Hidden in plain sight

Genetic conditions in Western Pennsylvania Amish and Mennonites are among the least studied. Pitt people are changing that and saving lives.

Written by Maureen Passmore | Photography by Martha Rial (except where noted)

A huge swath of rural Northwestern Pennsylvania is the very definition of verdant in the summertime. Lush forests of oak, red maple and spruce carpet both the mountains and the valleys—the wash of green broken only by patches of farmland and the occasional line of a narrow road. In pockets of this remote area, fields of wheat, barley or hay surround solitary houses or maybe a one-room school, and cars share the road with horse-drawn buggies.

Among the nine counties in this corner of the commonwealth, approximately 13,000 members of Old-Order Amish and Mennonite groups (collectively known as the Plain community) live in a way that has remained relatively unchanged for several hundred years.

This brings us to the story of 15-year-old Sarah (not her real name); she's Amish and, like most in the Plain community, is a descendant of Anabaptists who came to the United States in the 18th century to escape religious persecution. Plain community members live intentionally separate from mainstream culture, so the world for them hasn't changed much over the centuries. They don't use public utilities or other modern conveniences; they dress unadorned in muted colors and speak Pennsylvania Dutch. Formal education typically ends at eighth grade; and men and women adhere to conventional gender roles. They value humility and obedience, community and tradition, and they reject anything that draws attention to the individual (hence their preference not to be photographed).

This is Sarah's world; but it hasn't always been tranquil. After a long walk one summer day in 2010, she started to have trouble seeing. She found herself vomiting. Seizures came on.

Because of her alarming condition, she ended up in another corner of the commonwealth for some 21st century health care—in the emergency room of UPMC Children's Hospital of Pittsburgh. Sarah was seen by Jerry Vockley, an MD/PhD professor of pediatrics, who leads the Division of Genetic and Genomic Medicine in the University of Pittsburgh Department of Pediatrics and Children's Center for Rare Disease Therapy, and Amy Goldstein, a pediatric neurologist (now an attending physician at Children's Hospital of Philadelphia).

A blood test revealed a significant buildup of lactic acid. An MRI confirmed the teenager was having a metabolic stroke. The two physicians recognized the symptoms and made sure the patient was seen by the hospital's medical genetics service for appropriate testing.

Vockley looked over the genetic evaluation with his team—including Cate Walsh Vockley, a genetic counselor at UPMC Children's, and Lina Ghaloul Gonzalez, an MD (Res 12, Fel '13), who was then a trainee and is now a professor of pediatrics in the Division of Genetic and Genomic Medicine. They were able to pinpoint the cause of the illness. Sarah had a mutation associated with MELAS syndrome—short for mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes—one of the most common mitochondrial disorders. She was immediately put on a treatment plan of various medications to slow the progression of the disorder and prevent strokes, as well as anticonvulsant medications to prevent seizures.

Lina Ghaloul Gonzalez (left) and Cate Walsh Vockley (photo by Tom Altany/University of Pittsburgh)

But the team—having identified Sarah's as the first known MELAS case in the Plain community—knew their work was far from done. They knew that other members of Sarah's family could also have MELAS, even if they weren't showing symptoms. MELAS is a mutation in mitochondrial DNA, which is inherited maternally.

Centuries of living culturally, socially and geographically apart from the larger population has led to limited genetic diversity among Plain people. Researchers have documented a significant number of genetic diseases—mostly autosomal recessive disorders—in the Plain communities, and in the Eastern Pennsylvania area in particular. Suitable treatment exists for serious conditions, like maple sugar urine disease and glutaric aciduria type 1, and they are well managed with early diagnosis and intervention.

But genetic diseases in the Western Pennsylvania Plain community had not been well documented. (It's the least studied population of Plain people.) And detection of mitochondrial DNA mutations in the Plain community was concerning. If undiagnosed and untreated, these are potentially fatal conditions.

"We knew we had to test Sarah's other family members because a diagnosis could get them appropriate treatment—hopefully before anyone else had severe symptoms," like Sarah, says Ghaloul Gonzalez.

