HUMAN DE NOVO MUTATIONS

A Nature paper, by E. Eichler's group[1], presents the most complete and detailed analysis to date of human de novo mutations (DNMs) by sequencing and assembling the genomes of 28 individuals across four generations (CEPH 1463 pedigree) using five complementary sequencing technologies (PacBio HiFi, ONT, Illumina, Strand-seq, Element AVITI).

Key Results:

- 98–206 de novo mutations per transmission, with:
- 74.5 SNVs
- 7.4 non-TR indels
- 65.3 TR-related DNMs (including STRs and VNTRs)
- 4.4 centromeric DNMs
- Y chromosome: 12.4 DNMs/generation, largely in repetitive satellite DNA.
- Strong paternal bias for germline mutations (75–81%), while postzygotic mutations (PZMs) show no parental bias.
- TR DNMs affect more base pairs per generation than SNVs, and 32 TR loci show recurrent mutations, a novel observation in healthy pedigrees.
- Centromeric SVs: 18 de novo SVs were identified in centromeres, all validated with long reads.
- Y chromosome satellite regions show a >20-fold higher DNM rate than euchromatic regions.

Thanks to high-quality telomere-to-telomere assemblies, this study accesses and analyzes repetitive genomic regions, including centromeres and Y-chromosome satellites, that were previously inaccessible with short-read technologies.

This landmark pedigree study demonstrates that mutation rates and mechanisms vary drastically by genomic context, especially in repeats and centromeres, and underscores the necessity of long-read, multigenerational sequencing for accurate measurement.

1. https://www.nature.com/articles/s41586-025-08922-2