Largest genome study of cancer types finds many mutations

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Scientists at the Wellcome Trust Sanger Institute, where one-third of the human genome was sequenced, have now pioneered decoding the sequence of cancer genomes. They have carried out the broadest survey yet of the human genome in cancer by sequencing more than 250 million letters of DNA code, covering more than 500 genes and 200 cancers.

The survey, published in *Nature* today, shows that the number of mutated genes that drive development of cancer is greater than previously thought. Significantly, as well as driver mutations for cancer, each cell type carries many more passenger mutations that have hitchhiked along for the ride. The study shows that a challenge for cancer biologists will be to distinguish the drivers from the larger number of passengers.

"The human genome is a vast place and this, our first deep systematic exploration in cancer, has thrown up many surprises", said Professor Mike Stratton, co-leader of the Cancer Genome Project at the Sanger Institute. "We have found a much larger number of mutated driver genes produced by a wider range of forces than we expected."

All cancers are believed to be due to mutations – abnormalities in genes. The availability of the human genome sequence has opened the door to analysing hundreds to thousands of genes, which will ultimately allow us to acquire a complete catalogue of the mutations in individual cancers.

The team studied more than 500 genes of a type called kinases, some of

which have been previously implicated in causing cancers. One example is the BRAF gene: the 2002 pilot phase of the team's work showed that BRAF was mutated in more than 60% of cases of malignant melanoma. That observation has driven discovery of new drugs to treat melanoma, some of which are in clinical trials. The current study was much broader and included breast, lung, colorectal and stomach cancers, which are the most common cancer types.

The new research showed that mutations in cancers can be divided into drivers or passengers. Driver mutations are the ones that cause cancer cells to grow, whereas passengers are co-travellers that make no contribution to cancer development. The team identified possible driver mutations in 120 genes, most of which had not been seen before.

"It turns out that most mutations in cancers are passengers," explained Dr Andy Futreal, co-leader of the Cancer Genome Project. "However, buried amongst them are much larger numbers of driver mutations than was previously anticipated. This suggests that many more genes contribute to cancer development than was thought."

Our understanding of the roles of kinase proteins sheds light on some of the mutations. Kinases can act as a series of relays, switching on and off in our cells, to control cell behaviour, such as cell division.

Dr Futreal explains: "For example, we found that a group of kinases involved in the Fibroblast Growth Factor Receptor signalling pathway was hit much more than we expected, particularly in colorectal cancers."

The team also found that the mutations carry important coded messages within them. The type of mutation found varies markedly between individual cancers, reflecting the processes that generated the mutations, some of which were active decades before the cancer showed itself.

Patterns of mutations are an archaeological record written into the DNA of each cancer telling us about the factors that caused the cancer in the first place, which were often active many decades previously. Some of the patterns can be deciphered, such as the signatures of damage from ultraviolet radiation (sunlight) or cancer-causing chemicals in tobacco, but others are currently cryptic and will require decoding in the future.

"This study vindicates all of the effort that went into the Human Genome Project," commented Dr Mark Walport, Director of the Wellcome Trust. "Understanding the mutations that cause cancer is crucial in order to develop accurately targeted treatments."

The new research shows cancers in a different light and highlights many different insights into how cancers develop. The challenge will be distinguishing the drivers from the passengers.

In some cases this is straightforward. For many others, it appears, scientists will have to analyse much larger numbers of each cancer type. New, faster DNA sequencing technologies will play an important part in achieving the scale of study needed.

"The time is right to apply the powerful tools of genomics to obtain a comprehensive view of what goes wrong at the DNA level in cancer," said Francis S. Collins, MD, PhD, director of the National Human Genome Research Institute at the National Institutes of Health. "The important and interesting data on protein kinases in this report by Professor Stratton, Dr Futreal and colleagues further encourages the conclusion that a full assault on the cancer genome will yield many opportunities to revolutionize diagnosis and treatment."

Source: Wellcome Trust Sanger Institute