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Tracking DNA helps scientists trace origins of genetic errors

Scientists have shed light on how naturally occurring mutations can be introduced into our DNA.

The study, which focuses on how DNA replicates every time a cell divides, helps to make clear previously unexplained patterns in how our DNA changes over time. It also provides new insight into how the human genome has been shaped throughout evolution.

Researchers have devised a technique that helps them better understand the DNA replication process and to track where mistakes are likely to happen.

The study has revealed that some of the genetic switches that control when genes are activated are likely to be hotspots for DNA flaws, or mutations, to develop.

University of Edinburgh researchers developed a method to label – and track – pieces of new DNA as they are made and to identify which copying enzyme is responsible.

Several copying enzymes – called polymerases – are involved. One polymerase first makes short stretches of DNA that act as a scaffold so that the other copying enzymes can then replicate the remaining DNA.

As this scaffold DNA contains errors, the standard model assumed all of it was removed during the process. However, the researchers found that a small but significant fraction – up to 1.5 per cent – of the finished DNA is left-over scaffold.

These scaffold sections, and the mistakes they contain, become trapped in the DNA.

This tends to occur at points in the important regulatory switches that often control when genes are switched on and off. These sites are therefore more likely than other regions to have trapped scaffold DNA and its associated errors.

Mistakes in these crucial genetic sequences can change or destroy the regulatory switch, which can lead to genetic disease, alter susceptibility to common diseases or contribute to the development of cancer.

The researchers hope that this knowledge will aid in the hunt for disease causing mutations, particularly in the difficult to interpret regions of the genome that do not code for proteins.

The study, funded by the Medical Research Council, is published in the journal *Nature*.

Dr Martin Taylor, who co-led the study at the MRC Human Genetics Unit, said: “We have been aware of striking patterns in how DNA changes for several years but couldn't explain why the patterns were there. This new work gives us a mechanism and revealed previously unseen patterns that are probably the most important finding, as they point to sites in our DNA that are likely to have a high rate of damaging mutations.”

Professor Andrew Jackson, who co-led the study at the MRC Human Genetics Unit, said: “Our research groups are very proud to have devised an important new method to track polymerase enzymes that copy our genome within the cell itself. This shows us that despite DNA replication being an amazingly accurate process, errors do occur that cluster at important sites in the genome. This new insight into a fundamental biological process has been made possible by combining cross-disciplinary computational and laboratory expertise at the IGMM.”

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