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Editorial

Up Close and Personal with Adult-Onset Leukoencephalopathy

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The 1940s and 1950s were a busy and happy time for Phyllis Klingeman and Albert Tripp. They would bring nine children into the world in the rural town of Orwigsburg, Pennsylvania. Most of the children stayed put, or at least nearby, married their high school sweethearts, had kids, worked jobs, and called it a good life. It was only when one of the Tripp daughters, Ruth Nichols, began acting strange—losing one job after the next, asking to borrow money, making bad decisions, looking ragged—that the extended family began to wonder whether their beloved and fun Aunt Ruth was drinking. She'd lost her marriage and her house, and by the late 1990s there was a looming question of whether she would be homeless. She was only around 50 years old.

Ruth found a temporary bed in her mother's home, sometimes in her niece Heidi's house, and occasionally with other family members. Her niece Heidi recalls that she'd come home dirty with tattered clothes, and frozen pizza from a gas station that just sat wilting on the counter. When she asked for a key to the house, Heidi's new husband politely said no.

She left, and soon after Ruth's brother and sister-in-law drove her to the University of Pennsylvania where neurologists did indeed find something organically wrong with Ruth. They could not put a name to it, though. The close-knit family of aunts and uncles and cousins would show up at family gatherings and by the early 2000s Ruth was no longer talking and she sat slumped in a chair. Her left side was limp as if she had had a stroke.

She was living in a nursing home, where she died in 2005 at the age of 56.

Pathologists at the University of Pennsylvania did an autopsy on Ruth Nichols' brain and diagnosed a rare condition called Binswanger's dementia, a subcortical vascular dementia. The report said that there was extensive microscopic damage in her brain's white matter. Her neurologist thoughtfully told the family they had nothing to worry about. It was not hereditary.

Seven years after Ruth's death, a genetic mutation was discovered and linked back to the family. By that time, the same puzzling symptoms had already claimed Ruth's sister Phyllis and her brother Chuck. The pathological slides on Ruth and Phyllis were re-evaluated after Chuck's genetic test at death in 2013 came back positive for the CSF1R mutation. A year earlier, scientists at the Mayo Clinic in Florida identified the genetic mutation that causes adult-onset leukoencephalopathy with axonal spheroids and pigmented glia. It is called, for short, ALSP. It wasn't Binswanger's dementia after all.

Now that a genetic mutation was on the table, Heidi Edwards wanted to know whether she carried the genetic mutation. She also wanted the idea to take root in her cousins, too, but it was hard sell. She learned that she does not carry the genetic mutation. That same year, she started seeing changes in her sisters, Heather and Holly, both of whom were in their 40 s. The symptoms of ALSP include cognitive decline, personality change, depression, balance

problems, parkinsonism, spasticity, and seizures. One of her nephews, her sister Holly's 19-year-old son, tested positive for the mutation within six weeks of losing his mother. He is now 21.

Her mother and sisters have died, and Heidi is now the keeper of the stories of her family's mutation. She has cousins who are starting to show signs, but many would rather not get testing to know whether they carry the CSF1R genetic mutation. She feels that she has to fight for those that have passed and those who will succumb to this deadly disease in the future.

Phyllis Ann Tripp was born in 1954 and was raised smack in the middle of her eight brothers and sisters. In high school, she fell in love with John Brenneman. They married in 1972 and three years later the couple brought their first of three daughters into the world. The family of five grew up in John's childhood home in Cressona, a 12-minute drive southwest from where Phyllis was raised. Both small towns were populated by coal miners and their families.

The year Ruth died Phyllis, her sister, was already showing signs that something was wrong in her brain. In 2008, the family gathered at the cemetery to grieve the passing of a young cousin who died in a car accident. Phyllis was uncharacteristically aggressive and started yelling at her niece's boyfriend, who had been on the phone with her when she lost control of her car on the rain-soaked road. They'd been fighting.

