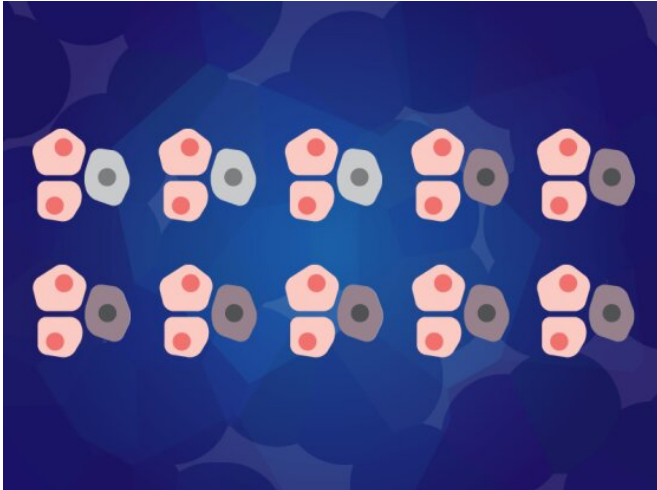


Scientists identify a key gene that is turned on in most cancer types

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Credit: Susanna Hamilton, Broad Communications

Physician-scientists at the Broad Institute of MIT and Harvard and Dana-Farber Cancer Institute have discovered that a gene called FOXR2 that is normally turned off in most tissues in the body is activated in at least 70% of cancer types and 8% of all individual tumors.

Their study, recently published in *Cancer Research*, may help scientists better understand how a variety of cancers develop. The research team has already started working with chemists and structural biologists to figure out how to target this gene with possible new treatments.

"The fact that this gene is normally switched off in most tissues means that we might be able to target it in a way that doesn't cause a lot of side effects," said senior author Pratiti Bandopadhyay, an associate member at the Broad and a pediatric neuro-oncologist at Dana-Farber.

Finding FOXR2

Jessica Tsai, a pediatric oncologist at Dana-Farber, a postdoctoral fellow in Bandopadhyay's lab, and first author of the paper was analyzing genome sequences of a kind of pediatric brain cancer called diffuse midline gliomas—fatal tumors in the middle of the brain—when she and her team found, to their surprise, that many of the cancers showed abnormal expression of FOXR2. This gene encodes a transcription factor, is located on the X chromosome, and is normally expressed only in the testis.

"Really, any normal tissue other than testis shouldn't have any FOXR2 expression, so that finding stood out to us initially," said Tsai.

To look for traces of the gene in other cancers, Tsai and her colleagues combed through cancer databases, analyzed human cell cultures, and sequenced tumors from animal models of cancer. They found that some of the most common pediatric and adult cancers—including osteosarcoma, melanoma, and [non-small cell lung cancer](#)—also showed FOXR2 expression, as well as diffuse midline glioma tumors from the Dana-Farber Tumor Bank. The team collaborated with David Jones from the German Cancer Research Center to confirm that many types of childhood tumors turn on FOXR2.

"Families who donated these tumors have really allowed us to look at genes like FOXR2 and describe their role in these devastating brain tumors," said Bandopadhyay.

Functional clues

Working with collaborator Tim Phoenix at the University of Cincinnati, the scientists studied mice with and without activated FOXR2, and discovered that expression of the gene boosts the growth rate of [brain tumors](#) including Diffuse Midline Gliomas. They also found that cells activate the gene through a process called hypomethylation, a chemical

modification that removes [methyl groups](#) from a gene. And the researchers discovered that a group of transcription factors called ETS were overexpressed when FOXR2 was active, possibly driving [tumor](#) formation.

The team suspects that FOXR2 could be part of a larger pattern where normally inactive testis genes are turned on in patients with cancer. Other studies have shown that proteins encoded by [genes](#) on the X chromosome called cancer testis antigens are abnormally expressed in tumors. These antigens have been a key target of drugmakers developing new cancer treatments.

Bandopadhyay and Tsai say that their study provides some early clues on how FOXR2 works, but that there is still a lot to learn. Next, they hope to break down the relationship between ETS and FOXR2 to better understand how the gene is activated. The team has also already partnered with other labs at the Broad and Dana-Farber Cancer Institute to explore how to develop cancer treatments targeting FOXR2.

More information: Jessica W. Tsai et al, FOXR2 is an epigenetically regulated pan-cancer oncogene that activates ETS transcriptional circuits, *Cancer Research* (2022). DOI: [10.1158/0008-5472.CAN-22-0671](https://doi.org/10.1158/0008-5472.CAN-22-0671). [aacrjournals.org/cancerres/art... regulated-pan-cancer](https://aacrjournals.org/cancerres/art...regulated-pan-cancer)

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