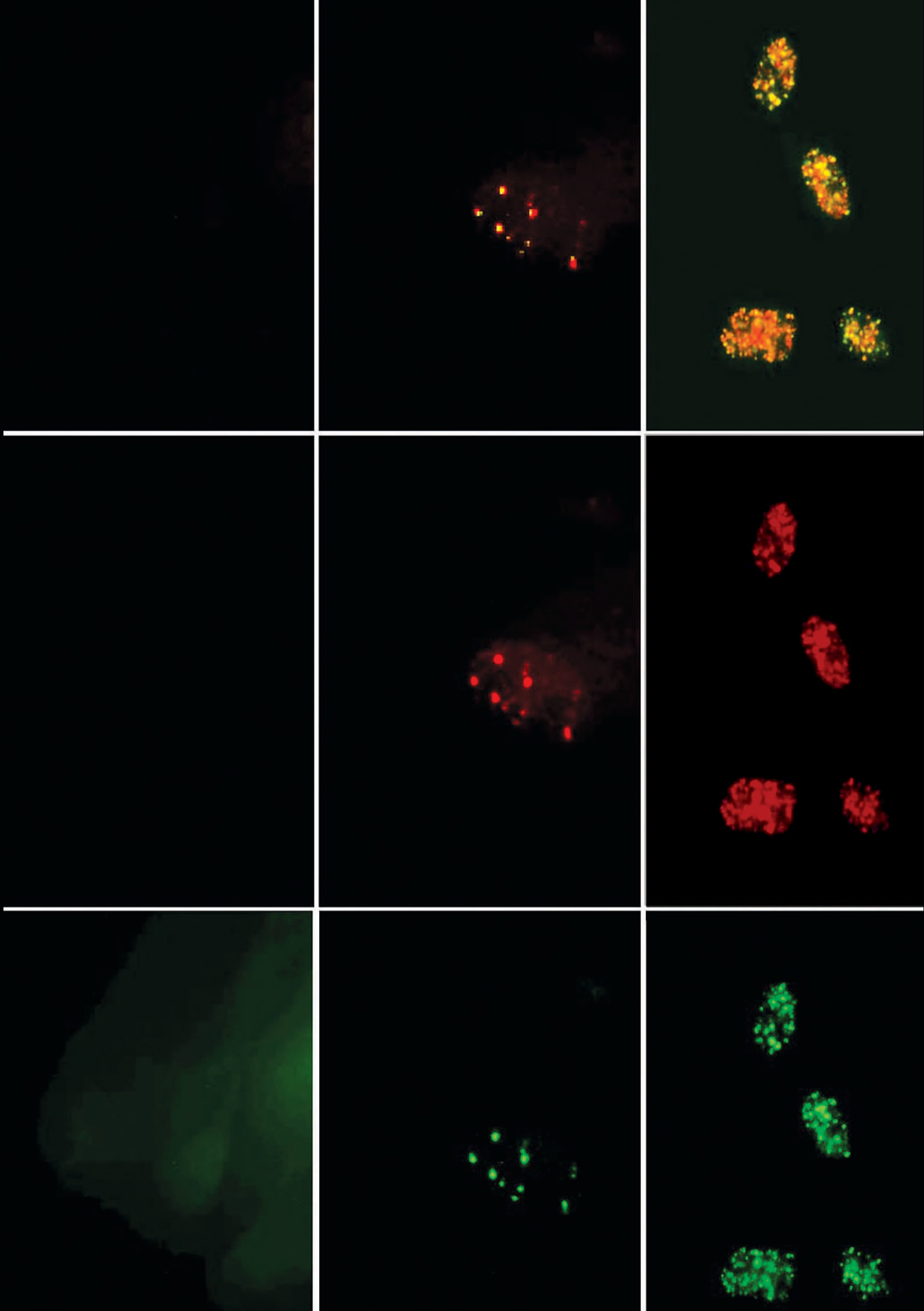


A PITT RESEARCHER AND A FAMILY IN CENTRAL PENNSYLVANIA ARE LEARNING FROM THE SAME RARE DISEASE | BY ERICA LLOYD

DIFFICULT GIFTS

Twelve years ago, Pam Fickel of Carlisle, Pa., gave birth to a beautiful baby boy. Blond, blue-eyed Douglas Jr. appeared to be the picture of perfect health. But after she brought Douglas home, the then 31-year-old Fickel started to think something "wasn't right." Her baby moved his hands and fingers in strange ways. And little Douglas was drooling so much, she'd have to change his shirt four, five, maybe six times a day. Because his formula stained the shirts, she found herself throwing soiled ones away and buying T-shirts in bulk from the thrift store.

