NEWS

The Twists and Turns in BRCA's Path

Nine years after the much-anticipated discovery of two breast cancer genes, genomic medicine for the disease remains elusive, but surprising insights abound

A mislabeled cell sample and a whim sent Alan D'Andrea down an unfamiliar path.

"We weren't intending to work on breast cancer," recalls the pediatric oncologist, who's based at Dana-Farber Cancer Institute in Boston. His life's interest is Fanconi anemia, a devastating genetic disorder that leaves young children prone to multiple cancers. But in 2002 a geneticist in his lab, examining what she thought was an unknown specimen, saw a familiar chromosomal pattern and diagnosed the tumor as coming from a Fanconi child. The sample, it turned out, had been mislabeled; it belonged to a woman with *BRCA1*, a gene discovered in 1994 that puts young women at high risk of hereditary breast and ovarian cancer.

So what was it doing here, being confused with Fanconi's? Of all the cancers Fanconi patients develop, breast and ovarian are rarely among them. But the *BRCA1* tumor cells so closely resembled Fanconi cancer cells, with their trademark pattern of starlike, broken chromosomes, that D'Andrea couldn't shake the mix-up from his mind.

At the time, six of the eight Fanconi anemia genes had been cloned, and researchers were struggling to find the rest. On the barest of hunches, D'Andrea gathered cells from children diagnosed with Fanconi's who had none of the cloned Fanconi genes. He sent them to the hospital's diagnostics lab with instructions to sequence for *BRCA1* and *BRCA2*, another closely related breast cancer gene identified in 1995.

This time, the diagnostics team was bewildered. A technician called D'Andrea and complained that some of these cells clearly weren't from a Fanconi child. They were from someone with mutations in *BRCA2*.

"Of course," he says, "it wasn't a mistake at all." This Fanconi gene *was* the *BRCA2* gene, and these children had mutations in copies they'd inherited from both parents. (Women with *BRCA2* have mutations in only one copy.) A single dose of mutated *BRCA2* conferred one condition; a double dose, it now appeared, conferred another.

ILLUSTRATION: TIM SMITH

This electrifying discovery is just one of the latest twists in the *BRCA* genes' strange odyssey. When the genes were discovered almost a decade ago, scientists were elated, predicting that the genes would illuminate not only this rare form of inherited cancer but common breast cancers as well. But that hope soon faded.

Recently, however, disappointment has given way to renewed excitement. Instead of solving the enigma of breast cancer, as many anticipated, the *BRCA* genes have begun weaving together a rich but also puzzling tapestry of defects that drive diverse cancers—prostate and pancreatic and, as D'Andrea found, the spectrum associated with Fanconi anemia. Meanwhile, it is undisputed that the mutated *BRCA* genes target the ovaries and, especially, the breasts; but why they do remains mysterious. The BRCA experience suggests that the path from gene discovery to genomic medicine will be longer and more circuitous than many envisioned at the outset (see sidebar).

Early hopes dashed

Some of the first evidence for a gene tied to hereditary breast cancer was released at a 1990 meeting, when geneticist Mary-Claire King, then at the University of California, Berkeley, told a hushed audience how her genetic sleuthing had paid off. By working with families riddled with breast and ovarian cancer—in many cases, across several generations, with several siblings in each—King and her colleagues had traced a suspect gene to a swath of chromosome 17. Her announcement ignited a race to isolate the gene itself.

Four years later, scientists at Myriad Genetics in Salt Lake City, Utah, nailed the gene, which they called *BRCA1*. (The company now holds patents on the diagnostic test to detect gene carriers.) Fifteen months later a second gene, *BRCA2*, was isolated by an international team led by Richard Wooster and Michael Stratton of the Institute of Cancer Research in Sutton, U.K. Having a single copy of either mutated gene appeared to confer at least an 80% chance of developing breast cancer; the risk of ovarian cancer was somewhat lower but still well above the lifetime norm, hovering between 20% and 65%.

