Milestone study probes cancer origin

By James Gallagher Health and science reporter, BBC News

New images show cancer close-up, as David Shukman reports

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Scientists are reporting a significant milestone for cancer research after charting 21 major mutations behind the vast majority of tumours.

The disruptive changes to the genetic code, reported in Nature, accounted for 97% of the 30 most common cancers.

Finding out what causes the mutations could lead to new treatments. Some, such as smoking are known, but more than half are still a mystery.

Cancer Research UK said it was a fascinating and important study.

A tumour starts when one of the building blocks of bodies, a cell, goes wrong. Over the course of a lifetime cells pick up an array of mutations which can eventually transform them into
deadly tumours which grow uncontrollably.

Cancer origins
The international team of researchers was looking for the causes of those mutations as part of the largest-ever analysis of cancer genomes.

"Start Quote

Hidden within the cancer genome are these patterns, these signatures, which tell us what is actually causing cancer in the first place - that's a major insight to have."

Prof Sir Mike Stratton Wellcome Trust Sanger Institute
The well-known ones such as UV damage and smoking mutate the DNA, increasing the odds of cancer.

But each also leaves behind a unique hallmark - a piece of "genetic graffiti" - that shows if smoking or UV radiation has mutated the DNA.

Researchers, led by the Wellcome Trust Sanger Institute in the UK, hunted for more examples of "graffiti" in 7,042 samples taken from the 30 most common cancers.

The found that 21 separate "graffiti signatures" could account for 97% of the mutations which led to cancer.

Prof Sir Mike Stratton, the director of the Sanger Institute, told the BBC: "I'm very excited. Hidden within the cancer genome are these patterns, these signatures, which tell us what is actually causing cancer in the first place - that's a major insight to have.

"It is quite a significant achievement for cancer research, this is quite profound. It's taking us into areas of unknown that we didn't know existed before.

"I think this is a major milestone."

Mysteries
Other signatures were related to ageing and the body's immune system. Cells respond to viral infection by activating a class of enzymes which mutate the viruses until they can no longer function.

"We believe that when it does that, there is collateral damage - it mutates its own genome as well and now becomes much more likely to become a cancer cell as it has a huge number of mutations - it's a double-edged sword," said Prof Stratton.

However, 12 of the signatures defy explanation for now.

It is hoped that if some of them can be pinned down to things in the environment then new ways of preventing cancer could be developed.

It may also spur further research. One of the unknown causes of mutation happens only in neuroblastoma, a cancer of nerve cells which normally affects children, so something unique is happening there.
Prof Nic Jones, Cancer Research UK's chief scientist, said: "We know that environmental factors like smoking and overexposure to UV rays can cause faults in DNA which can lead to cancer, but for many cancers we don't know what triggers the faults in our DNA that can lead to cancer mutations.

"The genetic fingerprints identified in this fascinating and important study identify several new processes driving the development of cancer.

"Understanding what's causing them could be an extremely important way to get the bottom of how cancer develops in the first place - and this will lead to new ways to prevent and treat the disease."

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Thriving cancer's 'chaos' explained

By James Gallagher Health and science reporter, BBC News

The way cancers make a chaotic mess of their genetic code in order to thrive has been explained by UK researchers.

Cancer cells can differ hugely within a tumour - it helps them develop ways to resist drugs and spread round the body.

A study in the journal Nature showed cells that used up their raw materials became "stressed" and made mistakes copying their genetic code.

Scientists said supplying the cancer with more fuel to grow may actually make it less dangerous.

Most normal cells in the human body contain 46 chromosomes, or bundles of genetic code. However, some cancerous cells can have more than 100 chromosomes.

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And the pattern is inconsistent - pick a bunch of neighbouring cells and they could each have different chromosome counts.

This diversity helps tumours adapt to become untreatable and colonise new parts of the body. Devising ways of preventing a cancer from becoming diverse is a growing field of research.

Chaos from order
Scientists at the Cancer Research UK London Research Institute and the University College London Cancer Institute have been trying to crack how cancers become so diverse in the first place.

It had been thought that when a cancer cell split to create two new cells, the chromosomes were not split evenly between the two.

However, lead researcher Prof Charles Swanton's tests on bowel cancer showed "very little evidence" that was the case.

Instead the study showed the problem came from making copies of the cancer's genetic code.

Cancers are driven to make copies of themselves, however, if cancerous cells run out of the building blocks of their DNA they develop "DNA replication stress".

The study showed the stress led to errors and tumour diversity.

Prof Swanton told the BBC: "It is like constructing a building without enough bricks or cement for the foundations.

"However, if you can provide the building blocks of DNA you can reduce the replication stress to limit the diversity in tumours, which could be therapeutic."

He admitted that it "just seems wrong" that providing the fuel for a cancer to grow could be therapeutic.

However, he said this proved that replication stress was the problem and that new tools could be developed to tackle it.

Future studies will investigate whether the same stress causes diversity in other types of tumour.

The research team identified three genes often lost in diverse bowel cancer cells, which were critical for the cancer suffering from DNA replication stress. All were located on one region of chromosome 18.

Prof Nic Jones, Cancer Research UK's chief scientist, said: "This region of chromosome 18 is lost in many cancers, suggesting this process is not just seen in bowel cancers.

"Scientists can now start looking for ways to prevent this happening in the first place or turning this instability against cancers."