"I knew this wasn't teething," she says, looking back.

Fickel shared her concerns at Douglas' 9-month checkup. The doctor and others told her she was being overly cautious. Before Douglas Jr. was born, Pam and Doug Fickel had lost Jane, their third daughter, to hydrocephalus. "I was being overprotective, they told me," says Fickel.

Imagine having cerebral palsy, cystic fibrosis, muscular dystrophy, and AIDS—and being highly susceptible to cancer. That's what it's like to have ataxia telangiectasia (A-T). This rare disease has pointed scientists toward a DNA damage control pathway central to good health. LEFT: Young human cells contain no detectable DNA damage (column 1). After more than 60 divisions (column 2), a protein called ATM (green) detects where both strands of DNA have been severed. ATM marks the breaks by labeling histone (red; it appears yellow when shown with ATM). Zapping the cells with ionizing radiation activates nearly all the ATM protein (column 3), which is responsible for kicking off the DNA repair process. Children with A-T don't have this vital protein.

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Douglas Fickel

COURTESY P. FICKEL

At a year, she tried again. *Please listen to me*. No one heard.

By the time Douglas' 15-month well-baby checkup came up, he was falling down 30 times a day. He'd knocked himself unconscious twice. The doctor watched Douglas take a few steps. He saw an eager boy toddling his way across the room and was about to pronounce him fit as a fiddle.

Fickel stopped him.

"I want to strip him down to his diaper," she announced.

Then Fickel suggested the little boy walk for the doctor again—this time all the way down the hall.

Without the cloak of cloth on the child, the doctor could see how Douglas' gait was different from that of other boys and girls. The toddler waddled forward, arms raised and contorted like duck wings, back arched, wrists limp, pointer and middle fingers spread out as though he was "signing a K badly," his mom recalls. This was how he always walked.

The doctor wanted to schedule a scan immediately. It could be a brain tumor, he said. It was Thursday, and the MRI people could fit Douglas in that day.

Fickel, who knew her boy had been living with whatever this was all his short life, said the appointment would have to wait until Tuesday. That's when Doug Sr. was returning from his hunting trip, and the couple had vowed they'd never again put the other in the position of hearing what they suspected would be a bad diagnosis alone.

"When I found out about Jane, I was by myself," says Fickel.

Fickel held her breath all weekend, hoping she'd made the right decision. Tuesday came and the doctors found nothing. More MRIs at the medical center in Hershey followed. Douglas was poked, prodded, and scanned for months, then years. The doctors always came up empty.

When Douglas turned 4, Fickel cancelled his appointments. Her son was walking pretty well. He wasn't falling down. Could he be getting better? At least he'd have some time away from all those tests.

At 5, red spider veins appeared in Douglas' eyes. When the Fickels went back to the doctor, he said, "The monster has reared its head."

He wasn't speaking of the Fickels' sweet son. The doctor was speaking of a rare disease known as ataxia telangiectasia, or A-T. When Douglas turned 4, his growth had outpaced the progression of his disease, so he seemed to get better for a while. But then the disease asserted itself again.

Ataxia refers to a patient's lack of motor control owing to progressive neurodegeneration. (The doctors in Hershey couldn't see anything on the brain scans because Douglas' brain probably appeared normal.) Telangiectasia (pronounced *teh-LAN-jick-TAY-sha*) refers to the fine spidery burst veins that often appear on the eyes and ears of children with the disease.

The burst veins are harmless. But most of the other symptoms of this childhood disease aren't.

