SMALL SUPERNUMERARY MARKER CHROMOSOMES (sSMCs)

Saether et al. (1) used long-read genome sequencing (lrGS) combined with the T2T-CHM13 assembly to characterize 10 small supernumerary marker chromosomes (sSMCs), which are hard to resolve with standard methods. The authors managed to resolve 9 out of 10 at base-pair resolution, identifying breakpoint junctions and inferring how they formed.

Simple sSMCs tend to form through microhomology-mediated end joining (MMEJ) or microhomology-mediated break-induced replication (MMBIR), while the complex ones show signs of chromoanasynthesis and breakage–fusion–bridge cycles. Haplotype analysis pointed to trisomy rescue as a key formation mechanism in four cases, including all three complex sSMCs.

Mosaicism rates across cases ranged from 13% to 100%, raising interesting questions about how this variability shapes both the phenotype and the ability to detect breakpoints. Nearly all simple sSMCs had at least one breakpoint within a centromere, consistent with centromeric instability playing a central role in their formation. In four of the 28 breakpoint junctions, the breakpoint was located in genomic sequence present in T2T-CHM13 but absent from GRCh38; a reminder of why the new reference genome matters.

Case RD_P274, a ring of chromosoe 10, remained unresolved due to breakpoints in highly repetitive acrocentric p-arm regions, highlighting that even lrGS has limits, and that cytogenetics and pangenome references will continue to play an important complementary role.

Deeper functional analysis of the genes within these segments and a richer clinical follow-up linking molecular complexity to patient outcomes, will be key to unlocking the full diagnostic and counseling potential of this approach.

1. 10.1101/gr.281175.125