

## REPEAT EXPANSION IN THE NORMAL HUMAN POPULATION

Repeat expansions in the germline and in somatic tissues are classically studied because they cause disease. More than 60 inherited disorders are due to pathogenic repeat expansions, many of them involving trinucleotide repeats.

A new study in Nature (1) takes a different perspective. Instead of focusing only on disease-causing expansions, it asks a broader question: what is the background level of repeat instability in the general population?

The authors analyzed whole-genome sequencing data from more than 900,000 individuals, combining two extraordinary resources: the UK Biobank (~490,000 participants) and the All of Us Research Program (US, ~415,000 participants).

The authors systematically examined over 356,000 polymorphic short tandem repeats across the genome, quantifying both germline mutation rates and somatic expansions in blood. The result is a population-scale map of repeat instability, revealing that many repeats are dynamic even in people without diagnosed repeat-expansion disorders.

In other words, repeat expansion is not only a rare pathogenic event. It is a widespread, measurable, genetically modulated biological process shaping human genomes throughout life.

(1) 10.1038/s41586-025-09886-z