A-T gradually cripples the development of the cerebellum so that as children with the disease grow older, they lose motor control. They have difficulty walking, and by their second decade, they are probably in wheelchairs. Eventually, their eyes won't stay on a page, so reading, as well as writing, becomes next to impossible. It's hard for them to talk. They are in constant motion—even as they sleep—so they are often very thin. It's not unusual for a bit of food to end up in a lung and cause pneumonia, which is particularly dangerous for them because A-T also compromises their immune systems. It is an exhausting disease.

The Fickels felt a strange sense of relief on hearing the diagnosis, as awful as it was. No more MRIs. And at least they knew what they were up against.

Imagine having cerebral palsy, cystic fibrosis, muscular dystrophy, and AIDS—that's analogous to what these kids and their families are dealing with. A-T–afflicted children are also highly susceptible to cancer. They are 1,000 times more likely to develop malignancies of the blood than the general population. Making matters worse, radiation therapy causes awful burns and is likely to kill them.

Why does it seem their own bodies have it in for them? It comes down to a gene called ATM, first cloned in the '90s by an Israeli researcher. The ATM cloning was "one of the last great" traditional cloning efforts before the Human Genome Project, says Christopher Bakkenist, assistant professor of radiation oncology at the University of Pittsburgh.

Only one in 40,000 children get A-T. But it turns out, the biology behind this rare disease is relevant to all of us.

Since the gene was cloned, scientists have learned that the ATM protein sits at the top of the DNA damage repair pathway. It's in charge of getting our bodies to respond appropriately when the most profound kind of DNA damage occurs—that is, when both strands in the double helix are completely severed.

We all experience double strand breaks throughout our lives. An x ray at the dentist's office induces them. Cosmic rays probably do. More importantly, the process our cells routinely go through to use oxygen results in double strand breaks. They are insidious. The good news? Unless you have A-T, your body knows how to cope with these lesions. It will either repair the problem or arrange for the cell to kill itself so it doesn't do something unwelcome as a mutation.

But Douglas and others with A-T don't have the ATM protein. So their bodies are subjected to the whims of rogue and mutant cells. Imagine trying to keep a Fiat running without a mechanic to fix and replace parts as they inevitably break. You'd probably need a push now and then.

When Douglas gets tired, he gets lots of help from his family, friends, and community. He was on a baseball team during elementary school. He didn't make many practices though—they were too taxing. Just sitting on the bench without losing his balance was a struggle. Sometimes at a game he'd sit in the outfield, and if a ball came his way, he'd yell to a teammate, "Could you get that for me?"

He learned to put his energy toward really important things. Like sliding into base. He'd say to his mom, "I've got to slide! I've got to slide!" That was the coolest thing to do, after

all. But the chance never seemed to present itself—until one time, when he was about 8. Douglas got all the way to third base and tagged it. Then he announced, "Okay, I'm safe. I'm safe, right?!" When the ump and other players agreed, he took several steps back toward second and slid into third.

"He was the happiest child in the world. He wouldn't let me wash his uniform," says Fickel.

She kept hoping that Douglas would be the exception, that he wouldn't end up in a wheelchair. He played kickball at the party for his 9th birthday. By 10 he couldn't; he depended on his wheelchair. Douglas, now 11, thinks it would be a good idea for him to meet the Steelers' Bill Cowher and give him some ideas for plays. He loves skateboarder Tony Hawk. His best friends are his older sisters, Sam and Emma. The world stops when country music star Toby Keith is singing.

Douglas still plays baseball, but now he rides an electric retrofit bike to get around the bases.

He hasn't been able to read since third grade, but he has a sharp memory. For a spelling test, he and his classmates were told to each pick 10 or so words from a list of 244. They would each be tested on the words they'd chosen.

Fickel got a call from the teacher.

"Douglas wants to do all 244," she said.

"Let him."

Guess who scored highest for accuracy.

Maybe you've heard this annoying adage from a wise grandmotherly type: Difficulty teaches us things we might not otherwise have known about ourselves. In the world of biomedical science, it's not unusual for researchers to study an anomaly to learn about what healthy bodies do. A-T offers a particularly revealing molecular dance. This harrowing and rare disease has pointed scientists toward vital clues to understanding the mechanisms involved in cancer and DNA repair.

Christopher Bakkenist has never met Douglas Fickel. But he, too, spends his days with A-T, though he doesn't have the illness.

