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Researchers Discover New Risk Factor for Colon Cancer

Studies in mice and humans have revealed that carriers of the rare disease, Bloom syndrome, are at increased risk for developing colorectal cancer.

In two studies, published in the September 20, 2002, issue of the journal *Science*, collaborative teams of scientists present evidence that a mutation in one of two copies of the Bloom syndrome gene (*BLM*) is sufficient to raise the risk of cancer in mice and humans. The results are the first to show that being a carrier of a recessive cancer syndrome gene can raise the risk of cancer, even if that individual does not have the disease itself.

"This is one step toward understanding a complex disease and identifying the combination of factors that may increase risk."

— **Joanna Groden**

The findings remind us that knowing your family history of disease is very important, said Howard Hughes Medical Institute investigator Joanna Groden, who led the team that conducted the experiments in mice. Even cancers that we think of as common and age-related can have a hereditary component.

In the case of Bloom syndrome, people who have two defective copies of the *BLM* gene are generally of short stature and have a variety of physical defects and a predisposition to developing many types of cancer. Bloom syndrome occurs in all ethnic populations, but it is more common in Jewish people of European descent (Ashkenazi Jews).

The *BLM* protein plays a role in helping ensure that chromosomes are copied properly during cell division. When the *BLM* protein is defective or missing, cells are more likely to acquire or keep DNA-copying errors that result in mutation. The chromosomes in cells without *BLM* also may have trouble getting untangled during cell division, sometimes causing pieces of chromosomes to break off.

Groden and her colleagues at the University of Cincinnati conducted a series of experiments in mice that were engineered to carry a single copy of the

mutant *Blm* gene. These mice, which also had one normal copy of the gene, made about half the normal amount of BLM protein.

Our hypothesis was that if there is less protein present, cells may be less competent at repairing breaks or carrying out replication, said Groden.

To test their idea, the scientists mated the BLM mice with another type of mouse that is prone to developing intestinal cancer. When they counted the number of intestinal tumors in the offspring, they found that mice carrying one *Blm* gene mutation developed twice as many tumors as mice without the mutation.

In another experiment, the researchers examined lung cells from the BLM mice that were cultured in the laboratory. After adding a chemical that increases the usually low rate of DNA damage during cell division, they compared DNA damage in normal cells with DNA damage in the BLM mouse cells. The experiments showed that there were twice as many fragments of broken chromosomes, counted as micronuclei, in the BLM mouse cells as there were in normal mouse cells.

There were subtle increases in the number of micronuclei, said Groden. This suggests that perhaps there is a reduction in the ability of the helicase to maintain or repair DNA that accompanies its reduction in amount.

The results of the mouse study spurred an investigation of the role of BLM in colon cancer incidence among Ashkenazi Jews, an ethnic group in which one percent of the population carries the gene mutation that causes Bloom syndrome. A collaborative team of investigators from Memorial Sloan-Kettering Cancer Center, the University of Michigan, and the Technion Faculty of Medicine in Haifa, Israel, studied 1,224 Ashkenazi Jews who developed colon cancer and 1,839 normal controls. They found that carriers of the Bloom disease gene were nearly three times as likely to have developed colon cancer.

This study shows that genes that are relatively common in the population can change a person's risk for colorectal cancer, said Groden. This is one step toward understanding a complex disease and identifying the combination of factors that may increase risk.

Groden points out that in a disease like colon cancer, knowing risk factors is especially important because screening is available that can catch the disease early and greatly increase the chances of a cure. According to the American Cancer Society, there will be 148,300 new cases of colon cancer in the United States in 2002, and 56,600 deaths, making colon cancer the third most common cancer for both men and women.

This is the kind of study that shows the power of using the mouse as a model for human disease, said Groden. It is always the hope of those of us in the mouse modeling community to study genes that will improve how we treat, diagnose and counsel people. If these discoveries encourage even a few people in the Ashkenazi Jewish population to learn their family history and

go for early colon cancer screening then thats terrific.