'Junk' DNA plays role in preventing breast cancer

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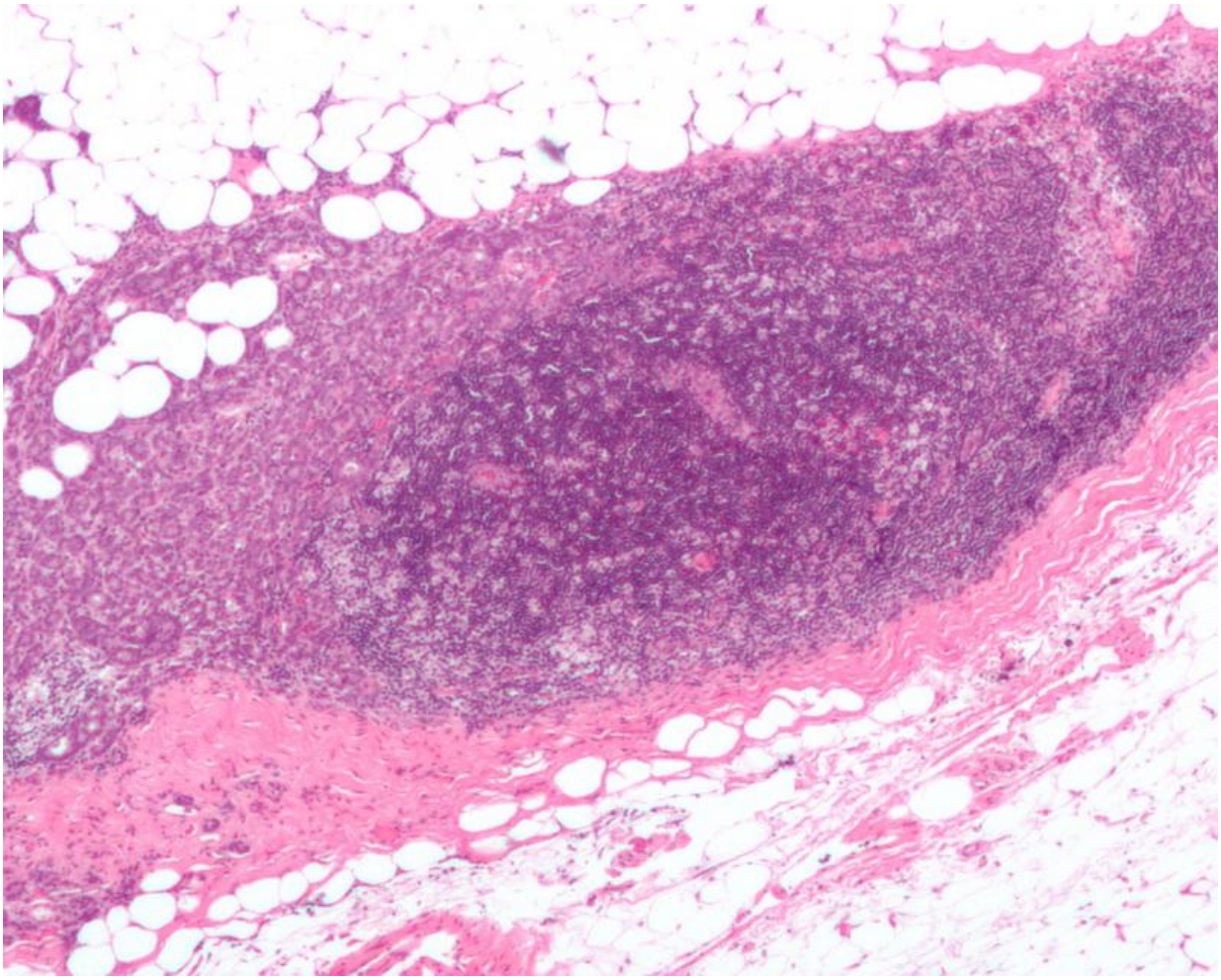

Micrograph showing a lymph node invaded by ductal breast carcinoma, with extension of the tumour beyond the lymph node. Credit: Nephron/Wikipedia

Supposed "junk" DNA, found in between genes, plays a role in suppressing cancer, according to new research by Universities of Bath and Cambridge.

The human genome contains around three metres of DNA, of which only about two per cent contains genes that code for proteins. Since the sequencing of the complete human genome in 2000, scientists have puzzled over the role of the remaining 98 per cent.

In recent years it has become apparent that a lot of this non-coding DNA is actually transcribed into non-coding RNA. However, there is still a debate as to whether non-coding RNA is just "noise" or whether it serves any function in the cell.

Part of the reason for this uncertainty is that it is very difficult to knock-out non-coding RNA without damaging the DNA, which can lead to off-target effects and false results.

Now a team of scientists from Bath, Cambridge and the USA has identified a piece of non-coding RNA - transcribed from a stretch of DNA that doesn't code for a protein - that stops cells turning cancerous.

The researchers hope their discovery, published in *Nature Communications*, will help develop new treatments for cancer.

Dr Adele Murrell, from the University of Bath's Department of Biology & Biochemistry, led the study. She explained: "The number of cells in our body are balanced by the level at which cells replicate and replace the ones that die. Sometimes the switches that control this growth get stuck in the 'on' position, which can lead to cancer.

"As the tumour grows and the cancer cells get crowded, they start to break away from the tumour, change shape and are able to burrow

through tissues to the bloodstream where they migrate to other parts of the body, which is how the cancer spreads. This process is called metastasis and requires a whole network of genes to regulate the transformation of cell shape and mobilisation.

"In our study we've identified that GNG12-AS1, a strand of non-coding RNA, prevents the growth switch getting stuck and suppresses metastasis. The specific genomic region where this non-coding RNA is located often gets damaged in breast cancer patients - this control is removed and the cancer cells spread."

The research team found that this non-coding RNA fragment maintains healthy cells through two mechanisms: Firstly by regulating the levels of DIRAS3, one of its neigbouring genes that is involved in cell replication;secondly by suppressing a network of genes that prepare cells to change their shape and prepare for metastasis.

The team were able to distinguish between these two mechanisms by using smaller interfering RNAs (siRNAs) to either specifically stop the non-coding RNA from being made, or to degrade the RNA immediately after it was made. Both approaches led to cells changing their shape and transforming into migratory cells. However, only the first approach affected DIRAS3 and the cell cycle.

The team anticipates their findings could be used understand how other non-coding RNAs function and to develop potential gene therapies to treat cancer.

The research was funded by Cancer Research UK.

Dr Kat Arney, science communication manager at Cancer Research UK, said: "Only a tiny fraction of our DNA contains actual genes, and we know that at least some of the bits in between - often dismissed as 'junk'

- play important roles in controlling how genes get switched on and off at the right time and in the right place.

"Research like this is helping is to unpick the precise details about how these regions work, shedding light on their potential role in the development of cancer and pointing towards new approaches for tackling the disease."

More information: Stojic et al (2016) "Transcriptional silencing of long noncoding RNA GNG12-AS1 uncouples its transcriptional and product-related functions" is published in *Nature Communications* DOI: 10.1038/NCOMMS10406

Provided by University of Bath