By 2009, Phyllis was slowing down and having trouble managing the finances at home. She was spending money she didn't have. There were mood swings and angry outbursts. By 2011, Phyllis had stopped walking. She would just sit on the couch, many times just naked. By Thanksgiving, she was bed-bound. On Christmas day, she fell into a coma. Six days later, her heart stopped and she was pronounced dead. She was 57.

Next, her brother Chuck started having similar symptoms. The family returned to the neurologist at Penn. Chuck was 55-years old and the doctor thought he might have Lewy body dementia. His progression was fast: he died within a year of his neurological exam. His brain was also sent to Penn and in March 2013, with the new CSF1R mutation discovered a year earlier, the genetic test came back positive.

After Chuck's official diagnosis, Penn neurologists, pathologists, geneticists, and researchers called a family meeting. Holly and Heidi and their mother's brother Skip and his wife Nancy were present. They wanted to explain the disease and let them know they were the only family in Pennsylvania with this rare mutation.

Unlucky them.

That was when Heidi decided she wanted testing. Holly, her twin, didn't want to know. (They had already had genetic testing to confirm that they were not identical.) Heidi found a company in California willing to do predictive genetic testing. She had to meet with a genetic counselor and a psychiatrist before they would approve her request. The team wanted to know what she would do if the test came back positive. There had been similar cases with other fatal genetic conditions where people killed themselves following a positive test. That was not the case with Heidi at all. She is a planner. She wanted to plan for the worst.

On December 23, 2014, Heidi and her husband drove to Penn and met with genetic counselor Beth Wood. Heidi was handed the report and she immediately scanned down to the highlighted line: NEGATIVE. She fell into her husband's arms. The two sat on the floor and cried. Heidi remembers thinking: *I can go on and live my life*.

The following year Heidi began keeping a diary. She took this on because she was noticing some odd behavior with her sisters. Heather was also acting strange. A social worker, she seemed agitated all the time, and aggressive, like their mother was when she started getting sick. Heather had two little children. She was only 40.

Heidi was having survivor's guilt, for sure. But something unnerving was happening at home. Her husband was having balance problems and growing extremely forgetful. She brought him to the ER and an MRI was showing he was in the middle of a stroke. He was admitted. It turns out he had previous strokes. He was 53, and has since had more strokes, and seizures. No one knows why.

His neurologist could only offer this missive: Live like you're dying.

By 2019, Heidi and her twin sister were seeing one another every weekend. On one outing, Holly was short of breath and her left side dipping down as she walked. When they got to a café for lunch, she asked Holly about testing. Later that week Heather and her daughter Madison visited Heidi and they were talking about Holly's changes. Heather excused herself to go to the bathroom. Madison started crying. "There is something wrong with my mom, too."

Holly was also showing signs. She wore a thermal lunch bag instead of her purse and when asked why, she responded. "I can't keep my water cold in a purse, can you?" Her face drooped and she was slurring her words. Her balance was off, too.

In September 2019, Heidi the planner convinced Heather to go to the emergency room. Heidi took the doctor aside and explained their family history. They ordered a CT scan and it showed white matter damage. They admitted her. Heidi called their Penn doctors. Two days later, they got Heather in for testing. She was positive for the mutation.

Two months later, the family learned about a study in Minnesota testing the benefits of a bone marrow transplant for conditions like ALSP. Heidi turned out to be the perfect donor. Heather became the third patient to undergo the procedure. That was in November. By March, COVID shut down all non-emergency transplants. By May 2020, she had declined significantly but they did the procedure anyway. The cells were transplanted June 1, 2020. She suffered graft versus host disease—her body was fighting the new cells in her body. She had a heart attack, and it took 35 minutes to revive her. She was on life support for 22 days before she passed. She was 45.

Meanwhile, Holly was limping through life. A single mother and physician recruiter, she was having a hard time because of her speech. She was 43. She thought that she would try the bone marrow transplant, but they could not find a good match. Heather was still tethered to life support when a call came through with a donor match in Europe. Holly was going to start the process on the same day Heather died. She opted out of the transplant and lived another ten months. She was 44.

In June 2020, Heidi started an ALSP foundation. Scientists estimate there may be ten thousand people in the world with ALSP. Her foundation has only found 100. Her work continues. She has also turned to her own family history to follow the tracks to the mutation.

