Media Release

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Untangling the development of breast cancer

Researchers announce the first comprehensive genome studies of the evolution of 21 breast cancers

In two back-to-back reports published online on 17 May in *Cell*, researchers have sequenced the genomes of 21 breast cancers and analysed the mutations that emerged during the tumours' development.

Led by researchers from the Wellcome Trust Sanger Institute, the team created a catalogue of all the mutations in the genomes of the 21 cancer genomes and identified the mutational processes that lead to breast cancer. They found that these mutations accumulate in breast cells over many years, initially rather slowly, but picking up more and more momentum as the genetic damage builds up.

By the time the breast cancers are large enough to be diagnosed, they are made up of a number of genetically related families of cells, with one such family always dominating the cancer.

All cancers are caused by mutations, called somatic mutations, acquired throughout a person's lifetime in the DNA of initially normal cells. Little is known about the processes that underlie the development of many somatic mutation patters. These studies delve more deeply into the evolution of breast cancers, discovering a number of new mutation processes that can cause many thousands of mutations in a tumour, and drive its development.

Nearly 50,000 people are diagnosed with breast cancer each year in the UK, and more than 12,000 die. Breast cancer is the most common cause of all deaths in women aged over 40 and is the second biggest cause of death from cancer for women in the UK, after lung cancer.

"To be able to deal with breast cancer in the most effective way, we need to understand fully the processes that cause it," explains Dr Peter Campbell, Head of Cancer Genetics and Genomics from the Wellcome Trust Sanger Institute. "Whole genome sequencing from cancers is not a new concept, but this is the first time that we've been able to delve fully into breast cancer genomes in such a thorough way. This has given us a full panoramic view of the cancer genome and has allowed us to identify mutational patterns rather than individual mutations in specific genes."

To determine the processes that underlie breast cancer, the team catalogued all the mutations that had arisen in the 21 breast cancers. One of the processes they found was characterized by pockets of massively mutated regions in the genome. This sudden 'downpour' of mutations is frequently seen in breast cancers. The team called this phenomenon, which has never been seen before, *kataegis* after the Greek for thunderstorm.

The team found that different mutational processes act at different times in the lifespan of a breast tumour. Some mutational processes act throughout the evolution of the cancer and some processes only emerge late on in the development of the cancer. One particular mutational signature was indicative of a form of inherited breast cancer, and is linked to an inability to correctly repair breaks in DNA.

"These findings have implications for our understanding of how breast cancers develop over the decades before diagnosis in adults and might help to find possible

targets for improved diagnosis or therapeutic intervention in the future," says Professor Mike Stratton, lead author and Director of the Wellcome Trust Sanger Institute. "Harnessing the power of whole genome sequencing, we were able to access the entire genome rather than focusing on mutations in specific regions."

Similar analyses will be undertaken in 1000s of cancer genomes, under the full programme of the International Cancer Genome Consortium, and the team expect many more mutational processes will be defined along the way.

"We are used to thinking about Darwinian evolution of species by natural selection taking place over centuries and millennia. But in cancer and infectious disease similar processes can be observed over much shorter periods," says Sir Mark Walport, Director of the Wellcome Trust. "These studies, which follow from the human genome project, are untangling the evolutionary processes that eventually lead to breast cancer, in a way that would have been impossible only a few years ago.

"We are starting to see the landscape of mutation that characterises this disease in something approaching its full complexity for the first time. As this work continues, we can hope to understand how breast cancer develops and thus how it might be treated more effectively."

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Publication Details
Nik-Zainal et al 'The Life History of 21 Breast Cancers'
Published in *Cell* on 25 May 2012.

Nik-Zainal et al 'Mutational Processes Molding the Genomes of 21 Breast Cancers'
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A full list of funding agencies can be found in the papers

Participating Centres
A full list of participating centres can be found in the papers.

Selected Websites

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End of Notes to Editors