UC San Diego
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Cancer-Causing Culprits Could be Caught by their DNA Fingerprints

Causes of cancer are being catalogued through an international study revealing the genetic fingerprints of DNA-damaging processes that drive cancer development. Researchers from University of California San Diego School of Medicine, Wellcome Sanger Institute, Duke-NUS Medical School Singapore, the Broad Institute of MIT and Harvard, with collaborators around the world, have created the most detailed list yet of these genetic fingerprints, providing clues to how each cancer develops.

These fingerprints will allow scientists to search for previously unknown chemicals, biological pathways and environmental agents responsible for causing cancer.

“We identified almost every publically available cancer genome at the start of this project and analyzed their whole genome sequences,” said first author Ludmil B. Alexandrov, PhD, assistant professor of in the departments of Cellular and Molecular Medicine and Bioengineering at UC San Diego. “The data from these thousands of cancers allowed us to describe mutational signatures in much more detail, and we are confident that we now know most of the signatures that exist.”

The research, published on February 5, 2020 in *Nature* as part of the global Pan-Cancer Project, will help delineate the causes of cancer, inform prevention strategies and define new directions for cancer diagnoses and treatments.

In the United States, the National Cancer Institute estimates 1.7 million new cases of cancer were diagnosed in 2018 and more than 600,000 people died from the disease. Approximately 38 percent of men and women in this country will be diagnosed with cancer in their lifetime.

Cancer is caused by genetic changes — mutations — in the DNA of a cell, prompting the cell to divide uncontrollably. Many known causes of cancer, such as ultraviolet light and tobacco use, leave a specific fingerprint of damage in the DNA, known as a mutational signature. These

fingerprints can help understand how cancers develop, and potentially how they might be prevented. However, past studies have not been large enough to identify all potential mutational signatures.

“Using our detailed catalogue of the range of mutational signatures in cancer DNA, researchers worldwide will now be able to investigate which chemicals or processes are linked to these signatures,” said co-senior author Mike Stratton, PhD, director of the Wellcome Sanger Institute. “This will increase our understanding of how cancer develops, and discover new causes of cancer, helping to inform public health strategies to prevent cancer.”

This study identified new mutational signatures that had not been seen before, from single letter typo mutations, to slightly larger insertions and deletions of genetic code. The result is the largest database of reference mutational signatures. Only about half of all mutational signatures have known causes.

“Some types of these DNA fingerprints, or mutational signatures, reflect how the cancer could respond to drugs,” said co-senior author Steven Rozen, PhD, director of the Center for Computational Biology and professor of Cancer and Stem Cell Biology at Duke-NUS Medical School. “Further research into this could help to diagnose some cancers and what drugs they might respond to.”

The global Pan-Cancer Project is the largest and most comprehensive study of whole cancer genomes. The collaboration has created a huge resource of primary cancer genomes, available to researchers worldwide to advance cancer research.

“The availability of a large number of whole genomes enabled us to apply more advanced analytical methods to discover and refine mutational signatures and expand our study into additional types of mutations,” said co-senior author Gad Getz, PhD, institute member of the Broad Institute of MIT and Harvard, professor of pathology at Harvard Medical School, and faculty member and director of bioinformatics at the Massachusetts General Hospital Cancer Center.

“Our new collection of signatures provides a more complete picture of biological and chemical processes that damage or repair DNA and will enable researchers to decipher the mutational processes that affect the genomes of newly sequenced cancers.”

UC San Diego School of Medicine

Established in 1968, University of California San Diego School of Medicine is consistently ranked among the top medical school programs in the country for primary care and research by *U.S. News & World Report* and among the top 10 medical schools for National Institutes of Health total funding. The school is internationally recognized as a place where discoveries are delivered — bringing breakthroughs from the research lab to patients' bedsides. Faculty members care for patients at UC San Diego Health, where primary care is available at several convenient locations throughout San Diego County and our advanced specialty care consistently ranks among the nation's best. For more information, visit medschool.ucsd.edu.

The Wellcome Sanger Institute

The Wellcome Sanger Institute is a world leading genomics research centre. We undertake large-scale research that forms the foundations of knowledge in biology and medicine. We are open and collaborative; our data, results, tools and technologies are shared across the globe to advance science. Our ambition is vast — we take on projects that are not possible anywhere else. We use the power of genome sequencing to understand and harness the information in DNA. Funded by Wellcome, we have the freedom and support to push the boundaries of genomics. Our findings are used to improve health and to understand life on Earth. Find out more at www.sanger.ac.uk or follow us on Twitter, Facebook, LinkedIn and on our Blog.

About Duke-NUS Medical School

Duke-NUS is Singapore's flagship graduate entry medical school, established in 2005 with a strategic, government-led partnership between two world-class institutions: Duke University School of Medicine and the National University of Singapore (NUS). Through an innovative curriculum, students at Duke-NUS are nurtured to become multi-faceted 'Clinicians Plus' poised to steer the healthcare and biomedical ecosystem in Singapore and beyond. A leader in ground-breaking research and translational innovation, Duke-NUS has gained international renown through its five signature research programmes and nine centres. The enduring impact of its discoveries is amplified by its successful Academic Medicine partnership with Singapore Health Services (SingHealth), Singapore's largest healthcare group. This strategic alliance has spawned 15 Academic Clinical Programmes, which harness multi-disciplinary research and education to transform medicine and improve lives. For more information, please visit www.duke-nus.edu.sg.

About the Broad Institute of MIT and Harvard

Broad Institute of MIT and Harvard was launched in 2004 to empower this generation of creative scientists to transform medicine. The Broad Institute seeks to describe all the molecular components of life and their connections; discover the molecular basis of major human diseases; develop effective new approaches to diagnostics and therapeutics; and disseminate discoveries, tools, methods, and data openly to the entire scientific community. Founded by MIT, Harvard, Harvard-affiliated hospitals, and the visionary Los Angeles philanthropists Eli and Edythe L. Broad, the Broad Institute includes faculty, professional staff, and students from throughout the MIT and Harvard biomedical research communities and beyond, with collaborations spanning over a hundred private and public institutions in more than 40 countries worldwide. For further information about the Broad Institute, go to www.broadinstitute.org.

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