Critical Genes Mutated In Stomach Cancer Identified

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http://www.asianscientist.com/2012/04/in-the-lab/stomach-cancer-gene-mutations-identified-2012/

AsianScientist (Apr. 11, 2012) - Researchers in Singapore have identified hundreds of novel genes that are mutated in stomach cancer, paving the way for treatments tailored to the genetic make-up of individual stomach tumors.

The study, which appeared online this week in *Nature Genetics*, was a collaborative effort involving three research groups affiliated with the Duke-NUS Graduate Medical School (Duke-NUS) and the National Cancer Center Singapore (NCCS), headed by Patrick Tan, M.D., Ph.D, Steve Rozen, Ph.D., and Teh Bin Tean, M.D., Ph.D..

Stomach cancer is the second leading cause of cancer death globally with more than 700,000 deaths each year, and is highly prevalent in East Asia. Treatment of this deadly disease is often difficult and unsuccessful because of late detection of tumors and a poor understanding of the causes of stomach cancer. In the United States, less than quarter of patients survive more than five years after diagnosis, even after treatment.

> "Until now, the genetic abnormalities that cause stomach cancers are still largely unknown, which partially explain the overall poor treatment outcome," said Dr. Tan who is associate professor at Duke-NUS and also leader of the Genomic Oncology Program at the Cancer Science Institute of Singapore, as well as a group leader at the Genome Institute of Singapore.

Rather than sequence the entire three billion letters of the human genomic blueprint in each tumor and tissue sample, the researchers used a strategy that focused only on the protein-coding portions of 18,000 genes, known as exons. Collectively referred to as the exome, this is thought to be the most functionally important part of the human genome even though it makes up only about one percent of the genome.

Through sequencing the exomes of tumor samples and normal tissue taken from 15 patients, the researchers were able to identify over 600 gene mutations that were previously not known to be mutated in stomach cancer.

Two of the 600 stomach cancer-associated genes identified, FAT4 and ARID1A, proved to be particularly interesting because of their roles in mediating cell adhesion and chromatin remodeling, respectively.

Mutations in the cell adhesion gene, FAT4, may potentially increase the mobility of cancer cells into surrounding tissue and to other parts of the body as metastases.

Chromatin remodeling genes like ARID1A are responsible for altering the chromatin structure of the

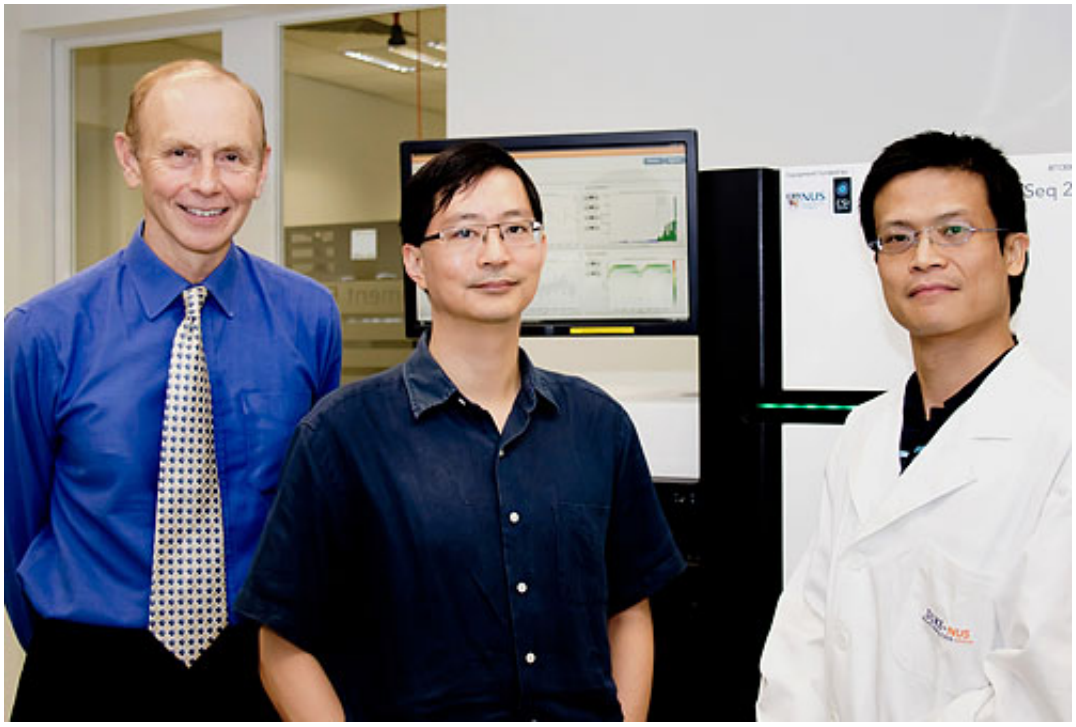
DNA and maintaining the stability of the genome. Mutations in ARID1A may lead to abnormal chromatin structures, genomic instability, and the accumulation of further genetic abnormalities.

To find out if FAT4 and ARID1A are frequently mutated in stomach tumors, the researchers analyzed a larger sample of about 100 stomach tumors and found these genes to be mutated in 5 percent and 8 percent of stomach cancers, respectively. In some patients, portions of the chromosome containing the two genes were found to be missing, evidence that genetic defects affecting these genes occur frequently in stomach cancer.

Further experiments in the lab demonstrated the importance of these two genes in driving stomach cancer, as manipulation of FAT4 and ARID1A function altered the growth of stomach cancer cells.

> "More research is required to realize the clinical implications of these findings. ARID1A and FAT4 are likely also involved in many other cancer types, not just stomach cancer," noted Dr. Tan, whose research team is actively working on translating the results of this study into clinical applications.

With more than 100,000 new cases of stomach cancer each year likely to be caused by mutations in FAT4 or ARID1A, it is hoped that drugs against these targets may someday lead to more effective treatment of stomach tumors and other cancers.



The article can be found at: Zang ZJ, Cutcutache I et al. (2012) Exome Sequencing Of Gastric Adenocarcinoma Identifies Recurrent Somatic Mutations In Cell Adhesion And Chromatin Remodeling Genes.

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Source: Duke-NUS Graduate Medical School; Photo: Duke-NUS.
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