New research shows whole genome sequencing provides extensive insights into Hodgkin lymphoma

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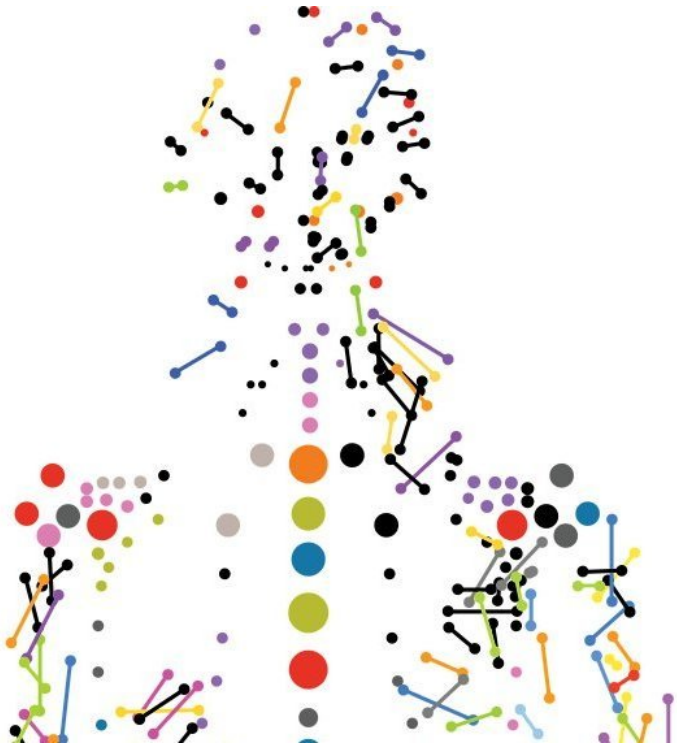

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A large research project, led by scientists at Sylvester Comprehensive Cancer Center in the University of Miami Miller School of Medicine, Memorial Sloan Kettering Cancer Center, and Weill Cornell Medical

College, has found that whole genome sequencing (WGS) can provide much more information about classic Hodgkin lymphoma (cHL) than exome sequencing, which reads only protein-coding genes.

The team showed that WGS can more readily detect DNA structural variations, such as gene duplications, and provides more precise data to track the mutations associated with disease progression. The study was published in the journal *Blood Cancer Discovery*.

"We found that by using whole genome sequencing, we can read virtually all the mutations in both protein coding and noncoding regions of the genome, as well as structural and copy number variations," said Craig Moskowitz, M.D., physician-in-chief, Oncology Service Line at Sylvester, professor of medicine at the Miller School, and a co-author on the study. "We found many genomic events that had never been recorded before. It's the best technology we've found to identify new cancer drivers."

While exome sequencing has been extremely fruitful, detecting point mutations and other variants that propel cancers, it paints an incomplete picture. Mutations in noncoding genomic regions can also govern gene expression. In addition, WGS identifies a wide range of structural variations, including chromothripsis, in which damaged chromosomes look like they've been hit by sledgehammers.

Mutational signatures and tumor chronology

The study identified many of these issues in cHL, as well as finding mutational signatures associated with chemotherapy. Perhaps most importantly, WGS provided temporal insights into how the cancers evolved. Reconstructing tumor chronology could play a major role in treatment selection.

"It's important to know how a tumor developed over time," said Francesco Maura, M.D., co-leader of the Myeloma Genomic Lab at Sylvester, assistant professor of medicine, and first author on the study. "We need to know which mutations were acquired and in what order. If we prescribe a targeted therapy, we want it to target genomic alterations that are shared throughout the tumor, rather than the subclones that came later and are relatively rare."

Because cHL cells (called Hodgkin and Reed Sternberg cells) are rare and difficult to study, the team had to invent a sophisticated sorting system that could isolate enough of them. These cells were later expanded to effectively sequence them. This approach, combined with WGS, could provide many new insights into cHL and other cancers.

While this research sheds new light on cHL, it is only a first step in a long process. This proof-of-concept study will provide an early template to conduct more in-depth genomic studies on blood and other cancers.

"Cancers are incredibly complex diseases, and we still have a long way to go before we fully understand them," said C. Ola Landgren, M.D., director of the Myeloma Research Institute, co-leader of Translational and Clinical Oncology Research Program, and co-author on the study. "By leveraging WGS, we can better assess tumor evolution, identify structural issues, and hopefully gain new therapeutic insights."

More information: Francesco Maura et al, Molecular evolution of classic Hodgkin lymphoma revealed through whole genome sequencing of Hodgkin and Reed Sternberg cells, *Blood Cancer Discovery* (2023). DOI: 10.1158/2643-3230.BCD-22-0128

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