The case studies would present opportunities to learn more about mitochondrial mutations that would be helpful for the general population, too. The mitochondrial respiratory chain requires hundreds of proteins for normal assembly and function, explains Walsh Vockley, and mutations in the proteins' genes can lead to a wide range of diseases. Cells have hundreds to thousands of mitochondria, energy-producing organelles, each with its own DNA. However, in a disease like MELAS, not all mitochondria in the cell have a mutation. The ratio of altered to normal mitochondria dictates the severity of the disease symptoms, which means that some disease phenotypes vary from person to person.

So there are hundreds of possible mutations in mitochondria and different ways they manifest. This makes the work of linking diseases to mitochondrial mutations tricky in many cases. Genetic researchers are often looking for the proverbial needle in the haystack. Sarah's family gave them threads to follow.

People with MELAS might end up with any or all of these conditions: Stroke, dementia, epilepsy, recurrent headaches, short stature, infertility, organ failure, progressive weakness (myopathy), dangerous lactic acid buildup, intestinal dysmotility (difficulty defecating that can lead to nutritional issues), maternally inherited diabetes and deafness.

MELAS is not curable; treatment involves medications to alleviate or help with symptoms. About 10% of people who carry the mutation have severe symptoms and the same percentage are asymptomatic. People who fall between those two extremes experience a variety of possible conditions.

Identifying MELAS in a Plain community opened the possibility that people could be treated and lives could be saved. In 2015, Ghaloul Gonzalez and Walsh Vockley and their team traveled to Sarah's community to sit down with about 30 of her family members for what would not be a routine consent conversation.

"What we're learning from the Plain community doesn't just go back to that community," says Ghaloul Gonzalez. The findings are likely to save lives in the larger population, as well.

In general, Plain people seek natural remedies and chiropractic care and only engage with conventional health care when those familiar options are exhausted. Also, few Plain community members in Western Pennsylvania live close to medical facilities—nor do they drive cars. When families in the region need care, they often pay an "English" person (a term for someone outside the Plain community) for a car ride, which can be expensive. Sarah's extended family listened intently to the team's description of MELAS. They learned what was at stake for them and why the medical professionals wanted to work with them.

"We explained that because Sarah had MELAS it was likely other family members did, too," recalls Walsh Vockley. "No one thought they had it; but, as we were talking to them, it became clear that many of them had undergone major medical interventions without a genetics evaluation, without knowing that there could be an underlying cause."

Sure enough, Sarah's family history uncovered that Sarah's mother had reported having migraines and hearing loss, symptoms of MELAS syndrome. Other family members had already experienced symptoms severe enough for conventional care, including organ transplants and hearing aids. By the end of the conversation, most of the family consented to genetic evaluation.

After testing the family's blood and urine samples, the team was not surprised to find that all participating at-risk adults and two children carried the mutation and none of the control group (unrelated spouses of maternal relatives) did. This discovery led to transformative care for Sarah and her family. It was now clear that the carriers' previous health issues were related to their mitochondrial DNA mutation.

It was also clear to Ghaloul Gonzalez and Walsh Vockley that Sarah's family was probably just one of many in the Western Pennsylvania Plain community with undiagnosed hereditary disorders. They knew they could help by identifying underlying genetic diseases in this population. So, in addition to providing genetic services at UPMC Children's Hospital of Pittsburgh, Ghaloul Gonzalez and Walsh Vockley developed the Plain Community Translational Medicine Program at UPMC Children's, the Plain Community Outreach Clinic in Mercer County and a research registry to discover new genetic disorders among Plain people of Western Pennsylvania.

As a part of the translational program, Ghaloul Gonzalez and Walsh Vockley work to increase in-hospital referrals of Plain community members to their genetic consulting services. In 2016, after a year-long review of medical records of 303 Plain patients at outpatient clinics and at UPMC Children's, their team found that 102 patients had a clinical presentation that suggested a genetic disorder; however, only 32 of the 102 patients had been evaluated by the Division of Genetic and Genomic Medicine.

