

A new route to evolution: How DNA from our mitochondria works its way into our genomes

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Scientists have shown that in one in every 4,000 births, some of the genetic code from our mitochondria—the 'batteries' that power our

cells—inserts itself into our DNA, revealing a surprising new insight into how humans evolve.

In a study published today in *Nature*, researchers at the University of Cambridge and Queen Mary University of London show that mitochondrial DNA also appears in some cancer DNA, suggesting that it acts as a sticking plaster to try and repair damage to our genetic code.

Mitochondria are tiny 'organelles' that sit within our cells, where they act like batteries, providing energy in the form of the molecule ATP to power the cells. Each mitochondrion has its own DNA—mitochondrial DNA—that is distinct to the rest of the human genome, which is comprised of nuclear DNA.

Mitochondrial DNA is passed down the [maternal line](#)—that is, we inherit it from our mothers, not our fathers. However, [a study published in PNAS in 2018](#) from researchers at the Cincinnati Children's Hospital Medical Center in the U.S. reported evidence that suggested some mitochondrial DNA had been passed down the paternal line.

To investigate these claims, the Cambridge team [looked at the DNA from over 11,000 families](#) recruited to Genomics England's 100,000 Genomes Project, searching for patterns that looked like paternal inheritance. The Cambridge team found mitochondrial DNA 'inserts' in the nuclear DNA of some children that were not present in that of their parents. This meant that the US team had probably reached the wrong conclusions: what they had observed were not paternally-inherited mitochondrial DNA, but rather these inserts.

Now, extending this work to over 66,000 people, the team showed that the new inserts are actually happening all the time, showing a new way our genome evolves.

Professor Patrick Chinnery, from the Medical Research Council Mitochondrial Biology Unit and Department of Clinical Neurosciences at the University of Cambridge, explained: "Billions of years ago, a primitive animal cell took in a bacterium that became what we now call mitochondria. These supply energy to the cell to allow it to function normally, while removing oxygen, which is toxic at high levels. Over time, bits of these primitive mitochondria have passed into the [cell nucleus](#), allowing their genomes to talk to each other.

"This was all thought to have happened a very long time ago, mostly before we had even formed as a species, but what we've discovered is that that's not true. We can see this happening right now, with bits of our mitochondrial genetic code transferring into the nuclear genome in a measurable way."

The team estimate that mitochondrial DNA transfers to nuclear DNA in around one in every 4,000 births. If that individual has children of their own, they will pass these inserts on—the team found that most of us carry five of the new inserts, and one in seven of us (14%) carry very recent ones. Once in place, the inserts can occasionally lead to very [rare diseases](#), including a rare genetic form of cancer.

It isn't clear exactly how the mitochondrial DNA inserts itself—whether it does so directly or via an intermediary, such as RNA—but Professor Chinnery says it is likely to occur within the mother's egg cells.

When the team looked at sequences taken from 12,500 tumor samples, they found that mitochondrial DNA was even more common in tumor DNA, arising in around one in 1,000 cancers, and in some cases, the mitochondrial DNA inserts actually *causes* the cancer.

"Our nuclear genetic code is breaking and being repaired all the time," said Professor Chinnery. "Mitochondrial DNA appears to act almost like

a Band-Aid, a sticking plaster to help the nuclear [genetic code](#) repair itself. And sometimes this works, but on rare occasions it might make things worse or even trigger the development of tumors."

More than half (58%) of the insertions were in regions of the genome that code for proteins. In the majority of cases, the body recognizes the invading mitochondrial DNA and silences it in a process known as methylation, whereby a molecule attaches itself to the insert and switches it off. A similar process occurs when viruses manage to insert themselves into our DNA. However, this method of silencing is not perfect, as some of the mitochondrial DNA inserts go on to be copied and move around the nucleus itself.

The team looked for evidence that the reverse might happen—that mitochondrial DNA absorbs parts of our nuclear DNA—but found none. There are likely to be several reasons why this should be the case.

Firstly, cells only have two copies of nuclear DNA, but thousands of copies of mitochondrial DNA, so the chances of mitochondrial DNA being broken and passing into the nucleus are much greater than the other way around.

Secondly, the DNA in mitochondria is packaged inside two membranes and there are no holes in the membrane, so it would be difficult for nuclear DNA to get in. By contrast, if mitochondrial DNA manages to get out, holes in the membrane surrounding nuclear DNA would allow it pass through with relative ease.

Professor Sir Mark Caulfield, vice principal for health at Queen Mary University of London, said: "I am so delighted that the 100,000 Genomes Project has unlocked the dynamic interplay between mitochondrial DNA and our genome in the cell's nucleus. This defines a new role in DNA repair, but also one that could occasionally trigger rare

disease, or even malignancy."

More information: Patrick Chinnery, Nuclear-embedded mitochondrial DNA sequences in 66,083 human genomes, *Nature* (2022). DOI: [10.1038/s41586-022-05288-7](https://doi.org/10.1038/s41586-022-05288-7).
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