Genes and Cancer: The Story of Wilms Tumor

Wilms tumor is one of the few cancers to be clearly associated with a chromosomal defect

It is rare for a baby to be born with no irises, but when such a child is discovered, it often gets extraordinary medical attention. Researchers, such as Judith Bader of the National Cancer Institute, will travel anywhere in the country to see such a child and examine the child's chromosomes. If a child who has no irises also has a deletion in chromosome 11, it is very likely that it will get Wilms tumor, a kidney cancer that affects children. Bader and other cancer specialists seek out possible Wilms tumor patients because this cancer is one of only a few so clearly associated with a chromosomal defect.

The story of how Wilms tumor was traced to a small chromosomal deletion is just the beginning of what will likely be a long tale of the search for genetic links to cancer. But it is an extremely promising beginning, according to Robert W. Miller of the National Cancer Institute. Miller is especially fond of the story because it illustrates one of his favorite themes—that astute clinical observations can be the key to major discoveries about the causes of cancer.

The Wilms tumor story began about 15 years ago, when Miller started wondering whether cancers are associated with birth defects. If they are, he reasoned, it may be feasible to think about predicting certain people's cancer risk on the basis of inherited malformations. If researchers could understand what caused the birth defects, they might be able to learn what caused the cancers as well.

When Miller began thinking along these lines, it was already known that children with Down's syndrome are at an increased risk of getting leukemia. Miller decided to investigate the possibility that children with Wilms tumor might have particular birth defects. He chose Wilms tumor, he recalls, because of its pathological characteristics; it occurs almost exclusively in early childhood and so the age group at risk is well defined. Besides, he had a hunch that a study of Wilms tumor would pay off. "It felt right," he says.

So for a few months, every time Miller gave a lecture at a medical center he asked to look at the hospital records. Soon he had seen the records of 440 children with Wilms tumor. And he noticed that six of them had no iris, a condition called aniridia. "At that time, few physicians except ophthalmologists even knew what aniridia meant," Miller says. It is an extremely rare condition, occuring in only one out of 75,000 children. So an incidence of one in 75 Wilms tumor patients with aniridia was 1000 times greater than expected. "We knew from studies of other cancers that none was associated with aniridia," Miller explains. "You don't need a statistician and a computer to tell you the association with Wilms tumor is real."

For the next 10 years, researchers gathered more and more clinical data on children with Wilms tumor and further defined its association with birth defects. By 1974, quite a few investigators suspected that these children had some sort of chromosomal anomaly, but no one could find any. One reason they were looking for chromosomal defects, says Park Gerald of Children's Hospital in Boston and Harvard Medical School, is that concurrent studies of retinoblastoma, a tumor of the retina that occurs mainly in children, were beginning to implicate a chromosomal deletion as one cause of that cancer.

Retinoblastoma is often an inherited disease, Gerald says. For this reason, the cancer was of interest to geneticists, including Alfred Knudson of the Fox Chase Cancer Center in Philadelphia. In 1971, Knudson analyzed the incidence of retinoblastoma and pointed out that it looked like a two-hit disease, meaning that two independent events must occur to cause the tumor. In children who inherit a tendency to get the disease, one of these events is presumably genetic. The other is thought to be environmental. The theory is that people who do not inherit a tendency to get retinoblastoma can get it only if two independent events occur, which is quite unlikely.

In the early 1960's a patient was found who had retinoblastoma and a deletion in chromosome 13. By 1974, eight other patients were found to have retinoblastoma and the same deletion. "It became very suspicious," Gerald says. But it has proved hard to argue that the deletion causes the disease, since despite an extensive search in the past 6 years, only 24 of some 1200 retinoblastoma patients have been shown to have the deletion, which makes its likelihood of being seen one in 50. Still, the retinoblastoma story was known to all the Wilms tumor researchers and was highly suggestive.