"We don't know why this is," says Ghaloul Gonzalez. "Maybe the physicians offer a genetics referral and families decline. Or, physicians know that families often have limited resources and can't pay for testing, so they don't call us. Now, every day, Cate gets a list of Amish and Mennonite patients who are in UPMC Children's. We have permission to look at their records and determine whether they need genetic evaluation. Then we approach the attending physicians about talking to the family."

Some Plain community families are fine with genetic evaluation. Some are hesitant—often for financial reasons. They usually don't have private insurance, so leaders or bishops in the community typically negotiate with UPMC to pay a certain percentage for services. To offer families services closer to their homes, the two women travel to Mercer County, to the Plain Community Outreach Clinic, once a month.

"We used to place ads in Amish newspapers about our services," says Walsh Vockley. "We went to a health fair at a fire station once to reach families. Families have now heard of us and are more willing to go to the clinic." Ghaloul Gonzalez targets testing for certain diseases based on symptoms and will screen for founder mutations, i.e., genetic variations that are more common among Plain people. If targeted testing does not reveal anything, she will try gene panel testing or whole-exome testing, which identify variations in any gene.

As a genetic counselor, Walsh Vockley collects a family history, interprets and discusses test results with patients, and, if patients need to see a specialist, coordinates their care. Because whole-exome testing is expensive, Walsh Vockley searches for ways to get families low-cost or free testing.

"If we're critically concerned about a child's health issue, we do our darndest to find ways to get answers," says Walsh Vockley. "Some testing companies will help with costs, but we can also get families free testing when they participate in research"—like the research registry they started.

The registry for the Western Pennsylvania Plain community is much like one that exists for Eastern Pennsylvania communities through the Clinic for Special Children (which refers some patients to UPMC/Pitt transplant surgeons). The little-studied Western Pennsylvania population has mutations common in all Plain communities, but, as Ghaloul Gonzalez discovered with MELAS in Sarah's family, its members also have unique genetic disorders and mutations.

Ghaloul Gonzalez and colleagues identified a Mennonite patient with a gene variant (of GUCY2C), which causes chronic diarrhea and other issues that can lead to life-threatening symptoms. The team studied an experimental drug for diarrhea, but it's not available for patient use. They hope their work will inspire other research for therapies.

"What we're learning from the Plain community doesn't just go back to that community," says Ghaloul Gonzalez. "We have learned more about diseases and mutations—in which populations they are inherited, who should be tested for which genetic disease and new ways these diseases present in people."

As for Sarah, since her original diagnosis after that walk several years ago, she has had other health setbacks, as expected with her disease. When doctors have the ability to help manage an illness early on, outcomes tend to be better, notes Ghaloul Gonzalez. She and Walsh Vockley can't stress enough the importance of early diagnosis of a genetic condition.

Take the case of a young Amish boy, John (not his real name), who was enrolled in the Ghaloul Gonzalez team's studies after physicians had ruled out any known causes of his immune deficiency. John started having serious health issues—severe infection, sepsis and pneumonia—when he was 10 months old. Throughout the next five years, John was treated for neutropenia (a low white blood cell count), as well as recurrent lung and blood infections before undergoing a transplantation of stem cells of the blood and bone marrow.

He didn't make it to his sixth birthday; John died after complications from a second stem-cell transplantation. It turned out that John had reticular dysgenesis, a severe immunodeficiency disease. It's caused by what's known as adenylate kinase 2 (AK2) deficiency. Diseases related to AK2 deficiency usually present during early infancy. Children born with reticular dysgenesis are likely to die within days or a few months after birth if not treated. Because John had a less severe and delayed presentation of reticular dysgenesis, he did not meet the clinical criteria for the disorder and was not flagged for genetic testing of an AK2 mutation. (The child had tested negative for known founder mutations among Plain people.) Through whole-exome sequencing, Ghaloul Gonzalez and her colleagues found that John did, indeed, have an AK2 mutation.

This discovery suggested that other people with combined immunodeficiency who don't seem to meet the clinical criteria for "classical" reticular dysgenesis should be tested for AK2 mutations—not just those within the Plain community.

