

Major advance enables study of genetic mutations in any tissue

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For the first time, scientists are able to study changes in the DNA of any human tissue, following the resolution of long-standing technical challenges by scientists at the Wellcome Sanger Institute. The new method, called nanorate sequencing (NanoSeq), makes it possible to study how genetic changes occur in human tissues with unprecedented accuracy.

The study, published today in *Nature*, represents a major advance for research into cancer and ageing. Using NanoSeq to study samples of blood, colon, brain and muscle, the research also challenges the idea that [cell division](#) is the main mechanism driving genetic changes. The new method is also expected to allow researchers to study the effect of carcinogens on [healthy cells](#), and to do so more easily and on a much larger scale than has been possible up until now.

The tissues in our body are composed of dividing and non-dividing [cells](#). Stem [cells](#) renew themselves throughout our lifetimes and are responsible for supplying non-dividing cells to keep the body running. The vast majority of cells in our bodies are non-dividing or divide only rarely. They include granulocytes in our blood, which are

produced in the billions every day and live for a very short time, or neurons in our brain, which live for much longer.

Genetic changes, known as somatic mutations, occur in our cells as we age. This is a [natural process](#), with cells acquiring around 15-40 mutations per year. Most of these mutations will be harmless, but some of them can start a cell on the path to cancer.

Since the advent of genome sequencing in the late twentieth century, cancer researchers have been able to better understand the formation of cancers and how to treat them by studying somatic mutations in tumour DNA. In recent years, new technologies have also enabled scientists to study mutations in [stem cells](#) taken from healthy tissue.

But until now, genome sequencing has not been accurate enough to study new mutations in non-dividing cells, meaning that somatic mutation in the vast majority of our cells has been impossible to observe accurately.

In this new study, researchers at the Wellcome Sanger Institute sought to refine an advanced sequencing method called duplex sequencing¹. The team searched for errors in duplex sequence data and realised that they were concentrated at the ends of DNA fragments, and had other features suggesting flaws in the process used to prepare DNA for sequencing.

They then implemented improvements to the DNA preparation process, such as using specific enzymes to cut DNA more cleanly, as well as improved bioinformatics methods. Over the course of four years, accuracy was improved until they achieved fewer than five errors per billion letters of DNA.

Dr. Robert Osborne, an alumnus of the Wellcome Sanger Institute who led the development of the

method, said: "Detecting somatic mutations that are only present in one or a few cells is incredibly technically challenging. You have to find a single letter change among tens of millions of DNA letters and previous sequencing methods were simply not accurate enough. Because NanoSeq makes only a few errors per billion DNA letters, we are now able to accurately study somatic mutations in any tissue."

The team took advantage of NanoSeq's improved sensitivity to compare the rates and patterns of mutation in both [stem cells](#) and non-dividing cells in several human tissue types.

Surprisingly, analysis of blood cells found a similar number of mutations in slowly dividing stem cells and more rapidly dividing progenitor cells². This suggested that cell division is not the dominant process causing mutations in blood cells. Analysis of non-dividing neurons and rarely dividing cells from muscle also revealed that [mutations](#) accumulate throughout life in cells without cell division, and at a similar pace to cells in the blood.

Dr. Federico Abascal, the first author of the paper from the Wellcome Sanger Institute, said: "It is often assumed that cell division is the main factor in the occurrence of [somatic mutations](#), with a greater number of divisions creating a greater number of [mutations](#). But our analysis found that blood cells that had divided many times more than others featured the same rates and patterns of mutation. This changes how we think about mutagenesis and suggests that other biological mechanisms besides [cell division](#) are key."

The ability to observe mutation in all cells opens up new avenues of research into cancer and ageing, such as studying the effects of known carcinogens like tobacco or sun exposure, as well as discovering new carcinogens. Such research could greatly improve our understanding of how lifestyles choices and exposures to carcinogens can lead to cancer.

A further benefit of the NanoSeq method is the relative ease with which samples can be collected. Rather than taking biopsies of tissue, cells can be collected non-invasively, such as by scraping the

skin or swabbing the throat.

Dr. Inigo Martincorena, a senior author of the paper from the Wellcome Sanger Institute, said: "The application of NanoSeq on a small scale in this study has already led us to reconsider what we thought we knew about mutagenesis, which is exciting. NanoSeq will also make it easier, cheaper and less invasive to study somatic mutation on a much larger scale. Rather than analysing biopsies from small numbers of patients and only being able to look at stem cells or tumour tissue, now we can study samples from hundreds of patients and observe [somatic mutations](#) in any tissue."

More information: Somatic mutation landscapes at single-molecule resolution, *Nature* (2021). [DOI: 10.1038/s41586-021-03477-4](https://doi.org/10.1038/s41586-021-03477-4)

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