In 2012, Zbigniew K. Wszolek, MD, a professor of neurology at the Mayo Clinic in Jacksonville, Florida, published a study identifying a CSF1R mutation in ALSP. Since then, scientists around the globe have identified at least a hundred other CSF1R mutations in ALSP families. For this neurologist, his story begins with a single patient. It was March 2003 and a 44-year-old woman showed up in his exam room with a two-year history of difficulty walking and talking. She was now getting around in a wheelchair and was mute. She also had dementia.

Dr. Wszolek had spent his career studying rare diseases. He loved a good detective story. The patient's mother, who had accompanied her to the visit, explained that her husband was mute and bed-bound and living in a nursing facility. Two weeks later, the patient's mother learned that her husband had three other siblings who had died with similar symptoms, and a younger sister died with a diagnosis of corticobasal degeneration. What he knew about CBD was that it did not run in families. He was able to get hold of autopsy tissue and asked Mayo neurologist Dennis Dickson to review the patient's report. Dr. Dickson said it was actually a condition called hereditary diffuse leukoencephalopathy with spheroids, HDLS. There was cerebral white matter degeneration with demyelination, and her brain was marked by axonal swelling.

He'd never heard of HDLS but by November he handed his patient a tentative diagnosis. The family was from Indiana, and he called Bernardino Ghetti, MD, at the University of Indiana and asked if he'd ever seen a patient with HDLS. He studied the slides. "You are right. It is not Alzheimer's disease," he said. "It is HDLS." Dr. Ghetti and Dr. Dickson worked together at Albert Einstein College of Medicine as residents, and remembered their first patient with HDLS. It was so out-of-the-box that it stuck in their heads.

Dr. Wszolek decided to look for the gene for this disease. For years, his lectures would include a final slide about his hunt for this mysterious gene. A colleague at one of his lectures said that he'd just seen a young woman with this disease. The family was from a small town in South Carolina. Her father died a year earlier, and an autopsy showed axonal spheroids, or swelling. They traveled to the town to study the family and identified seven affected relatives. Only two of the seven were still alive. They were still no closer to identifying the gene culprit.

By 2011, Dr. Wszolek had identified 27 families with HDLS and 14 of those families had brain autopsies or biopsies done while they were still alive. Now, he had enough samples to send them down to Rosa Rademakers, PhD, a neuroscientist and genetic sleuth at the Mayo Clinic. She was able to identify the gene mutation in CSF1R. The gene is expressed in microglia and regulated by a gene called TREM2, which has been linked to dementias. It turns out that HDSL and ALSP are identical conditions.

He continues to collect cases.

By 2022, about 300 patients have been identified. CSF1R is short for colony stimulating factor 1, a cytokine that regulates the body's stress response and has a major role in regulating microglia and macrophage activity in the brain.

Dr. Wszolek heard about experimental trials of bone marrow transplantation for leukodystrophies.

Florian Eichler, MD, a neurologist at Harvard Medical School and Massachusetts General Hospital, also studies single gene disorders. Dr. Eichler had a handful of patients who seemed to get a bit better after a bone marrow transplant. It took Dr. Wszolek two years to convince his Mayo colleagues to give it a try. His first case was a 37-year old engineer who was having problems with walking and carrying out simple cognitive tasks. She had to leave her job. Three years after the transplant she was well enough to go back to work. The hope is that the transplant, with a new population of immune cells from a healthy donor, will penetrate the blood brain barrier and find their home where microglia normally live. (Microglia are the armed guards of the brain's immune system.)

But while some patients do better, others do not. So far, Holly was the only one who died as a result of the bone marrow transplant itself. They have revised their protocols to ensure that people too far along in the disease process do not receive a bone marrow transplant. They understand that they can't do it too early or too late. It is the Goldilocks Principal. But no one knows when it is just right.

Dr. Wszolek's story does not end here. He recently examined a patient with all the signs of this disease but had no mutation in the gene. "There is another gene that awaits discovery," he said.

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