

# Gene mutation, tissue location, signaling networks drive cancer incidence and severity

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The KRAS gene is one of the commonly mutated genes in cancer. More than 40 percent of colorectal cancers have a mutated KRAS gene, or oncogene, that is at least partially responsible for cancer development.

Mutated KRAS genes are commonly found in other cancers as well, including pancreatic, lung, myeloma and endometrial, and not all KRAS mutations in the same organ tissue cause the same disease severity, according to three new studies from researchers at the Cancer Center at Beth Israel Deaconess Medical Center (BIDMC). Using mouse models of cancer, the research shows for the first time that cancer disease incidence and severity are influenced by both the specific type of KRAS mutation as well as by the tissue in which the mutation is located. These findings were recently published in *Cancer Discovery*, *Cell Reports*, and *Cell Systems*.

"The unifying theme of these three papers is that the way we practice precision medicine today is not precise enough," said principal investigator and author Kevin Haigis, Ph.D., Director, Cancer Genetics Program at the Cancer Research Institute at the Cancer Center at BIDMC. "Basket trials, in which patients with a particular genetic mutation like KRAS are grouped into the same basket and given a drug against that mutation, are not sufficient. Our work shows for the first time that every single mutant form of KRAS differs in terms of cancer-causing ability and downstream signaling of relevant molecular pathways."

## **Mutation Subtypes influence Disease Severity**

Although KRAS is generally the most commonly mutated oncogene, it comes in many different forms, or alleles. In the past, various mutant forms were considered redundant. "This conventional assumption informs the way clinical trials are done today, with people grouped as either KRAS mutant or KRAS wild-type with no mutation," explained Haigis, who is also Associate Professor of Medicine at Harvard Medical School. "Our new research shows that you simply cannot place all KRAS mutant cancers in the same basket—each allele is actually quite distinct from one another. Clinicians need to know exactly which mutation a

patient has and create a mutation-specific basket for a clinical trial."

While circumstantial evidence points to various KRAS alleles activating different biological pathways, Haigis's group is the first to genetically engineer a mouse model in which groups of mice possess different KRAS alleles. In this way, they were able to study various mutant KRAS alleles in several cancer types in an experimentally controlled system.

In the group's *Cancer Discovery* study published in April, the team looked at colorectal cancer caused by rare or common KRAS mutations. Homing in on a KRAS mutation associated with a region of the gene known as codon 146, their mouse model showed that animals with the 146 mutation live longer than animals with another type of KRAS mutation, called G12D. "In colon cancer, the 146 mutation does cause colon cancer, but those colon cancers are much weaker and the mice survive longer," Haigis explained. They also saw that the proteome, or the signaling pathways, is dramatically different between the two types. "That's why we think cancers with different mutations will respond differently to drugs."

In a similar paper published in *Cell Reports*, Haigis' team, with colleagues from Northeastern University, compared the molecular signaling produced by different KRAS alleles. They found that the codon 12 KRAS allele produced strong signaling—not surprising given that the codon 12 mutation is the most common KRAS mutation in all cancer patients, regardless of organ type. They also tested the codon 13 KRAS allele in colon cancer, which accounts for about 10 percent of all KRAS mutations in colon cancer and produces a very weak oncogenic signal, similar to the 146 signal in the *Cancer Discovery* paper.

These observations are important because treatment guidelines for the most commonly used FDA therapy for colon cancer (a therapy against epidermal growth factor receptor, or EGFR) recommend its use only in

[colon cancer](#) patients without KRAS mutations. This is based on the fact that when the drug was in development, researchers saw that patients with KRAS mutations did not appear to respond well to it. "But some [clinical trials](#) show that patients with the codon 13 KRAS mutation do respond to EGFR therapy," said Haigis. "When you begin to separate the mutations from one another, there may be therapies that are available on the market that will help some patients. Even if those mutations are rare, those patients exist."

## Mutations Have Tissue Specificity

In a paper published in *Cell Systems*, Haigis and colleagues kept the KRAS mutation constant and altered either the organ in which it was located or other elements of the mouse's genetic background. Although pancreatic and colon cancers both commonly have KRAS mutations, the other genes that are mutated in those cancers are quite different. For example, more than 85 percent of colon cancers have adenomatous polyposis coli (APC) mutations, which are never seen in pancreatic cancer. Instead, pancreatic tumors commonly have p53 [mutations](#). The team genetically engineered mice so that they have mutant KRAS either in the colon or the pancreas. They then engineered them further to have other mutated genes, either APC or p53. "What we showed was that the signaling properties of KRAS are different depending on what organ you are in and what other genes are mutated," said Haigis. "KRAS, like any oncogene, has to tap into the intrinsic signaling network of the tissue to produce cancer and the permissive network only exists in certain tissues."

## Looking Ahead: the future of precision medicine

In combination with other researchers, Haigis recently received an award from the Cancer Research UK Grand Challenge to further study this

concept. "The concept that no single factor can predict whether a cancer responds to a particular therapy will be key to the future of precision medicine," he said. "Clinicians and scientists need to know which tissue the cancer comes from, which oncogene is mutated and which allele is created, and the other genes that are mutated; all of that determines if and how well a [cancer](#) will respond to a given drug. That is precision medicine and that's the level we have to get to."

**More information:** Emily J. Poulin et al. Tissue-Specific Oncogenic Activity of KRASA146T, *Cancer Discovery* (2019). [DOI: 10.1158/2159-8290.CD-18-1220](https://doi.org/10.1158/2159-8290.CD-18-1220)

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