In the meantime, it has also become clear that Wilms tumor is associated not only with aniridia, but also with other malformations including overgrowth of one side or parts of one side of the body, overgrowth of the viscera of the abdomen, large red or brown birthmarks, genitourinary abnormalities, and mental retardation. Vincent Riccardi of Baylor College of Medicine was especially interested in the association between Wilms tumor, aniridia, genitourinary abnormalities, and mental retardation, which he called the AGR triad.

In 1974, Riccardi says, he saw the AGR triad in a 10-year-old boy who had been said to have normal chromosomes. He repeated the analysis and found that the boy had a deletion in the short arm of chromosome 11. About 3 months later, a little girl was referred to him by doctors in Mexico. The girl had ambiguous genitals, was retarded, and had no iris (Riccardi says no one had noticed this before). "I reasoned that she would have a deletion of the short arm of chromosome 11," he recalls. He then showed that the girl did have the deletion, which appeared identical to the boy's deletion.

A few years later, Riccardi was in Milwaukee and was told of a boy with aniridia, ambiguous genitals, and mental retardation. Riccardi found that he, too, had the same deletion. He then checked back to see what had happened to the Mexican girl and learned that she had developed Wilms tumor. "This was the connection that led us to associate Wilms tumor with the deletion," he says.

At about this time, Riccardi began collaborating with Uta Francke, a cytogeneticist now at Yale Medical School. She used a new technique for chromosomal analysis developed in 1975 by Jorge Yunis of the University of Minnesota

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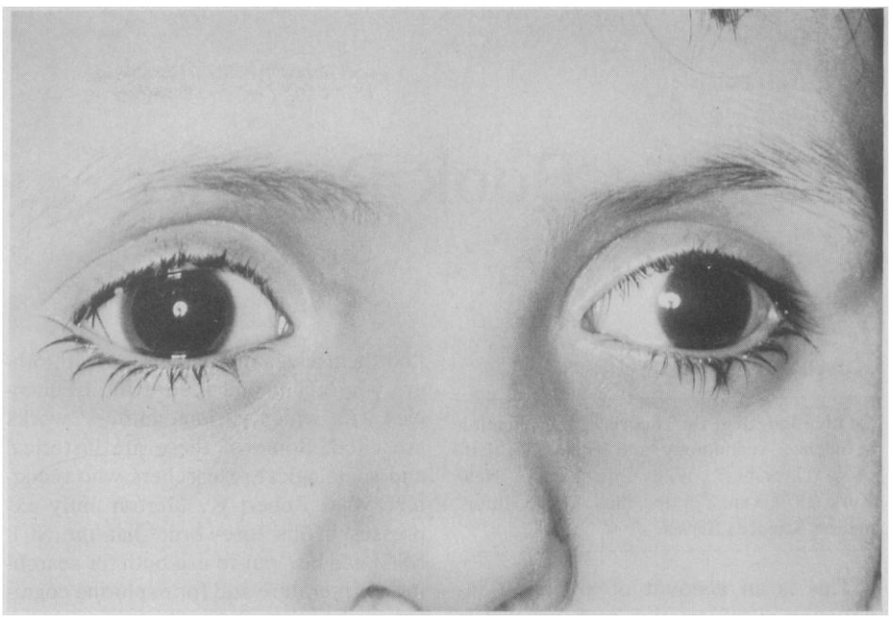
Medical School. To analyze chromosomes, investigators stain them with dyes that make them appear as lengths of light and dark bands. They detect deletions by noticing that bands, or parts of bands, are missing. With older techniques, they looked at chromosomes at times when they are condensed and saw only about 320 bands per set of chromosomes. Yunis's technique involves looking at chromosomes when they are elongated, when up to 1500 bands can be seen.