Bakkenist, who was raised in the middle of England, studied and trained at the University of London, Oxford University, and St. Jude Children's Research Hospital in Memphis. Last year he joined the faculty at Pitt. He is 38, reserved, a still talker, and gravely serious about his research. His work is inspired by the idea that scientists can "actually make an impact and change the way people look at the world." If you ask how, he'll say the path is simple: "You put the diseased children first. As soon as we put ourselves first, we've lost it."

Before coming to Pitt last year, he worked as a postdoc with prominent ATM researcher Michael Kastan at St. Jude. By then, scientists had identified a number of important proteins that the ATM pathway activated, including a tumor suppressor called p53. This protein itself is profoundly powerful.

"It's mutated in 50 percent of all 100 kinds of cancer," notes Robert Abraham (PhD '81), vice president of oncology for Wyeth Research in Pearl River, N.Y., who studied pharmacology at Pitt.

"There's a very solid argument out there that if [cancer] patients don't have a p53 mutation, they have a mutation somewhere else in the p53 pathway. It's like a necessary milestone a cancer cell has to pass to become a fully malignant cell."

Several labs identified other important proteins that are set off downstream of ATM (which is a kinase, so it sets off chemical reactions). But no one could figure out exactly how ATM sounded the alarm that DNA damage was taking place, notes Abraham.

"One of the burning questions in the field was, *How does ATM actually respond to double strand breaks?"*

During his fellowship, Bakkenist created a sensitive reagent that allowed him to see in detail what was happening during the ATM response. Bakkenist and Kastan were then able to show that ATM is made up of at least two inactive molecules. When both DNA strands break after a blast of ionizing radiation, ATM releases two single, and no longer dormant, ATM molecules. The scientists also described the unexpected transfer of phosphates that takes place within the protein itself before the single ATM molecules send phosphates downstream to activate important proteins like p53. Those downstream actors stop the cell cycle to allow repair to occur or to set in motion the extinguishing of unrepairable cells.

A news article in *Nature* notes that Kastan and Bakkenist revealed that "the sensitivity, extent and speed of the ATM response are truly astonishing. Doses of irradiation that cause only a few [double strand breaks] in a human cell activate the majority of ATM within minutes."

It was a seminal finding, says Abraham: "The failure of this pathway explains the whole syndrome."

But how is ATM tipped off to a double strand break?

Chromosomes are made up of building blocks called chromatin that include DNA and proteins. Kastan and Bakkenist showed that changes to chromatin structure let ATM know there's a problem.

Bakkenist can see how such findings could open the door to better cancer therapies:

"If you can inhibit the [ATM] protein, you may be able to increase the efficacy of DNA damage therapy, including radiotherapy, in human cancer. The other approach is, if you can activate ATM artificially, you may be able to temporarily activate p53 as well. If you transiently activate p53, before the cancer is actually developed, you may be able to use the p53 to kill off precancerous cells.

"So you may be able to use it as a prophylactic cancer therapy, to prevent human cancer."

ATM has a sister protein that sits next to it at the top of the DNA damage pathway. It's called ATR (ATM related) and orchestrates the response to another brand of DNA damage—that caused by UV light. This response blocks the progression of DNA replication. (Mutations that pass through this pathway can show up as skin cancer.) Bakkenist is now interested in studying ATR, and Abraham is optimistic about what he'll find:

"This is really important work. I think that Chris is better positioned than just about anybody else to pursue this work. These are very large proteins that pose many challenges."

Because her son is at risk of developing cancer, Pam Fickel carefully monitors his lymph nodes to make sure they don't grow larger.

She had uterine cancer a few years ago. Fickel is a carrier of the mutated ATM gene (as is her husband; both parents must be carriers for a child to get the disease). There's a school of thought that says if she had been given radiation therapy or a drug that mimicked strong doses of ionizing radiation, the results could have been fatal.

Fickel knew about this risk only because of Douglas' strange disease. So Douglas, just by being himself, may have saved his mom's life. ■

FOR MORE INFORMATION, WE RECOMMEND THE A-T CHILDREN'S PROJECT: www.atcp.org