Just 5% of breast cancer cases are linked to the *BRCA* genes. But other cancer genes identified previously, such as that for the childhood eye cancer retinoblastoma, had shed light on cases of the same cancer in patients who didn't inherit the mutated gene. Geneticists hoped that *BRCA* would do the same for the 95% of breast cancer patients who are not *BRCA* carriers. "We thought *BRCA* would unravel the mystery of carcinogenesis in the breast," says Larry Norton, head of the solid tumor division at Memorial Sloan-Kettering Cancer Center in New York City.

Immediately, researchers began testing breast and ovarian tumors from women with no family history of disease. They reasoned that, even though these women hadn't inherited either of the defective genes from a parent, the genes could have mutated before or during cancer's development. If so, they would be visible in cancerous cells.

To their dismay, says Norton, such sporadic cancers didn't contain mutated copies of either *BRCA* gene, leading researchers to reluctantly conclude that *BRCA1* and *BRCA2* could shed no light on common breast and ovarian cancers. Since then, however, researchers have learned that both *BRCA* genes interact with other genes and proteins—a crowd collectively known as the BRCA pathway. Although the *BRCA* genes themselves appear unconnected to common, nonhereditary cancers, emerging evidence suggests that defects in other parts of the BRCA pathway might be critical not only in driving breast cancer but other cancers as well.

Following the BRCA path

Researchers have spent the better part of a decade trying to decipher the *BRCA* genes' function. Both genes, they now know, help mediate damage to a cell's DNA, but explaining precisely how has been daunting. (A pair of papers on pages 636 and 639 seek to more precisely pin down *BRCA1* functions by analyzing discrete sections of the gene.)

Hints that BRCA affects DNA damage, which in turn spurs hereditary cancers, emerged in the late 1990s. David Livingston and Ralph Scully of Harvard Medical School in Boston reported in *Cell* that when a cell divides, the healthy BRCA1 protein interacts with another protein called RAD51. This protein helps direct chromosome recombination, the swapping of pieces that takes place during an early stage of cell division. The implication was that BRCA1 also participates in this process.

An ocean away, cancer biologist Ashok Venkitaraman and others in his lab at the University of Cambridge were puzzling over a mouse model of *BRCA2*. A physician, Venkitaraman had been studying chromosome abnormalities in leukemias and lymphomas. When evidence began building that the *BRCA* genes triggered similar abnormalities, he shifted to this new terrain.

Over the course of a frenetic week in the summer of 1997, Venkitaraman's group found that mouse cells with *BRCA2* don't divide properly, and chromosomes in the offspring cells wound up with structural defects. (It was these same defects in Fanconi's that sparked D'Andrea's confusion years later.) Furthermore, Venkitaraman's group found, the damaged cells could acquire a second defect, which prevented them from self-destructing the way they should.

Despite such insights, the function of both *BRCA* genes—and how they differ—remains frustratingly fuzzy. One of the most enduring puzzles is why breast tissue is so susceptible to mutated *BRCA1* or *BRCA2*—which, in women who inherit one of the genes, is found in every cell in their body. Although the genes have been tentatively linked to an increased risk of other cancers, including pancreatic cancer and breast and prostate cancer in men, there's no question that associated tumors occur disproportionately in women's breasts and, to a lesser extent, in their ovaries. Scientists studying other inherited cancer genes, such as those linked to retinoblastoma or the childhood kidney cancer Wilms tumor, have also struggled with this question.

In BRCA's case, one potential culprit is the hormone estrogen. Cancer biologist Chuxia Deng of the National Institute of Diabetes and Digestive and Kidney Diseases in Bethesda, Maryland, studies mice that are born without a *BRCA* gene. Treating those mice with estrogen, he found, overstimulates genes and proteins in a hormone-activating pathway. Deng is now testing whether those effects spur tumor formation.

