Genes that cause pancreatic cancer identified by new tool

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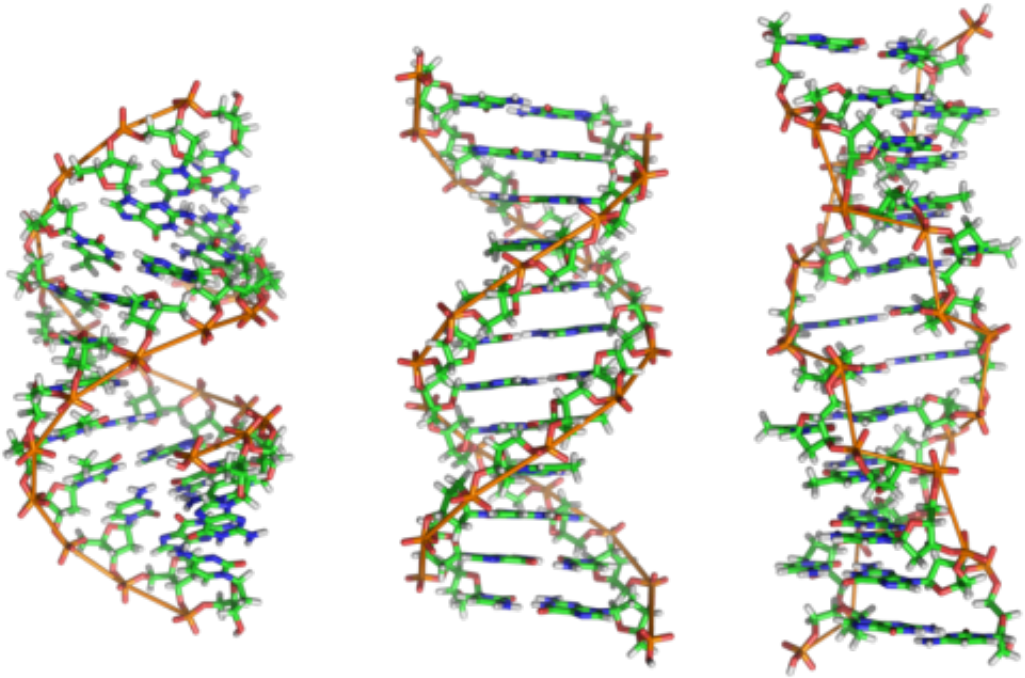

From left to right, the structures of A-, B- and Z-DNA. Credit: Wikipedia

A technique that can identify causes of cancer invisible to genetic sequencing has uncovered large sets of previously unknown pancreatic cancer genes. It is hoped that this study will boost research into a disease that is still poorly understood and for which five-year survival rates have stood at around 5 per cent for the past four decades.

The technique works by introducing sections of DNA called piggyBac

transposons into the mouse genome. Transposons jump around within the genome, reinserting themselves at random and causing a different mutation in each cell of the mouse. This triggers cancer development, and tracking the transposon´s fingerprints in the tumours allows discovery of the affected cancer-causing genes. The PiggyBac tool was engineered for the first time to allow cancer induction in individual tissues within the mouse, and the method can now be used to study any type of cancer.

While genome sequencing can identify all categories of genetic alterations with high accuracy, some of these changes are difficult to interpret. For example, hundreds or thousands of genes are found to be transcriptionally or epigenetically dysregulated within a cancer, meaning that they are not mutated but just being turned on or off. Pinpointing the few cancer-causing events among these large gene sets is extremely difficult. PiggyBac screening can facilitate this search for the needle in the haystack because transposons jump directly into the relevant genes. Moreover, the tool monitors tumour development in mice and therefore researchers are also able to see the consequences of cancerous mutations and how they help the disease to progress.

"Recent advances in cancer genome sequencing have given extraordinary insights into the genetic events underlying cancer. Nevertheless, we are still far from understanding the complexity of the molecular processes driving cancer development," says Professor Roland Rad, from the Technische Universität München and the German Cancer Research Center. "Unbiased genome-wide screening in mice allows us to see cancer from a different angle and answer biological questions that cannot be addressed with other approaches."

The study has identified many genes previously unknown to be involved in pancreatic cancer, including Foxp1, which was hit by transposons at very high frequencies in the 49 mouse tumours studied. Where Foxp1

was induced, tumours spread from the pancreas to other organs, suggesting that the gene drives cancer progression. This finding was confirmed when researchers looked at human samples and found high levels of the FOXP1 gene product in cancers that had metastasised.

In a number of mice, transposons had become inserted in noncoding regions of the genome. These insertions pinpointed enhancer areas, which are involved in the regulation of cancer-causing genes. In addition, similarly to humans, mice developed various subtypes of pancreatic cancer, which not only have distinctive microscopic appearances but also show different clinical behaviours. The study discovered molecular processes being responsible for triggering the formation of these cancer subtypes.

Researchers will now be able to look more closely at the pancreatic cancer genes that have been discovered by this study in the hope of finding effective drugs for a disease that is set to be the second leading cause of cancer death by 2030. Laboratories have also begun using the technique to investigate cancers in other tissues.

More information: Rad R, et al. (2014) A conditional piggyBac transposition system for genetic screening in mice identifies oncogenic networks in pancreatic cancer. *Nature Genetics*. DOI: 10.1038/ng.3164

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