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Team identifies recurrent fusion genes in gastric cancers

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Studying the gastric cancers of 15 Southeast Asian patients, researchers at The Jackson Laboratory, the Genome Institute of Singapore and other institutions identified five recurrent fusion genes, one of which appears to lead to cellular changes involved in acute gastritis and cancer.

Worldwide, close to a million cases of gastric cancers are diagnosed each year, and some of the world's highest incidence rates are in Asia (particularly in Korea, Japan and China).

The researchers, led by JAX Professor Yijun Ruan, Ph.D., and Axel M. Hillmer, Ph.D., of GIS, published their findings in the journal *Cell Reports*.

Recurrent fusion genes are separate genes fused together to produce a single protein product. The most famous example of a fusion gene is the BCR-ABL protein, nicknamed the Philadelphia chromosome, which directly causes about 90 percent of chronic myelogenous leukemia cases.

Profound chromosomal disruptions and rearrangements are found in many cancers. As a result, simple linear sequencing of tumor genomes fails to capture all of the genomic perturbations that contribute to cancer initiation, maintenance and metastasis. Structural variants - copy number variants, inversions and fusion gene products which can all contribute to malignancy - are difficult to find using standard array-based hybridization and next-generation sequencing protocols.

The researchers used a DNA-PET (paired-end-tag) sequencing method developed by Ruan's group which can detect and characterize genomic structural rearrangements, to analyze the gastric cancer patient cells, and identified five recurrent fusion genes. One of the fusions combined CLDN18, which is essential for tight junctions in the stomach that prevent leakage, and ARHGAP26, which is involved in cell adhesion.

Working in both normal and transformed (cancerous) cell lines, the researchers found that CLDN18-ARHGAP26 expression changed the characteristic of both cell types significantly. They noted that the cells adhered poorly to each other and to the extracellular matrix, increasing susceptibility to damage and diminishing healing. The changes point to an increased indication for acute gastritis, a risk factor for gastric cancer. The CLDN18-ARHGAP26 expression also promotes invasive tendencies in the cells, which aids in cancer progression once the cancer initiates.

"This work exemplifies the complexity of cancer genomes undergoing genomic rearrangement and the need for developing new sophisticated genomic analysis approaches which will ultimately provide critical insights into cancer progression," Ruan says.

More information: Yao et al.: Recurrent fusion genes in gastric cancer: CLDN18-ARHGAP26 induces loss of epithelial integrity. *Cell Reports*, July 2015, dx.doi.org/10.1016/j.celrep.2015.06.020

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