Broken genomes behind breast cancers

December 23 2009

The first detailed search of breast cancer genomes to uncover genomic rearrangements is published today. The team characterised the ways in which the human genome is broken and put back together in 24 cases of breast cancer.

Rearrangements involve reshuffling and reorganisation of the genome and include deletions, duplications and novel juxtaposition of DNA sequences. The study shows that breast cancer samples can differ greatly in the extent to which they are subject to genomic rearrangements: some are relatively undisturbed whereas others are fractured extensively and then reassembled with more than 200 rearrangements present.

While it is known that the majority of cancer genes important in blood cancers are activated by rearrangement, the role of this process in the common adult cancers is much less clear. This new study builds on pioneering work from the team using next generation sequencing to characterise comprehensively rearrangements in adult solid tumours.

"We have looked at the level of the DNA sequence at just how splintered and reorganised the genome is in many breast cancers. We were, frankly, astounded at the number and complexity of rearrangements in some cancers." says Professor Mike Stratton of the Wellcome Trust Sanger Institute. "Just as important, the genomes were different from each other, with multiple distinctive patterns of rearrangement observed, supporting the view that breast cancer is not one, but several diseases."

The information obtained from this study will add a new dimension to tumour classification and thus refine diagnosis and treatment.

In the study, the team used next-generation DNA sequencing to produce maps of genome rearrangements in 24 breast cancer samples, which were chosen to include the major subtypes of breast cancer and also included examples of breast cancers arising in BRCA1 and BRCA2 breast cancer families.

One breast cancer showed just a single genomic rearrangement - while others showed more than 200. The study provides detailed insights into the ways that the genome in some cancers have broken and also the processes that were used by the cancer cell in gluing the broken bits of genome back together again.

"It looks as though some breast cancers have a defect in the machinery that maintains and repairs DNA and this defect is resulting in large numbers of these abnormalities," says Dr Andy Futreal of the Wellcome Trust Sanger Institute. "At the moment we do not know what the defect is or the abnormal gene underlying it, but we are seeing the result of its malfunction in the hideously untidy state of these genomes. Identifying the underlying mutated cause will be central to working out how some breast cancers develop."

The broad groups of rearrangement were associated with different subtypes of breast cancer: HER2 positive breast cancers - those that are responsive to herceptin - have similar patterns of disruption. By the same measure, triple-negative breast cancers, which don't respond to treatment with herceptin or hormones, looked similar.

The size of the DNA regions that are deleted, duplicated or removed ranges from a few hundred letters of DNA code to several millions. Most changes were rearrangements within the same chromosome, but

there were also a substantial number involving the joining of two different chromosomes.

Dissecting out the complexity and the diversity of the breast cancer genomes is important for understanding how the cancers arise. Importantly, however, the apparent loss of DNA repair systems raises the possibility of new therapeutic opportunities in some breast cancers.

"It appears that in different subtypes of breast cancers, distinct mechanisms of DNA repair are impaired, leading to different types of genomic disorganisation," suggests Dr Jorge Reis-Filho, team leader from the Breakthrough Breast Cancer Research Centre at The Institute of Cancer Research.

"If we damage further an already-faulty DNA repair system using tailored therapies, one can kill tumour cells selectively, without harming normal cells. There are already some highly interesting results suggesting that breast cancers with defects in DNA repair are more sensitive to drugs that cause additional DNA damage."

More information: Stephens PJ et al. (2009) Complex landscapes of somatic rearrangement in human breast cancer genomes. Nature.

Source: Wellcome Trust Sanger Institute