With Yunis's technique, it was much easier to see the chromosomal deletions associated with aniridia and, possibly, with Wilms tumor. It has been less than 2 years since Riccardi first published a paper on this association. But already, says Gerald, he, Bader, and Frederick Li of the National Cancer Institute have seen eight patients, each of whom has aniridia, a chromosome 11 deletion, and Wilms tumor. Gerald estimates that at least 20 patients worldwide have been shown to have aniridia and the deletion and that 90 percent of them also have Wilms tumor. "I would now be willing to say that if you don't see the deletion in a patient with aniridia and Wilms tumor, the deletion is too small to spot, but it is there." (Francke says as many as 20 contiguous genes can be deleted but not seen because of the limits of present banding techniques.)

A specific clinical application of this work, Yunis says, is that families who have had children with Wilms tumor may want to consider using amniocentesis to detect the deletion in unborn children. Gerald says that if a baby is born with aniridia, doctors should look for a deletion in chromosome 11. If they see such a deletion, they should carefully monitor the child for Wilms tumor by examining its kidneys with ultrasound. Wilms tumor is often curable with surgery or chemotherapy if it is detected early.

Interesting as the clinical ramifications may be, Gerald, Miller, and the others working on Wilms tumor think the implications of their findings go beyond this advice for patients with aniridia. They think that chromosomal abnormalities could be responsible for many cancers and that the study of Wilms tumor could serve as a model for understanding them.

Noting that most malignancies occur in the latter part of life, Gerald asks whether childhood malignancies are a different entity entirely. If so, it may be misleading to draw general conclusions from a study of Wilms tumor. But he thinks the childhood tumors may be like those occurring in adults in that both may be associated with genetic abnormalities and both may require a second environmental event before they occur. If the second event is likely the tumors tend to develop early in life, rather than later. As evidence for his belief, Gerald points to a recently published study of a family that tended to get renal clear cell carcinoma, a kidney tumor. The age of occurrence is the late 30's or early 40's and it appears to be a genetically determined adult cancer.



One of a pair of identical twins, both of whom have no irises and both of whom have the chromosomal deletion associated with Wilms tumor. Only one twin developed the tumor, indicating that the deletion alone is not sufficient to cause the cancer.

Gerald believes that the gene that, when damaged, causes Wilms tumor lies near genes that, when damaged, cause aniridia, mental retardation, and other anomalies associated with the tumor. That is why the deletions in chromosome 11 are associated with these birth defects.

Miller suggests a way to decide how the deletion causes Wilms tumor. He notes that the tumor, itself an overgrowth of cells, is associated with several other forms of overgrowth, including an overgrowth of one side of the body or part of it, too large cells of the abdominal viscera, and benign tumors. It may be possible, he says, to discover what these overgrowths have in common and thus the mechanisms behind Wilms tumor.

According to Gerald, Wilms tumor might also serve as a sociological and epidemiological model for cancer and its prevention. Because not everyone with the deletion gets Wilms tumor, it should be possible to find out what it is in the environment that causes the tumor in those who are genetically susceptible. By knowing that a certain group is at risk for cancer, researchers have a new way to study what causes some but not others to get the disease. "It's amazing how little idea there is in human biology of looking at a genetically predisposed population to see what in the environment causes cancer," Gerald says.

But Gerald suspects that researchers' reluctance to study populations at risk may partly reflect their concern about the effects of telling people that they are likely to get cancer. "A lot of people say that telling people they might have a disease when they may never get it is worse than the disease itself," he says.

Wilms tumor, however, is not a lifelong threat. Those who do not get it in childhood probably never will. And it is often curable. For these reasons, Gerald believes clinicians can learn through Wilms tumor how to develop ways to tell people about their risk for cancer. In the telling, Gerald admits, doctors may find that they are mistaken in thinking people do not want to know their risk of cancer, just as they were mistaken in the past in thinking that patients with cancer do not want to be told they have it. Or doctors may find that patients do fear being told of their cancer risk but that, with education, these fears can be alleviated.

The discovery that Wilms tumor is sometimes associated with a chromosomal deletion, then, is far more than a scientific anomaly. Its implications touch on the entire field of cancer causes, early detection, prevention, and sociology.

—GINA BARI KOLATA