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One to 10 mutations are needed to drive cancer, scientists find

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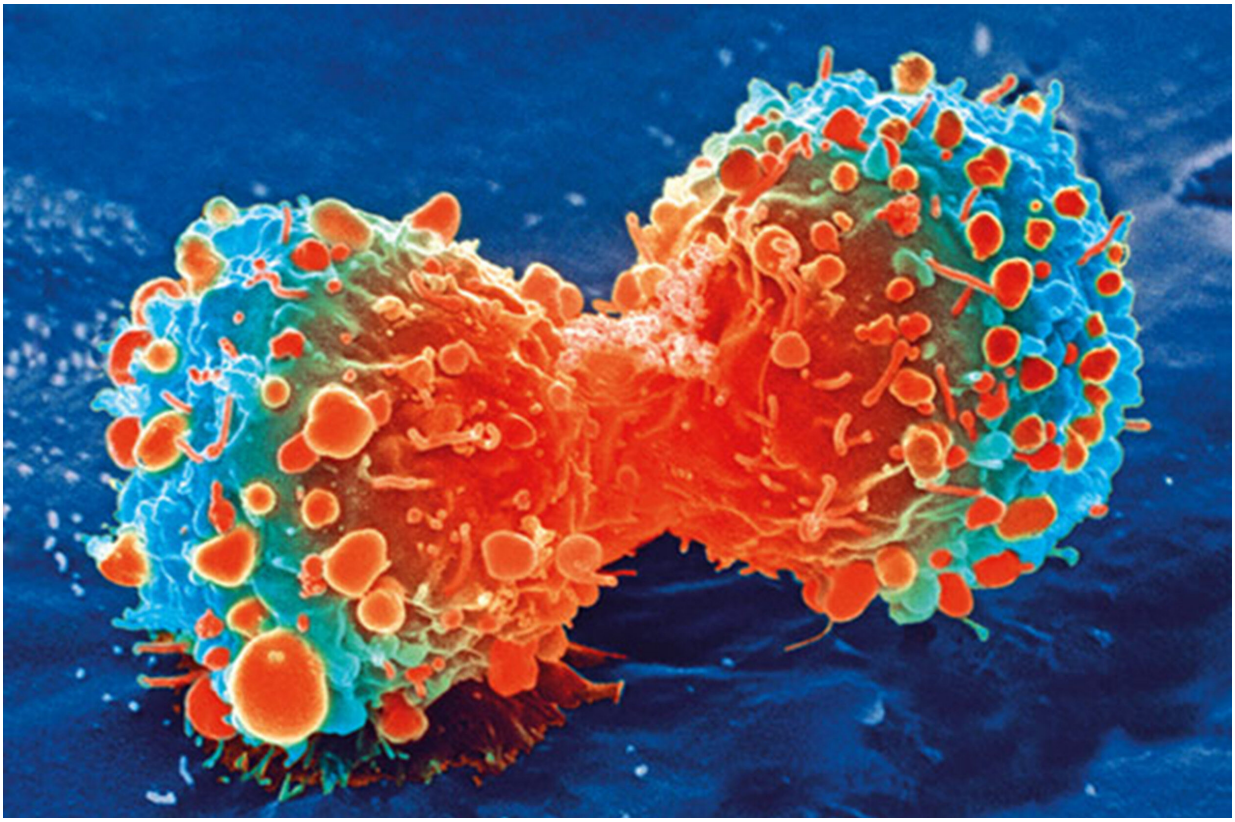

Cancer cell during cell division. Credit: National Institutes of Health

For the first time, scientists have provided unbiased estimates of the number of mutations needed for cancers to develop, in a study of more than 7,500 tumours across 29 cancer types. Researchers from the

Wellcome Trust Sanger Institute and their collaborators adapted a technique from the field of evolution to confirm that, on average, one to ten driver mutations are needed for cancer to emerge.

The results, published today (19th October) in *Cell*, also show the number of mutations driving cancer varies considerably across different cancer types.

In the study, the team developed an approach to discovering which genes are implicated in cancer evolution and how many mutations in those genes drive cancer. In the future, such approaches could be used in the clinic to identify which few mutations in an individual patient are driving his or her cancer, from amongst the thousands of mutations present.

Over 150 years ago, Charles Darwin described how different species evolve through the process of natural selection. Cancers also develop by natural selection, acting on the mutations that accumulate in the cells of our bodies over time. In this study, scientists applied an evolutionary perspective to quantifying natural selection in 7,664 tumours across 29 different cancers.

One of the striking findings of the study was that mutations are usually well-tolerated by cells in the body. This was surprising because mutations that individuals inherit from their parents are often poorly tolerated, and are generally lost from the human species over time. In the body's cells, however, as a cancer develops, nearly all mutations persist without impacting on the survival of the cell.

The team also catalogued the main cancer genes responsible for 29 different cancer types. Researchers discovered several new cancer genes and determined how complete the current lists of cancer genes are.

Dr Peter Campbell, lead author from the Wellcome Trust Sanger Institute, said: "We have addressed a long-standing question in cancer research that has been debated since the 1950s: how many mutations are needed for a normal cell to turn into a cancer cell? The answer is - a small handful. For example, about 4 mutations per patient on average drive liver cancers, whereas colorectal cancers typically require 10 or so driver mutations."

Dr Inigo Martincorena, first author from the Wellcome Trust Sanger Institute, said: "In the study, we revealed that around half of these key mutations driving cancer occur in genes that are not yet identified as cancer genes. There is already much insight into the most important genes involved in cancer; but there are many more genes yet to be discovered. We will need to bring together even larger numbers of cancers studied by DNA sequencing, into the tens of thousands, to find these elusive genes."

The new methods from this study are a step forward in personalised cancer care. In the future, similar techniques could be used in the clinic to identify the specific mutations responsible for a given patient's cancer, among the thousands of mutations that are typically found in each tumour.

Professor Sir Mike Stratton, an author of the study and director of the Wellcome Trust Sanger Institute, said: "We now know of hundreds of genes, that when mutated, drive cancer. This research shows that across cancer types a relatively consistent small number of such mutated genes is required to convert a single normal cell into a cancer cell, but that the specific genes chosen differ according to cancer type. The study also shows that we have not yet identified many these driver genes and they will be the target for further searching in the future. This increasingly precise understanding of the underlying changes that result in cancer provides the foundation for the discovery and use of targeted therapies

that treat the disease."

More information: Inigo Martincorena et al. (2017) Universal patterns of selection in cancer and somatic tissues, *Cell* (2017). DOI: 10.1016/j.cell.2017.09.042

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