New cancer algorithm flags genetic weaknesses in tumors

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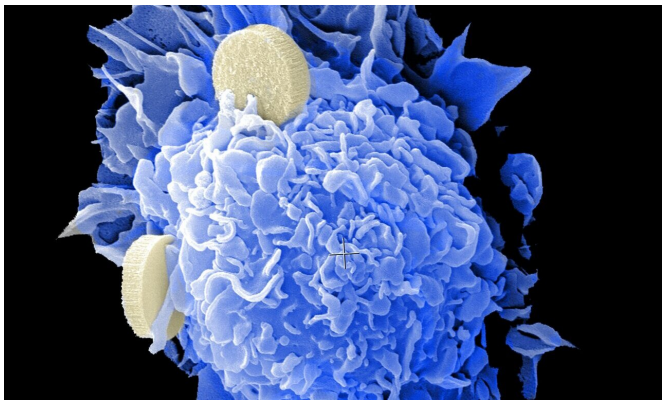

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A new way to identify tumors that could be sensitive to particular immunotherapies has been developed using data from thousands of NHS cancer patient samples sequenced through the 100,000 Genomes Project. The MMRDetect clinical algorithm makes it possible to identify tumors that have 'mismatch repair deficiencies' and then improve the personalization of cancer therapies to exploit those weaknesses.

The study, led by researchers from the University of Cambridge's Department of Medical Genetics and MRC Cancer Unit, identified nine DNA repair genes that are critical guardians of the human genome from damage caused by oxygen and water, as well as errors during cell division.

The team used a genome editing technology, CRISPR-Cas9, to 'knock out' (make inoperative) these repair genes in healthy human stem cells. In doing so, they observed strong mutation patterns, or mutational signatures, which offer useful markers of those genes and the repair pathways they are involved in, failing.

The study, funded by Cancer Research UK and published today in the journal *Nature Cancer*, suggests that these signatures of repair pathway defects are on-going and could therefore serve as crucial biomarkers in precision medicine.

Senior author, Dr. Serena Nik-Zainal, a Cancer Research UK Advanced Clinician Scientist at Cambridge University's MRC Cancer Unit, said: "When we knock out different DNA repair genes, we find a kind of fingerprint of that gene or pathway being erased. We can then use those fingerprints to figure out which repair pathways have stopped working in each person's tumor, and what treatments should be used specifically to treat their cancer."

The new computer algorithm, MMRDetect, uses the mutational signatures that were identified in the knock out experiments, and was trained on whole genome sequencing data from NHS cancer patients in the 100,000 Genomes Project, to identify tumors with 'mismatch repair deficiency' which makes them sensitive to checkpoint inhibitors, immunotherapies. Having developed the algorithm on tumors in this study, the plan now is to roll it out across all cancers picked up by Genomics England.

The breakthrough demonstrates the value of researchers working with the 100,000 Genomes Project, a pioneering national whole genome sequencing endeavor.

Parker Moss, Chief Commercial and Partnerships Officer at Genomics England, said: "We are very excited to see such impactful research being supported by the 100,000 Genomes Project, and that our data has helped to develop a clinically significant tool. This is a fantastic example of how the sheer size and richness of the 100,000 Genomes Project data can contribute to important research.

"The outcomes from Dr. Nik-Zainal and her team's

work demonstrate perfectly how quickly and effectively we can return value to patient care by bringing together a community of leading researchers through Genomics England's platform."

The study offers important insights into where DNA damage comes from in our bodies. Water and oxygen are essential for life but are also the biggest sources of internal DNA damage in humans.

Dr. Nik-Zainal said: "Because we are alive, we need oxygen and water, yet they cause a constant drip of DNA damage in our cells. Our DNA repair pathways are normally working to limit that damage, which is why, when we knocked out some of the crucial genes, we immediately saw lots of mutations."

"Some DNA repair genes are like precision tools, able to fix very specific kinds of DNA damage. Human DNA has four building blocks: adenine, cytosine, guanine and thymine. As an example, the OGG1 gene has a very specific role of fixing guanine when it is damaged by oxygen. When we knocked out OGG1, this crucial defense was severely weakened resulting in a very specific pattern of guanines that had mutated into thymines throughout the genome."

To be most effective, the MMRDetect algorithm could be used as soon as a patient has received a cancer diagnosis and their tumor characterized by genome sequencing. The team believes that this tool could help to transform the way a wide range of cancers are treated and save many lives.

Michelle Mitchell, Chief Executive of Cancer Research UK, said: "Determining the right treatments for patients will give them the best chance of surviving their disease. Immunotherapy in particular can be powerful, but it doesn't work on everyone, so figuring out how to tell when it will work is vital to making it the most useful treatment it can be.

"Our ability to map and mine useful information from the genomes of tumors has improved massively over the past decade. Thanks to initiatives like the 100,000 Genomes Project, we are beginning to see how we might use this information to benefit patients. We look forward to seeing how this research develops, and its possibilities in helping future patients."

More information: A systematic CRISPR screen defines mutational mechanisms underpinning signatures caused by replication errors and endogenous DNA damage, *Nature Cancer* (2021). DOI: 10.1038/s43018-021-00200-0

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