Gene for Rare Disease Gives Cancer Clues

Cancer plays an intimate role in the lives of Bloom's syndrome patients. From as early as childhood, cancers of all kinds strike repeatedly before stealing the victims' drastically shortened lives.

Although this inherited disease occurs with a scarcely detectable frequency—only 184 cases have been reported worldwide since the syndrome was recognized—scientists have longed to understand how the underlying genetic defect causes the numerous cancers that plague its sufferers and causes them to die, on average, before the age of 21.

Now, researchers from the New York Blood Center report that Bloom's syndrome arises from mutations in a gene, called *blm*, that is essential to the process by which chromosomes copy themselves. Their finding sheds light not only on this mysterious and obscure disorder but also on the generation of cancers through accumulated mutations.

"Basically, what happens in Bloom's syndrome is happening in all of us," says lead investigator James L. German. "It's just happening a lot faster."

Bloom's syndrome was first described in 1954 by dermatologist David Bloom, who noted a characteristic set of manifestations—normal body proportions but very short stature, a sun-sensitive rash on the face reminiscent of lupus, and a small, narrow head.

Bloom's syndrome is a recessive genetic disorder, so only a person who inherits a mutated copy of the gene from each parent suffers the disease. Though the mutation is vanishingly rare, it is somewhat more common among people of Ashkenazi Jewish descent. An estimated 1 in 100 Ashkenazi Jews carries one copy of the mutated gene.

In the 1960s, Bloom enlisted German's help to study the chromosomes of these patients. Bloom's patients have chromosomes—the paired DNA structures in a cell's nucleus—with an inordinate number of breaks. As a result, every time a cell divides, its DNA gets exchanged much more readily between chromosomes of a pair. Every break and DNA exchange offers an opportunity for a mutation to alter a vital gene.

German observed an elevated cancer rate and linked it to this high mutation frequency. But, unlike other cancer syndromes that promote a specific type of cancer, Bloom's syndrome increases the occurrence of "the generality of cancers," says German.

By studying the DNA of Bloom's patients who were born to first cousins, German determined that the *blm* gene is on chromosome 15. As German and his colleagues Nathan A. Ellis and Joanna Groden, who is now at the University of Cincinnati College of Medicine, report in the Nov. 17 CELL, Bloom's syndrome results from mutations in the gene needed to produce an enzyme classified as a DNA helicase. The enzyme helps uncoil double-stranded DNA and appears to be essential for maintaining chromosome stability.

"The fact that the distribution of cancers seen in Bloom's is similar to that found in the general population indicates that this gene may tell us something about cancer in general," says German.

Geneticist Stephen T. Warren of Emory University School of Medicine in Atlanta agrees that the finding may have implications beyond Bloom's patients. If mice could be made deficient in this enzyme, they might be susceptible to cancer, says Warren, "and could be exquisitely valuable in testing carcinogenic compounds."

Warren also notes that researchers could study carriers of *blm* to see if they are susceptible to more cancers than the general population.

German now plans to study how correctly functioning *blm* helps the chromosomes remain stable. *—L. Seachrist*

Brain scans set sights on mind's eye

The mind's eye, which creates mental images of objects and scenes from the outside world, has winked elusively at scientists who have tried to trace its location in the brain—until now. A new study finds that people who visualize various objects experience blood flow surges, signaling enhanced cell activity, in brain areas that handle the earliest stages of visual processing.

The extent and exact location of these cerebral surges depend on the size of the imagined object and resemble activity changes that accompany the actual viewing of objects, assert Stephen M. Kosslyn, a psychologist at Harvard University, and his colleagues. Mental imagery may rely on the brain's ability to generate internal pictures from signals supplied by regions responsible for vision, the scientists contend in the Nov. 30 NATURE.

In contrast, some researchers have argued that it is verbal interpretations of what we see that seem visual in retrospect.

"The fact that stored visual information can affect processing in the earliest visual areas suggests that knowledge can fundamentally [influence] what one sees," Kosslyn holds. "We may see different things, depending on what we expect to see, although our expectations are often pretty accurate."

For instance, memories of our physical surroundings may feed into mental images that guide our movements through space with great precision, even when vision is blocked (SN: 8/12/95, p.104).

Kosslyn's group used positron emission tomography (PET) scans to examine blood flow in the brains of 12 men as they performed three types of tasks. For a resting baseline, each volunteer closed his eyes, relaxed, and imagined complete darkness in front of his mind's eye.

In a listening baseline, participants heard a series of item names, such as "anchor," each followed by a direction to make a spatial judgment about the item, such as deciding whether the anchor's rightmost or leftmost point was higher. They had only 1 second to make each spatial judgment and were told not to visualize anything during these trials.

In an imagery task, volunteers heard the names of items and memorized pictures of them. Participants then visualized items as small, medium, or large and made spatial judgments.

Imagery-specific activation of tissue in the primary visual cortex became apparent when imagery data for specific items were compared to the listening baseline for the same objects. The primary visual cortex responded in different patterns to small, medium, and large images.

"This is a nice demonstration that the visual cortex is activated by mental images in the same ways it would be activated by visual perceptions," asserts Larry R. Squire, a neuroscientist at the Veterans Affairs Medical Center in San Diego.

For reasons still unclear, Kosslyn notes, the resting baseline task also activated the visual cortex enough to muddy comparisons between it and the imagery task. *—B. Bower*