If you think cancer genes are simple, you don't know JAK

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Cancer-causing genes can work in more powerful and sneaky ways than have been realized. Scientists have shown that a gene named JAK that is closely related to a common cancer-causing gene in people tips the scales toward cancer in an unexpected manner. JAK disrupts the activity of an organism's DNA on a broad scale, thwarting a critical molecular event very early on in an embryo's development.

A team from the University of Rochester Medical Center made the finding, published in the Sept. 7 issue of Public Library of Science (PLoS) Genetics, through research involving fruit flies, which share much of the same complex cellular signaling as humans. Sorting out the major molecular processes in fruit flies or other comparatively simple organisms first has often allowed scientists studying diseases like cancer to speed the development of new treatments by years or even decades.

By manipulating the DNA of fruit flies and analyzing their body types as they develop – as maggots – the team made a surprising finding: The cancer-promoting effects of a mutation to the DNA sequence of a gene that normally suppresses cancer can be passed from parents to offspring, even if the mutation itself is not passed to the offspring. Under some circumstances, having one parent with the mutation is enough to ultimately
affect the offspring, even when the mutation itself is not passed to the next generation.

The work offers a stark illustration of a reality that scientists are coming

to fully respect only recently: Even though the DNA code has been traditionally considered the only way to pass genetic information through the generations, there are other, more subtle genetic legacies, types of a “molecular memory” that can go from generation to generation as well.

The team made the finding with a cancer-causing gene, or oncogene, known as an activated JAK kinase. A biochemical system extremely similar to JAK is vital for people’s health, but when its signals run amok, the system can play a role in the development of leukemia or lymphoma.

For decades, scientists have been teasing out DNA’s secrets, learning how one snippet of DNA controls another, how some genes wield incredible power over others, and how the DNA code encrypts all kinds of biochemical signals – start, stop, turn on, turn off, and so on. Scientists have made great progress understanding the complex signals that govern diseases like cancer, often finding that a key gene that should be on is turned off, or that a gene that is supposed to be off is turned on, or that a mutant gene creates a faulty protein that doesn’t work correctly.

Now researchers are trying to make more sense of the glut of genetic information becoming available. For instance, what does a given sequence of chemical bases that make up our DNA, such as ACTGGGCTAGTTGGCAGT, really mean for our health" Scientists are turning more attention to the big picture, looking at broad mechanisms that determine how our bodies interpret the DNA, the master blueprint that controls how an organism develops and functions. It’s part of a body of work known as “epigenetics.” The main idea is that genetic information can be regulated on a more global scale than just on a gene-by-gene basis, which has been the focus of much genetic research thus far.

The team, based in the University’s Department of Biomedical Genetics and the James P. Wilmot Cancer Center, has shown how epigenetic

information can play a significant role in causing cancer.

“You might assume that a fruit fly that inherits a mutation that can increase cancer is more at risk for the disease than its sibling that does not inherit that mutation,” said geneticist Willis Li, Ph.D., the lead author of the study and associate professor in the Department of Biomedical Genetics.

“We have found an example where this is not true. We found that the cancer-causing effects of certain mutations can persist in cells that don’t even carry the damaged gene, and that these effects can be passed from one generation to the next even though they’re not actually in the DNA code. The mutation’s effects on the DNA of one of its parents affect the genes of its offspring. Even though the mutation is in one fly but not in another, both are affected equally,” said Li.

To understand the work, it helps to think of large stretches of DNA, sometimes encompassing many genes, as valuable parcels of information that must be handled with precision and great care, not only as they are passed from generation to generation but also during the lifespan of an individual. Such packages contain little flags or markings. Just as a regular package might have the words “handle with care” stamped on it, our DNA has chemical signals that tell the body things like, “Don’t turn this set of genes on” or “Turn these genes on only in case of emergency.” No matter what’s “inside the package” – no matter the specific DNA code – such chemical signals on the outside provide instructions that help the body determine what to do with the DNA.

The instructions frequently come through a mechanism known as DNA methylation, which the body uses often to turn genes off. Normally, such chemical markings are wiped clean and reset very early in an organism’s life through a process known as epigenetic reprogramming. But Li’s team showed that JAK – specifically an activated JAK kinase known as

HOP-Tum-l – can disrupt that reprogramming, so that the offspring inherit the methylation pattern of a parent. In other words, the specific pattern of genes that are destined to be turned on or off – the instructions for what to do with the DNA – is mistakenly passed on from parent to offspring.

While scientists have known that epigenetic information can be passed from generation to generation, Li says this is the first time the phenomenon has been linked to a cancer-causing gene.

To do the study, Li's team focused on the interaction between JAK and a gene known as Krüppel, best known for playing a major role in the development of a fruit fly's body. It turns out that Krüppel also enhances an organism's ability to suppress tumors, and if the normal gene is knocked out or replaced by a faulty version, an organism is more likely to develop cancer when another cancer-causing gene like JAK is present.

His team found that some flies with a normal version of Krüppel got just as many tumors as their brethren with the bad copy – about three times as many tumors as most fruit flies with the normal version – simply because one of their parents harbored the JAK oncogene. Scientists believe the JAK mutation somehow messed up the "package" that contained Krüppel, and this damage causes problems a generation later, even when the faulty Krüppel gene is no longer around.

"In Jurassic Park, all the knowledge that was needed to re-create dinosaurs was gotten out of ancient DNA embedded in amber," said Dirk Bohmann, Ph.D., a colleague and fellow fruit-fly researcher who was not directly involved in the study. "Willis and other scientists are showing that there is so much more that goes into controlling and regulating genetic information than just knowledge of the DNA code. Michael Crichton would have a harder time making that film today, given what has been discovered in recent years.

“This work tells us that we have to pay more attention to the ways in which DNA is packaged. It’s not just about the DNA sequence,” Bohmann added.

Last year in a paper in Nature Genetics, Li first showed that JAK is a more powerful oncogene than previously thought, with the ability to turn on cancer-causing genes that are normally silent, through another epigenetic mechanism involving gene packaging. The new work shows that the gene is also able to suppress cancer-suppressing genes that are normally turned on, making JAK even more of a threat than had been known.

Work like Li’s is getting the attention of pharmaceutical companies, which are developing drugs that target an organism’s DNA governance at the epigenetic or “packaging” level. Such work provides a new target for developing drugs to stop cancer, and it reminds scientists just how much more research is necessary before we fully understand the workings of ACTGGGCTAGTTGGCAGT and the countless other DNA sequences in our body.

Source: University of Rochester