MUTATION RATE IN HUMANS

Recent advances in sequencing technologies have dramatically improved our ability to measure human de novo mutation (DNM) rates. Historically, most studies relied on the analysis of parent-offspring trios using short-read sequencing (SRS) technologies, which mainly captured single-nucleotide variants (SNVs) and small indels, while leaving large repetitive regions, such as centromeres and segmental duplications, largely unexplored.
One of the earliest direct estimates of the human mutation rate, as reported in 2009[1], was based on the sequencing of approximately 10 Mb of euchromatic Y chromosome DNA across a deep-rooting pedigree. This landmark study, based on short-read data, primarily captured point mutations and did not account for larger structural variations or highly repetitive DNA regions.
In contrast, the present study[2] (by the group of E.E.Eichler) represents a major step forward. By sequencing a four-generation, 28-member human pedigree using five complementary sequencing platforms (short-read and multiple long-read technologies), researchers assembled near-complete, telomere-to-telomere genomes for most individuals. This comprehensive strategy allowed the detection not only of SNVs and small indels but also of larger and more complex variants — including tandem repeat expansions/contractions, large de novo structural variants, and mutations in centromeric and other heterochromatic regions previously inaccessible to short-read sequencing.

Main results of the study include:

- A total of 1,037 de novo SNVs were detected across 20 offspring, refining the per-generation mutation rate estimate, to 51.9/generation.
- A clear paternal age effect was confirmed for SNVs (with about 1.28 additional mutations per year of paternal age).
- Tandem repeat mutations were more frequent than previously thought, occurring at approximately 3.3 mutations per genome per generation.
- Large-scale de novo structural variants were identified, including mutations within centromeric satellite DNA.
- The contribution of postzygotic mutations was characterized in detail, revealing a significant but minor proportion of all DNMs.
- No significant association was observed between recombination hotspots and the formation of large de novo structural variants.
- Rates of mutation varied substantially between different genomic regions and repeat classes.

Altogether, this study provides the most comprehensive direct measurement of the spectrum and rate of de novo mutations in humans to date, overcoming the limitations of previous trio-based, short-read studies. These results refine our understanding of human genetic variation, mutation processes, and inheritance patterns at a genome-wide level.

1. https://www.cell.com/current-biology/fulltext/S0960-9822(09)01454-7?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0960982209014547%3Fshowall%3Dtrue
2. https://www.nature.com/articles/s41586-025-08922-2