Novel gene defect for colorectal cancer

Six years after the genetic mutations that predispose some people to colorectal cancer were first identified, researchers have uncovered another, more unusual defect that can double a person's risk. This mutation is prevalent among Ashkenazi Jews, appearing in 6 percent of those tested.

The mutation changes the genetic spelling of the *APC* gene, which encodes a protein thought to participate in apoptosis, a process of cell death that keeps unchecked cell growth at bay. The mutation at first seemed minor. It changes a single amino acid, with apparently little effect on the protein's production or efficacy.

However, that small mutation lays a trap, the researchers found. When a cell replicates, the defect tends to scramble further the spelling of the mutated *APC* gene—and these subsequent variations encode truncated APC proteins that may not work at all.

"It creates a sort of Achilles' heel in the gene," says Kenneth W. Kinzler of Johns Hopkins Medical Institutions in Baltimore, a coauthor of the study, which appears in the September NATURE GENETICS. He compares the mutation to a bridge whose supporting beams have been sawed halfway through: The bridge may hold up for a while, but "eventually, something bad happens."

Researchers at Johns Hopkins came upon the mutation, designated *I1307K,* in a 39-year-old man who had a history of colorectal cancer but didn't carry any of the known colorectal cancer mutations discovered in the early 1990s. The person's mutation was considered a harmless polymorphism, one of many genetic variations in a population.

The scientists noted that the man was Jewish. When they began to look for the *I1307K* mutation in other colorectal cancer patients, they found it only in other Ashkenazi Jews.

The researchers tested blood samples from 243 healthy non-Jews and found that none of them had the mutation. Among 766 Ashkenazi Jews without known cancers, however, 6.1 percent carried *I1307K.* In a test of 211 Ashkenazi colorectal cancer patients, 10.4 percent had the mutation.

"Of any cancer-predisposing mutation in a defined population, this is by far the most prevalent," says Kenneth Offit of Memorial Sloan-Kettering Cancer Center in New York, a coauthor of the study.

Ashkenazi Jews moved north from the Mediterranean region after the fall of Rome and maintained their lineage in Central and Eastern Europe. They comprise roughly 85 percent of Jews worldwide. The newly discovered mutation reflects "a genetic legacy of 30 generations of relative isolation in Eastern Europe," Offit says.

There are at least 6 million Ashkenazi Jews in the United States, roughly 360,000 of whom could have the genetic mutation. Ashkenazi Jews have an estimated 8 to 15 percent chance of developing colorectal cancer in their lifetimes. For individuals who have the mutation, that chance climbs to 16 to 30 percent, according to the researchers.

Johns Hopkins now offers a $200 blood test that can detect the mutation.

The findings may lead researchers to reexamine some other polymorphisms. "Many polymorphisms that appear to be common and harmless in the population may need to be looked at more closely because they may predispose [an individual] to cancer in an unexpected way," Kinzler says. Other genetic variations could prove important in non-Jewish populations.

"[Our study] focuses attention on the familial risks of cancer," Offit says. He hopes the results will encourage families, Jewish or not, with histories of colorectal cancer to seek a colonoscopy, a procedure that detects precancerous polyps. These growths can be removed to prevent cancer.

Every year, up to 160,000 people in the United States are diagnosed with colorectal cancer, and roughly 60,000 die of it. —*N. Seppa*

Dioxin's fowl deed: Misshapen brains

It started with blue herons.

Eight years ago, scouting for changes induced by dioxins in wildlife, Diane S. Henshel opened the skull of a heron she had hatched from an egg collected near a dioxin-spewing pulp and paper mill. At most, Henshel had expected to find subtle biochemical changes. Instead, the Indiana University neurobiologist recalls, she "found this brain vastly different from any I had seen—grossly different, left to right." When she looked at the brain of a heron from a clean site, it fit her original expectations—confirming that something had been very wrong with the first one.

Since then, she has found unusually large left brains in other dioxin-tainted herons, cormorants, and eagles. Yet when she exposed the eggs of white leghorn chickens to TCDD, the most potent dioxin, she noticed no such changes.

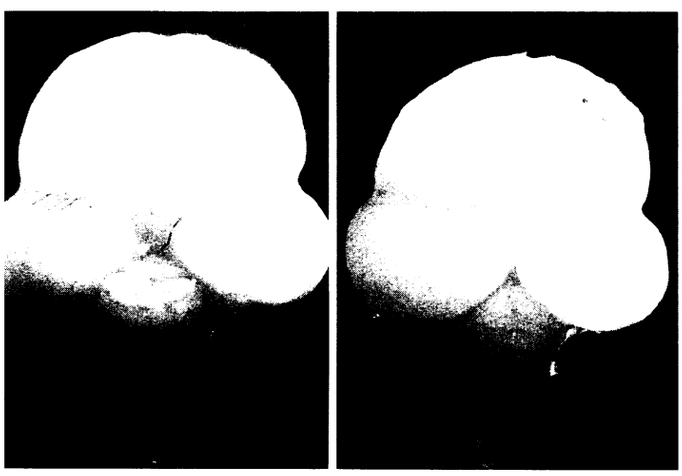
A few years ago, while using a photo of those chicken brains to illustrate the lack of an effect, she saw that there might be a subtle asymmetry after all. So she injected a new set of eggs with TCDD, between 10 and 1,000 picograms per gram of egg. Then, throughout the birds' incubation and after hatching, she studied their brains.

Now, she reports millimeter-scale asymmetries in dioxin-treated chickens—effects not seen in unexposed fowl. Though affected structures again appear larger on the left side of the brain, this may simply reflect less growth of equivalent sites on the right, Henshel observes. She and her colleagues in Bloomington report their findings in the just-published July ENVIRONMENTAL HEALTH PERSPECTIVES.

At all doses, TCDD altered the tectum, the brain's relay station for auditory and visual signals, beginning early in development. High doses changed the forebrain—critical to motor function and integrated thinking—early in development, but even low doses triggered asymmetries at a later stage. Since the tectum undergoes a growth spurt earlier than the forebrain, Henshel notes, these data suggest that sensitivity to dioxin may be heightened in regions undergoing expansive growth.

Her group now has preliminary data linking these asymmetries to a host of subtle behavioral changes in chicks, even those with the low exposures.

"I have found gross deformities in [dioxin-exposed birds]—twisted beaks, missing eyes, clubbed feet," says Michael Gilbertson of the International Joint Commission in Windsor, Ontario. "What's interesting here," he says, "are the structural deformities in the brain," because they seem consistent with reports of cognitive problems in children who were exposed in the womb to dioxinlike compounds (SN: 9/14/96, p. 165). —*J. Raloff*



Henshel/EHP

Brain of untreated chicken (left photo) is symmetrical, but dioxin-exposed bird (right photo) has larger structures on the left side.