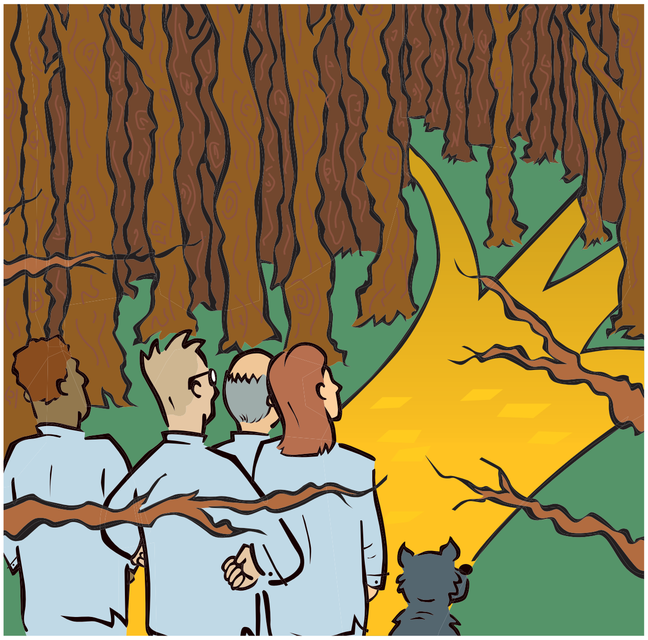

ILLUSTRATION: TIM SMITH

Scientists also wonder whether a find announced last fall could help explain why female *BRCA* carriers, and not males, disproportionately develop *BRCA*-driven cancers. Harvard's Livingston and his colleagues reported that when cells contain a mutated *BRCA1* gene, the X chromosome structure—and expression of at least one of its genes—goes awry.

Females have two X chromosomes; during embryonic development, one of the chromosomes is randomly silenced in somatic, or nonsex, cells. This prevents women from receiving a double dose of X chromosome genes in somatic cells. But cells with mutated *BRCA1*, Livingston and his colleagues reported in *Cell*, couldn't fully shut down their second X chromosome. This may explain why women, as opposed to men, so often develop cancer when they inherit a malfunctioning *BRCA1* gene, he says.

As they continue dissecting *BRCA* gene functions, scientists are returning to the questions that preoccupied them in the mid-1990s, when the genes were first discovered. They're trying to link features of sporadic breast cancers with the BRCA pathway, that swath of proteins with which one or both genes interact. Soon after linking *BRCA2* to Fanconi anemia, for example, D'Andrea gathered a small number of breast and ovarian tumor samples from women who didn't have mutations in either *BRCA* gene. In about 20% of the samples, he and his colleagues found, another gene in the pathway was abnormally silent. "We don't really know much about whether other components of the pathway are dysfunctional" in many nonhereditary breast cancers, says Alan Ashworth, director of the Breakthrough Breast Cancer Research Centre at the Institute of Cancer Research in London, although he and others are looking.

Weaving a web

Using BRCA as a clue to unlock cancer's mysteries is proving fruitful far beyond breast and ovarian cancer. "BRCA proteins are unveiling a functional network," says Venkitaraman. "And the proteins that are in that network are implicated in a wide range of cancers."

One of those proteins is behind a genetic disorder called ataxia-telangiectasia (AT). Like Fanconi's, AT predisposes children to multiple cancers; scientists have also long debated whether one mutated *AT* gene ups the chance of breast cancer. In 1999, geneticist Stephen Elledge, now at Harvard Medical School in Boston, and his colleagues at Baylor College of Medicine in Houston, Texas, reported an intriguing connection between AT and *BRCA1*. It was already known that like *BRCA1*, the normal *AT* gene helps correct DNA damage. But Elledge's team uncovered a deeper biochemical link: When DNA damage occurs in normal cells, the healthy AT protein zooms into action and modifies the BRCA1 protein to enhance its performance. Only when healthy AT protein is present can BRCA1 do a superior job.

Like so many other BRCA discoveries, it's still not clear how this one fits into the bigger picture. But it's another sturdy link in the chain uniting cancer-causing proteins that had long been studied separately. –JENNIFER COUZIN