A DEEP LOOK INTO SOMATIC MOSAICISM

Somatic mosaicism is now recognized as a pervasive feature of human biology, with diverse classes of somatic mutations accumulating across tissues over time. The study by Luquette et al., in bioRxiv (1) aims to characterize somatic mosaicism in unprecedented depth and represents the first output of a dedicated consortium established for this purpose. Using single-cell PTA sequencing on lung and colon samples from a 74-year-old deceased individual, the authors obtain a high-resolution view of somatic genomic diversity in normal tissues. They showed not only extensive catalogs of point mutations but also a remarkably rich spectrum of large-scale chromosomal alterations, including full-chromosome aneuploidies, broad sub-chromosomal copy-number changes, and complex structural rearrangements that remain invisible in bulk sequencing. Loss of chromosome Y emerges as the most frequent whole-chromosome event, accompanied by occasional XYY gains arising independently in distinct developmental lineages. The study also identifies several copy-neutral loss-of-heterozygosity events, whose genomic signatures are consistent with mechanisms of somatic homologous recombination—such as mitotic recombination, gene conversion, or break-induced replication—although the authors do not discuss the mechanistic interpretation. In addition, V(D)J-mediated deletions in T-cell receptor loci (a physiological somatic recombination process that generates T-cell receptor diversity) highlight the ability of single-cell sequencing to detect programmed DNA remodeling. Together, these findings demonstrate that normal tissues harbor a far broader and structurally more complex array of chromosomal variation than previously appreciated, underscoring the power of single-cell genomics to capture the full scale and complexity of somatic genome instability.

1. https://doi.org/10.1101/2025.10.31.685648 (bioRxiv)