Found: 1 in 3 billion

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Vancouver scientists from the Ovarian Cancer Research (OvCaRe) Program at BC Cancer Agency and Vancouver Coastal Health Research Institute have discovered that there appears to be a single spelling mistake in the genetic code of granulosa cell tumours, a rare and often untreatable form of ovarian cancer.

This means that out of the three billion nucleotide pairs that make up the genetic code of the tumour, one - the same one in every tumour sample - is incorrect. The discovery, published online June 10th in the *New England Journal of Medicine,* marks the beginning of a new era of cancer genomics, where the complete genetic sequence of cancers can be unravelled and the mutations that cause them exposed. For women with granulosa cell tumours it represents the first specific diagnostic tool and clear path to develop much needed treatments for this cancer.

"This is really a two-fold discovery," says Dr. David Hunstman, lead author and genetic pathologist at the BC Cancer Agency and Vancouver General Hospital and associate professor in the Department of Pathology and Laboratory Medicine at the University of British Columbia. "It clearly shows the power of the new generation of DNA sequencing technologies to impact clinical medicine, and for those of us in the area of ovarian cancer research and care, by identifying the singular mutation that causes granulosa cell tumours, we can now more easily identify them and develop news ways to treat them."

In the past when scientists wanted to look at the sequence of a tumour, it was a laborious process, with each gene individually decoded into

thousands of nucleotides and all data accumulated and sorted. Most studies could only look at one or at most a few of the 20,000 genes in the human genome whereas the new sequencing technologies allow scientists to look at everything at once. Through a collaboration between OvCaRe and the BC Cancer Agency's Genome Sciences Centre, the research team used "next generation" sequencing machines that are able to decode billions of nucleotides at rapid speed and new computer techniques to quickly assemble the data. "This task would have been unfathomable in terms of both cost and complexity even two years ago," says Dr. Marco Marra, Director of the BC Cancer Agency's Genome Sciences Centre.

The OvCaRe team decoded four tumour samples of the relatively rare granulosa cell tumour, which affects five percent of ovarian cancer patients. Using the new sequencing technology and bioinformatics, they discovered a single nucleotide located in the FOXL2 gene was mutated in every sample. The research team further validated their work by examining a large number of additional tumour samples from across Canada and around the world, and are satisfied they have been able to validate that this mutation is present in almost all granulosa cell tumours and not in unrelated cancers. Most types of cancers, including ovarian cancers, have a broad range of genetic abnormalities. This finding shows that granulosa cell tumours have a characteristic single DNA spelling mistake that can serve as an easy to read identity tag for this cancer type.

"Although it has been suggested that hundreds of any cancer type would have to be sequenced at great depth to make clinically useful discoveries," says Huntsman, "we had hypothesized that knowledge could be gained from much smaller studies if the cancers were carefully selected and represented clinically homogenous diseases. There are many rarer cancer types, like granulosa cell tumours that fit that bill and based upon our success in decoding granulosa cell tumours we are focusing on other rare tumours in what could be described as a guerrilla war on cancer. We hope that these studies will not only help future patients with

rare tumours but will also teach us about more common ones as well."

"This cancer is unique," says Dr. Dianne Miller, gynecologic oncologist at BC Cancer Agency and Vancouver General Hospital. "For patients with this tumour type, it means they should all have the same response to the same treatment. And now that we have this pathway, we can look for existing cancer drugs that might work on this particular gene mutation to make the cancer disappear."

The OvCaRe team was able to make this discovery because of the multidisciplinary nature of the group, which crosses two provincial health authorities and is made up of gynaecologists, pathologists, bioinformatics specialists, and oncologists. Further enhancing the team's success is the centralization of patient treatment and record keeping.

"We are excited by this paper," says Dr. Michael Birrer, professor, Department of Medicine, Harvard Medical School and director GYN/Medical Oncology, Medicine, Massachusetts General Hospital. "The ovarian cancer research and care community now has new biologic insights into this poorly understood tumour and a potential therapeutic target. More importantly, this tour de force study reveals the power of genomic approaches to cancer, particularly rare tumours."

Source: University of British Columbia (news : web)