Family Mission

By joining studies, the Noonans are helping unravel the mystery of Alzheimer's disease.

BY JAMIE TALAN

Julia Tatro Noonan brought 10 children into the world before she began forgetting. She was 39. Today, almost 50 years later, her legacy is felt in the homes of generations of Noonan children and grandchildren. The family's genetic pedigree puts members at risk for the form of Alzheimer's disease (AD) known as early-onset. This uncommon form of dementia strikes people younger than 65 and accounts for roughly five percent of all AD cases.

To the Noonan clan, the enemy is a mutation in a gene on chromosome 21 that makes amyloid precursor protein (APP). The mutation leads to an accumulation of sticky protein called amyloid beta, which clumps into the "plaques" thought to damage brain cells in AD.

Dozens of Noonan family members are participating in studies they hope will lead to a better understanding of the disease. "We won't stop until scientists find a cure," says Julie Noonan Lawson, one of Julia's children.

THE NOONAN CLAN Back row left to right: Butch, John, Bob, and Eryc Noonan. Front row left to right: Maureen Noonan Preskenis; Patricia Noonan Barbato; Julie Noonan Lawson; Kathi Noonan Korobko; Fran Noonan Powers. Butch, Maureen and Fran have the APP mutation and developed AD.

COURTESY JULIE NOONAN LAWSON

FROM MYSTERY TO FAMILY HISTORY

Julia Noonan had just given birth to her last child when her memory starting to lapse. Doctors thought she was depressed. When her identical sister Agnes began showing similar signs in 1975, the cause of Noonan's illness was still unclear. After all, neither of the twins' parents had ever had any cognitive problems.

Noonan was committed to a psychiatric hospital in her early forties and then a nursing home. She forgot the faces of the children she loved and the man she married. Her older children took care of the younger ones. At her death, they hoped they buried the disease too.

But 15 years later, in the early 1990s, some of Julia Noonan's children began forgetting. Lawson knew something had to be done.

"We saw research as the only way to solve this puzzle," Lawson recalls.

Her brother, Malcolm "Butch" Noonan, was 39 when he began calling scientists for help in shedding light on the mystery. Something had robbed his mother and aunt of a lifetime of memories, and two of his sisters were lapsing as well.

Julia Noonan died at age 54. Her children—the youngest was in junior high at the time—went about finishing school, falling in love, having children, and embarking on careers. Then, in 1994, her oldest daughter Maureen began forgetting.

Around the same time, Maureen's younger sister Fran began showing signs of what Julie Lawson described as "blankness." Lawson remembered that look from her childhood. "When I saw that blankness in my sister's face, I knew," Lawson says.

Maureen and Fran were officially diagnosed with AD in the late 1990s.

ROLLING UP THEIR SLEEVES

Most research doors were closed to Butch. The majority of AD studies would not enroll people under 55, and the Noonan sisters were both under 50.

Then Julie Lawson met Trey Sunderland, M.D., a psychiatrist focused on AD at the National Institutes of Health (NIH). He designed one of the first studies to follow healthy adults with a family history of the disease. Federal scientists collected blood and spinal fluid from participants and put these middle-age adults—who had all lost a parent to AD—through a battery of tests that measure memory and other cognitive abilities.

Dr. Sunderland agreed to take the Noonans into the federal study. "They are so committed to research," he says. "Their strength, individually and in numbers, is amazing."

Noonan brothers John and Eryc were the first to join—and then Butch, who by 1996 knew that something was wrong with his memory. He would take measurements on a carpentry project and forget the numbers walking from one room to the next. That same year, 22 oth-

er family members joined the NIH study.

Eryc, the youngest Noonan sibling, has seen his family haunted by the disease since before he can recall. His mother would forget to change his diapers and feed him. He joined the NIH study at 33. "My whole life has been about forgetting, about being forgotten," Eryc says.

