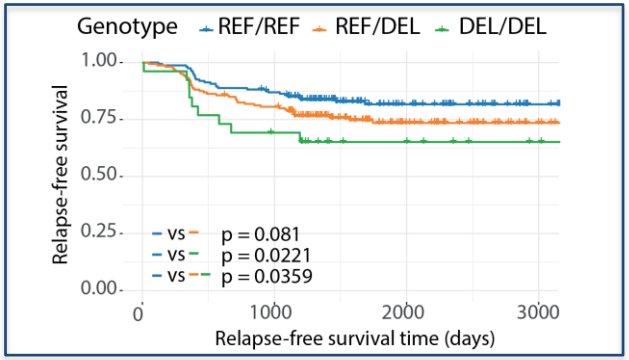
⇒ Polymorphic germline SVs are numerous, exert direct and indirect impacts on hundreds of genes, and may shape the biology and outcome of colorectal cancer.

A 55 kb germline SV affecting the *BTNL8/3* genes

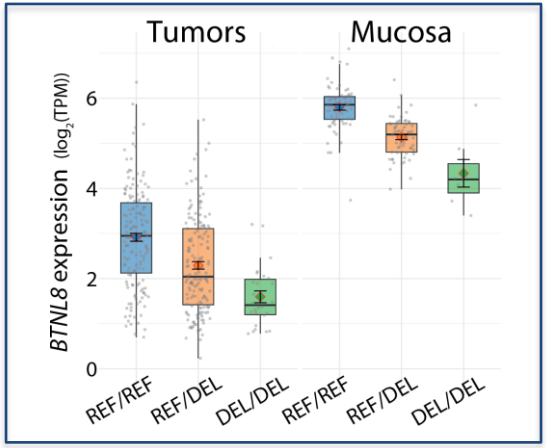
A common SV deletes major parts of *BTNL8/3*



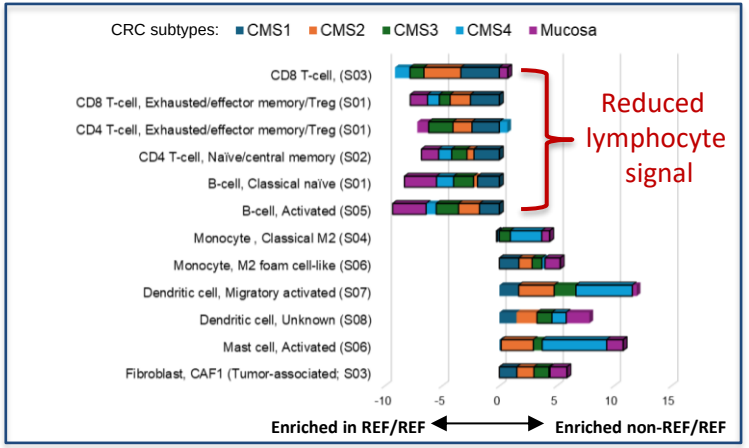
Patient RFS is associated with SV genotype



BTNL8/3 expression is SV genotype-associated



SV genotype may influence lymphocyte content



Acknowledgements

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