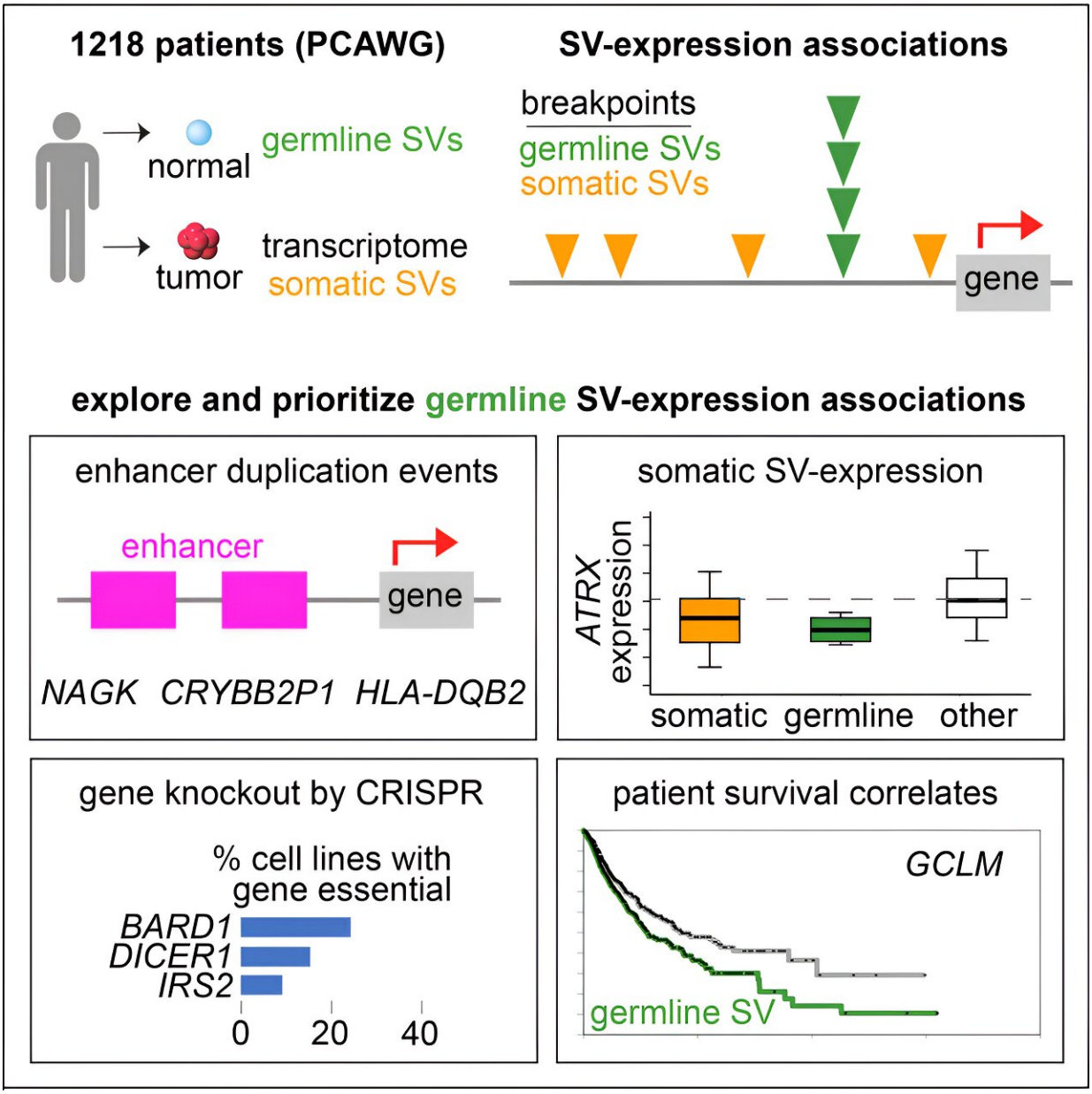
Genetic germline variations influence expression of cancer cell genes, finds study

March 4 2024, by Molly Chiu



Graphical abstract. Credit: *Cell Reports Medicine* (2024). DOI: 10.1016/j.xcrm.2024.101446

Researchers at Baylor College of Medicine's Dan L Duncan Comprehensive Cancer Center and Human Genome Sequencing Center investigated the extent to which forms of genetic variation called germline or inherited structural variation influence gene expression in human cancers. The findings, published in the journal *Cell Reports Medicine*, show that specific germline structural variations represent potential candidates for cancer genetic testing, including those involving genes with therapeutic targeting implications.

"Structural variation is one type of genomic variation and can be beneficial, neutral or, if it affects functionally relevant regions of the genome, can seriously affect gene function and contribute to disease, including cancer," said corresponding author Dr. Chad Creighton, professor of medicine and co-director of cancer bioinformatics at the Dan L Duncan Comprehensive Cancer Center at Baylor.

Structural variations are larger differences in the genome that occur when a piece of DNA is duplicated, deleted, or switched around, which can impact genetic instructions encoded in DNA and affect the expression of nearby genes. Previous studies led by the researchers have shown that structural variations occurring in specific cell types, like breast cells, can strongly influence gene expression in ways that contribute to transforming a healthy breast cell into a cancer cell.

"It's known that germline structural variation also can contribute to the molecular profile of cancers," Creighton said. "Here we study the extent of its contribution."

The researchers worked with data developed by the Pan-Cancer Analysis of Whole Genomes consortium, which includes whole genome sequencing data from 2,658 cancers across 38 tumor types involving 20 major tissues of origin. The team integrated these data with RNA data to identify genes whose expression was associated with nearby germline structural variations.

"We found most of the genes associated with germline structural variations would not necessarily have specific roles in cancer, but for some genes, the expression variation might be associated with other conditions," Creighton said. "At the same time, several genes affected by germline structural variation could conceivably contribute to cancer, for instance, if these genes have an established cancer association or an association with patient survival."

This study shows that germline structural variation would represent a normal class of genetic variation passed down through generations and may play a significant role in cancer development. The researchers propose that the subset of genes with cancer-relevant associations arising in this study would represent strong candidates for further investigation on their value in genetic testing.

Fengju Chen, Yiqun Zhang and Fritz J. Sedlazeck also contributed to this work.

More information: Fengju Chen et al, Germline structural variation globally impacts the cancer transcriptome including disease-relevant genes, *Cell Reports Medicine* (2024). DOI: 10.1016/j.xcrm.2024.101446

Provided by Baylor College of Medicine