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Homing in on shared network of cancer genes

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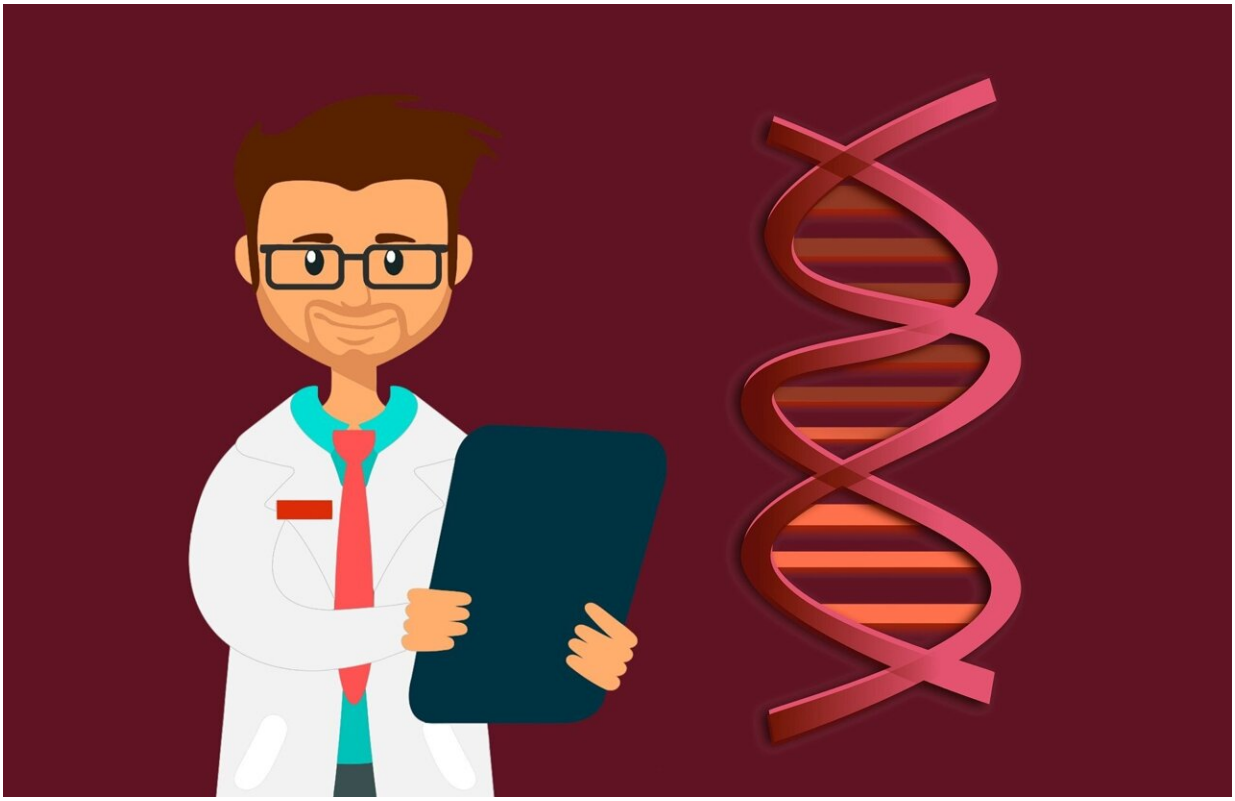

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Wilmot Cancer Institute researchers are a step closer to understanding the complex gene interactions that cause a cell to become malignant. In a new *Cell Reports* study published today, the group used network modeling to hone in on a set of such interactions that are critical to malignancy, and likely to be fertile ground for broad cancer therapies.

Discrete genetic mutations that can be targeted by drugs have only been identified for a small fraction of cancer types. But those mutations rely on a downstream network of non-mutated genes in order to cause cancer. Those downstream genes—and their intricate interactions—may be common across many cancers and could offer a giant leap forward in cancer therapy.

One of the lead authors of the study, Hartmut "Hucky" Land, Ph.D., who is the deputy director of the Wilmot Cancer Institute and the Robert and Dorothy Markin Professor of Biomedical Genetics at the University of Rochester Medical Center and has worked to identify common core features of cancers for over 10 years. His goal is to find cancers' shared vulnerabilities and exploit them.

"Targeting non-mutated proteins that are essential to making cells cancerous is a broader approach that could be used in multiple cancers," said Land, "but it's hard to find these non-mutated, essential genes."

That is why Land turned to Matthew McCall, Ph.D., MHS, a Wilmot Cancer Institute investigator who is an associate professor of Biostatistics and Computational Biology at URMC, for collaboration. McCall, who is the other lead author of the study, developed a new network modeling method, called TopNet, that the group paired with genetic experiments in cells and mice to pinpoint functionally relevant gene networks.

Land's group previously identified a very diverse set of non-mutated genes that are crucial to cancer. In this study, the group wanted to see how those genes interact—starting with a subset of 20 genes. Increasing or decreasing expression of one gene in cultured cells would have numerous effects on the expression levels of the other genes in the set.

"There were so many interactions, you could waste a lot of time, energy

and money testing interactions that might not be useful," McCall said. "To hone in on the interactions that are more likely to be useful, we used network modeling, and compared our model networks back to the lab findings," McCall said.

For context, the number of possible gene network models considered by TopNet was many times greater than the estimated number of atoms in the universe. After weeding out models that didn't closely fit the observed data and further focusing in on gene interactions that appeared in at least 80 percent of the models, the team was left with a manageable set of 24 high-confidence gene interactions. Subsequent experimentation demonstrated that these interactions often play an important role in malignancy.

"Dr. McCall's elegant and mind-boggling methodology is essentially helping us disentangle a hair ball of genetic networks," said Land. "These networks are usually very messy and it's nearly impossible to extract useful information from them. But Dr. McCall has found a way to cut through this Gordian knot."

The group has already tested a sampling of the genetic interactions revealed by TopNet, and confirmed via experiments in cells and mice that the interactions are functionally linked. Next, the group intends to test the limits of TopNet, with the intent to use this method to find potential cancer therapies that are broadly effective.

More information: Helene R. McMurray et al, Gene network modeling via TopNet reveals functional dependencies between diverse tumor-critical mediator genes, *Cell Reports* (2021). DOI: 10.1016/j.celrep.2021.110136