Recognition of reticular dysgenesis before a transplant is crucial; conditioning regimens can lead to better outcomes.

If doctors had known of John's diagnosis sooner, his life might have been saved.

John's parents agreed to be tested for the mutation and were found to be carriers, though they do not have the disease. (That's typical for most autosomal recessive disorders.)

The couple now has another child who was screened a few hours after birth. A few days later, the results came in. He was found to be a carrier like his parents; but, to their great relief, he's not expected to be affected. He continues to do well at 4 years of age.

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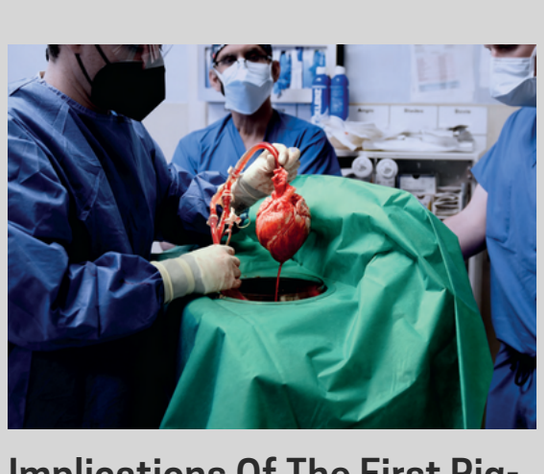
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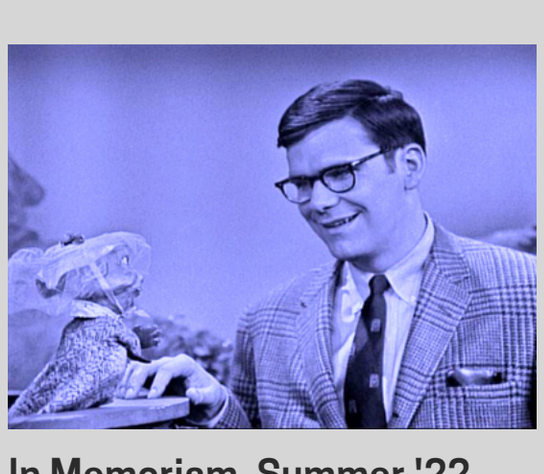
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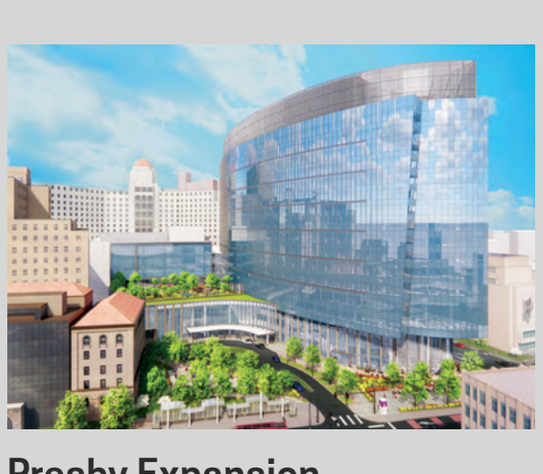
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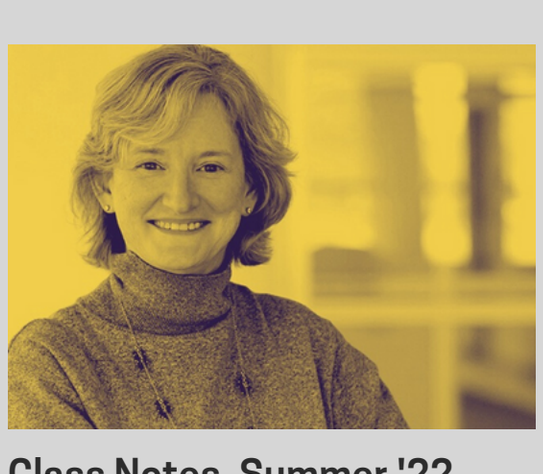
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