

Veterinary college team IDs gene that drives ovarian cancer

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High-grade serious ovarian carcinoma (HGSOC) is the fifth-leading cause of cancer-related deaths in women in the United States, yet little is known about the origins of this disease.

Now, scientists at the College of Veterinary Medicine have collaborated on a study that pinpoints which specific [genes](#) drive—or delay—this

deadly [cancer](#).

"We've taken the enormous collection of genomic mutation data that's been mined on [cancer genetics](#) and tried to make functional sense of it," said John Schimenti, professor of genetics in the Department of Biomedical Sciences and senior author of the study, which published Sept. 1 in *Cell Reports*.

Schimenti teamed with biomedical sciences colleague Alexander Nikitin, professor of pathology and director of the Cornell Stem Cell Program, and members of their respective labs to gain a better understanding of HGSOC.

Cancer researchers have known for a while that the disease is almost always caused by multiple genetic 'hits.' One mutation alone does not turn a cell cancerous; generally at least two or three are required, and often different combinations of genes can cause the same cancer.

Adding complexity, Schimenti said, is the fact that once one key genome-destabilizing mutation arises, others will follow. Sequenced tumors yield a plethora of mutations—some are the originators of the cancer itself, while many others are spinoffs.

"It's a longstanding issue in cancer research," he said. "What are the genetic drivers, and what are the passengers in the process?"

To address these complexities, the researchers wanted to test combinations of possible genetic suspects, and then parse out which of the many associated mutations were sparking the cancer.

To do so, they turned to the Cancer Genome Atlas, an international collaborative database that compiles the [genetic information](#) from patient tumor samples and the mutated genes associated with them. They

took a list of 20 genes known to mutate in HGSOC and, using CRISPR gene-editing technology, created random combinations of these mutations in cultured [cells](#) from the ovary surface, including regular epithelial cells and epithelial stem cells, to see which cell type was more susceptible to the mutations.

The researchers then noted which combination of mutations turned which group of cells cancerous—pinpointing both the genes driving the process and which cell type the cancer originated in.

The study revealed what the team had originally suspected—that ovarian surface stem cells were more apt to become cancerous when hit with [mutations](#). They also unexpectedly discovered genes that had the opposite effect.

"We found there were various genes that would help the process along, but interestingly, there were other genes that, when mutated, actually inhibited the cancer initiation process," Schimenti said.

Knowing which are the cells of origin and which genes are necessary in initiating this highly aggressive form of ovarian cancer can be powerful information, both for ovarian and other types of cancers. "The cancer driver screening methodology we used should be applicable to answering the same kinds of questions for cells and cancers in other organs and tissues," Nikitin said.

Schimenti said the findings could be particularly useful for ovarian cancer patients who have their tumors biopsied and sequenced for genetic data.

"In the past, you would know which genes were mutated but you wouldn't know what role they played," he said. "Now you know which ones are important. And eventually, you could develop drugs to target

the mutated genes that you know are causing the problem."

More information: Robert Joseph Yamulla et al. Most Commonly Mutated Genes in High-Grade Serous Ovarian Carcinoma Are Nonessential for Ovarian Surface Epithelial Stem Cell Transformation, *Cell Reports* (2020). [DOI: 10.1016/j.celrep.2020.108086](https://doi.org/10.1016/j.celrep.2020.108086)

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