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>
> **—DENNIS SELKOE, M.D.**

The researchers took blood samples from the Noonan children and sent them out for genetic testing. Maureen and Fran's DNA both contained a rare mutation in the gene for APP. It had only been a few years since the gene was identified as one culprit in the disease.

By 2001 Butch became the third Noonan sibling to be diagnosed with AD. He was being treated by Kenneth S. Kosik, M.D., a neurologist at Harvard Medical School.

In the weeks following the identification of the Noonan family mutation, Dr. Kosik called a family meeting to talk genetics. Almost 50 family members came to Harvard to hear the details of their genetic lottery and give blood for research.

Each one of Julia Noonan's children has a 50-percent chance of harboring the APP mutation and getting early-onset AD. By 2001, it was known that Maureen, Fran, and Butch had the mutation, which meant that their children also had the same odds: 50-percent.

Family members were given the option of knowing whether they had the mutation or not. John was the first Noonan sibling who chose to find out. Then Eryc. Both tested negative.

THE NOONAN'S GIFTS TO SCIENCE

In 2000, after tests showed changes in his memory and learning abilities, Butch was diagnosed with mild cognitive impairment (MCI), a term often used to describe the beginning of cognitive problems. He became an activist and continued to speak out on behalf of people with AD long after he was officially diagnosed with MCI and then, later, AD.

Butch always followed his heart. He loved cooking and became a chef. He was great with his hands and turned his talents to carpentry and plumbing. And he loved listening to people, so he decided in his thirties to become a therapist—his final career until he was forced to retire in 2008.

He was also clear about how he wanted to die. Early on, he hired a videographer and stated his wishes: There would be no extreme life-saving measures. If he can't feed himself, he declared, no one is to lift a fork to his mouth.

Butch died in 2010. Two months before he died, clinicians took a patch of skin from his body. The skin cells would be used to grow "induced pluripotent stem (iPS) cells." In a test tube, they can become any type of cell in the body. Each one carries with it the full complement of his genes, including the mutant APP gene. Julie also donated a small chunk of skin that will be used to grow iPS cells and neurons that do not have the APP mutation.

"Being able to grow these cells in the lab and see how they behave will be invaluable to science," says Dennis Selkoe, M.D., co-director of the Center for Neurologic Diseases at Brigham and Women's Hospital and Vincent and Stella Coates Professor of Neurologic Diseases. Butch's cells could also be used to test new medicines.

At his death, Butch's brain went to Marilyn Albert, Ph.D., an AD researcher at Johns Hopkins Medical Institute in Baltimore, MD. Dr. Selkoe will also obtain samples of Butch's brain, to help figure out what role different forms of amyloid beta play in AD.

"We could never hope to solve the mystery of this disease if it were not for the Noonans and families like them," Dr. Selkoe says.

Dr. Sunderland, who is now a consultant at the Armed Forces Retirement Home in Washington, D.C., said that families with this genetic mutation have provided scientists with the single most important discovery in the field: that amyloid beta is the target protein that accumulates abnormally in the brain in AD.

The Noonans, who started a cycling fundraiser called Memory Ride and have raised 2.3 million dollars for research, recently signed on to the Dominantly Inherited Alzheimer Network (DIAN), which will be one of the largest databases of early-onset AD families in the world. Reisa Sperling, M.D., director of the Center for Alzheimer's Research and Treatment at Brigham and Women's and a DIAN investigator, says that the hope for treating this disease is to identify those at risk and begin treatment at least a decade before the brain starts showing pathological signs—well before symptoms develop.

"If we know that someone will get AD, we need to understand whether there is anything we can do to alter the course of the disease," Dr. Sperling says. She hopes that results from DIAN will make a strong argument to begin a drug study for people with the APP mutation.

"Butch always said that he wanted to do anything that would help stop this disease," Dr. Sperling says. "I think he knew that it might not help him, but it could help others." NN

For more information on participating in AD trials, see RESOURCE CENTRAL on page 36.