# Gene mutations linked to hereditary kidney cancer predisposition, but potential Achilles' heel identified

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Researchers at the UCLA Jonsson Comprehensive Cancer Center have confirmed that a large number of genetic variants of unknown

significance are in fact verified mutations that predispose patients to a rare hereditary syndrome that increases the risk of kidney cancer.

By functionally characterizing the behavior of these mutations, researchers and clinicians can better predict which patients have this condition and possess an increased risk of developing kidney cancer.

The findings, published in *Cancer Discovery*, could also help guide the development of a new treatment strategy for the condition, known as hereditary leiomyomatosis and renal cell cancer (HLRCC). People who are diagnosed with HLRCC are at an increased risk of developing smooth muscle tumors in the skin and uterus as well as a particularly aggressive form of kidney cancer resembling type II papillary renal cell carcinoma.

"The problem with this particular type of kidney cancer is that it can spread at a very small size so if you don't catch it early it can metastasize to other parts of the body very quickly, making it very hard to treat," said study author Dr. Brian Shuch, director of the Kidney Cancer Program and the Alvin & Carrie Meinhardt Endowed Chair in Kidney Cancer Research at UCLA. "Patients with this condition currently have limited treatment options."

However, diagnosing the cancer early isn't the only problem, said Shuch. A significant number of patients harboring genetic variants of unknown significance may not receive regular kidney cancer screening despite suspicion that the variant they are carrying can lead to a cancer diagnosis. While it is known that alterations to a specific gene called fumarate hydratase can lead to HLRCC, a large number of variants have yet to be characterized as disease causing, or pathogenic, which are associated with a higher cancer risk.

"There are a lot of patients who have this condition and who have a

strong family history of kidney cancer," said Shuch. "But there's really nothing they can do since we don't know if the variant they are harboring has any significance. They are basically just told to keep in touch."

To better understand these variants and see which ones might be more prone to developing cancer, researchers looked at the activity of 74 variants of the fumarate hydratase gene that were previously considered to have unknown significance but had high enough concern where enzymatic data could reclassify them.

This gene works in a key metabolic pathway, called the Krebs Cycle, and the syndrome occurs when patients inherit one bad copy of the gene. Similar to other cancer syndromes, cells are predisposed to cancer when there is damage to the remaining healthy copy ultimately leading to kidney cancer.

"Understanding genetic variants is crucial for learning about diseases because they provide us insights into the genetic basis of traits and disease," said Dr. Heather Christofk, director of Basic and Translational Research at the UCLA Jonsson Comprehensive Cancer Center and senior author of the study. "By discovering which genetic variants increase the risk for conditions, we can possibly prevent them from occurring with medical intervention or surveillance to reduce risk of disease manifestations and/or minimize potential harm."

After analyzing the data, the team found that nearly half of the variants were entirely inactive, which indicated that they were likely contributing to the development of cancer and therefore associated with the genetic condition.

To further investigate the effects of these variants, the researchers created cell lines that expressed different fumarate hydratase gene variants with various degrees of activity. These cell lines had differing

levels of fumarate, the primary factor in driving the onset of cancer. They then measured the levels of fumarate and examined its impact on how cells process energy and nutrients.

They discovered that when fumarate accumulates due to fumarate hydratase deficiency, it disrupts many processes that are essential for cell growth. As a result, these cells become dependent on other key pathways including the purine salvage pathway which helps generate the building blocks to replicate DNA.

"One way to stop tumor growth from occurring, is to potentially target this pathway," said Dr. Blake Wilde, the study's first author and postdoctoral fellow in the Christofk laboratory. "We found that these tumors rely on this alternative pathway, which uses nutrients from the environment in order to synthesize nucleotides. Generating nucleotides is essential for the tumor cells to replicate and sustain growth."

Luckily, noted Wilde, there are already approved drugs developed to target the purine salvage pathway that are used in the clinic for treating people with autoimmune disorders as well as other cancers that use this pathway.

One drug is called 6-mercaptopurine, and the team found that when tested in both cell cultures and mice, this type of kidney cancer was extremely sensitive to the drug, decreasing the levels of nucleotides and reducing tumor growth.

"Based on these findings, not only can we now better characterize a lot of patients who have a variant and did not previously know if they really had an increased risk of kidney cancer, we can possibly repurpose this well-tolerated drug to be a rapidly translatable treatment strategy," Christofk said. "And we are hoping this is something that we can repurpose quickly for those affected by these variants."

**More information:** Blake R. Wilde et al, FH variant pathogenicity promotes purine salvage pathway dependence in kidney cancer, *Cancer Discovery* (2023). DOI: 10.1158/2159-8290.CD-22-0874