Mosaic chromosomal alterations study provides valuable insights into drivers of cancer risk

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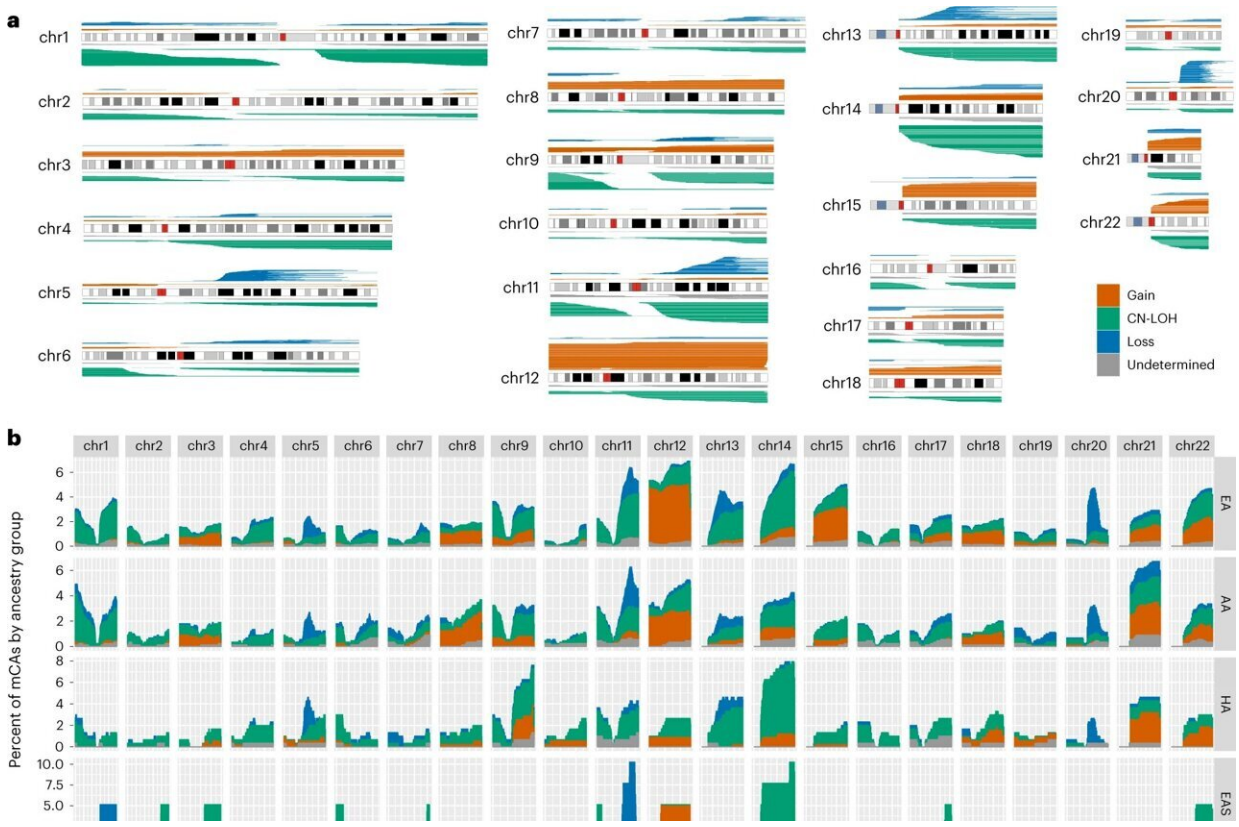

Genomic distribution of autosomal mCAs. **a**, mCA calls across autosomal chromosomes. **b**, Histogram of mCA calls across the genome for each genetic ancestry group. The *X* axis is shown in 1 Mb windows for each chromosome and the *Y* axis is the percent of mCA calls for a given genetic ancestry group that span the genomic window. Credit: *Nature Genetics* (2023). DOI: 10.1038/s41588-023-01553-1

As people age, the DNA in their cells begins to accumulate genetic mutations. Mosaic chromosomal alterations (mCAs), a category of mutations acquired in blood cells, are linked with a 10-fold increased risk of developing blood cancer.

mCAs hold promise as a tool to identify people at high risk of developing certain cancers and diseases, but they have not yet been studied among a large, diverse cohort of people—a critical step required before such testing can be developed.

University of Kentucky Markey Cancer Center researcher Yasminka A. Jakubek, Ph.D., has led the first large-scale effort to understand the co-occurrence of mCAs among individuals of diverse ancestries. The study was published in *Nature Genetics*.

The research team—consisting of more than 50 scientists representing institutions across the U.S.—detected mCAs using existing DNA sequencing data from the National Heart, Lung and Blood Institute's Trans Omics for Precision Medicine Program. The diverse cohort of more than 67,000 included individuals in the U.S. with African, East Asian, European and Hispanic ancestries. Prior studies have mainly focused on individuals with European and Japanese ancestries.

"mCAs are promising biomarkers for cancer risk assessment and early detection," said Jakubek, an assistant professor in the UK College of Medicine's Department of Internal Medicine. "Studies that are inclusive are important to ensure that mosaic mutation-based disease risk models and clinical biomarker studies perform equally well regardless of a person's genetic ancestry."

While mCAs can arise through unrelated molecular mechanisms, a

person's genetic ancestry can contribute to the risk of developing certain mCAs. Humans have 22 pairs of autosomal chromosomes and one pair of sex chromosomes (XX or XY). The study found that mCAs affecting autosomal chromosomes are more common in people with European ancestry.

The research team also looked at mosaic alterations on specific chromosomes and found differences in the rate of mutations across individuals of different ancestries. The most notable finding was an increased rate of mCAs on chromosome X among people with African and Hispanic ancestries who were born with XX sex chromosomes.

The team also identified new inherited genetic variants that are associated with an increased risk for mCAs and loss of X.

In addition to paving the way for a blood test that could identify people at risk of developing certain cancers, the research gives scientists valuable insights into drivers of genomic instability, a key characteristic of cancer cells.

"The long-term goal of our study is to lay a foundation for advances in precision medicine by studying the mutations that we accumulate as we age," Jakubek said. "It's critical that people of diverse background are included and participate in studies such as this one to avoid inequity in future medical advances."

More information: Yasminka A. Jakubek et al, Mosaic chromosomal alterations in blood across ancestries using whole-genome sequencing, *Nature Genetics* (2023). DOI: 10.1038/s41588-023-01553-1

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