

Enzyme corrects more than one million faults in DNA replication

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Scientists from the Medical Research Council (MRC) Institute of Genetics and Molecular Medicine (IGMM) at the University of Edinburgh have discovered an enzyme that corrects the most common mistake in mammalian DNA.

The mistake is the inclusion of individual bits of RNA within the DNA sequence, which the researchers found occurs more than a million times in each cell as it divides. The findings, published in *Cell*, suggest the RNase H2 enzyme is central to an important [DNA repair](#) mechanism necessary to protect the human genome.

Each time a cell divides it must first make an identical copy of its entire [genetic material](#), known as the genome. During this process, which is called DNA replication, the integrity of the [genetic code](#) is safeguarded by cellular 'proofreading' and error checking mechanisms.

But sometimes mistakes creep into the genetic code, which if not corrected could lead to genetic disease or cancer. Accidental incorporation of RNA is one such mistake. The individual building blocks of RNA (ribonucleotides) are very similar to those that make up DNA, however, they are much less stable and if they remain incorporated in DNA they cause harmful breaks in the [double helix](#). Such breaks are common in [cancer cells](#).

The researchers made the discovery while working on a rare childhood auto-immune disease known as Aicardi-Goutières syndrome, which is

caused by mutations in the RNase H2 genes. It leads to inflammation of the brain soon after birth and can be fatal within the first few years of life.

To study this condition in more detail, the scientists knocked out one of the RNase H2 genes in mice. They found that without the enzyme, the developing mouse embryos accumulated more than 1,000,000 single embedded bits of RNA in the genome of every cell, resulting in instability of their DNA.

Dr Andrew Jackson from the MRC IGMM at the University of Edinburgh, who led the research, said:

"The most amazing thing is that by working to understand a rare genetic disease, we've uncovered the most common fault in [DNA replication](#) by far, which we didn't even start out looking for! More surprising still is that a single enzyme is so crucial to repairing over a million faults in the DNA of each cell, to protect the integrity of our entire genetic code.

"We expect our findings to have broad implications in the fields of autoimmunity and cancer in the future, but first we need to find out more about what effect the incorporation of RNA nucleotides is actually having on the genome."

Professor Nick Hastie, director of the MRC IGMM at the University of Edinburgh, said:

"This study is a fantastic example of clinicians working alongside laboratory scientists towards a shared goal of improving our understanding of human health and disease. Such progress would not be possible without the critical mass of scientists at the IGMM, with capabilities in many key areas coupled with access to patient data and clinical expertise."

More information: The paper, 'Enzymatic removal of ribonucleotides from DNA is essential for mammalian genome integrity and development', by Reijns et al, is published in *Cell*.

Provided by University of Edinburgh

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