Newborn's deadly heart arrhythmia caused by mosaic of mutant cells

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Astrea Li, with her father Edison Li and mother Sici Tsoi, began going into cardiac arrest soon after her birth three years ago. It took a broad team of physicians and researchers to understand the reasons behind Astrea's heart problem. Credit: Norbert von der Groeben

Researchers have solved the mystery of an infant with severe long QT syndrome, found to be caused by a lethal genetic defect in only 8 percent of her cells.

A team led by researchers at the Stanford University School of Medicine has solved a genetic mystery, diagnosing a sick baby and opening a new way for doctors to identify what might be causing genetic diseases with no obvious source.

Three years ago, when a newborn baby at Lucile Packard Children's Hospital Stanford began going into cardiac arrest every few hours, doctors and nurses scrambled to save her life.

Her parents, Sici Tsoi and Edison Li, had not even seen their new baby after the emergency C-section delivery. They waited, puzzled to hear how she was. Tsoi said she had no idea how bad things were and just hoped for the best. "All I knew was that I gave birth, and I was very happy," she said.

The doctors soon diagnosed the baby with a heart arrhythmia called long QT syndrome. But the deadly genetic mutation causing the problem was hidden away inside baby Astrea's heart. It took a huge and diverse group of researchers, and a combination of some of the fastest and most cutting-edge genome sequencing ever conducted, to uncover the mystery of her illness: a heart composed of a mosaic of cells, 92 percent healthy and 8 percent defective.

Getting on the case

At a regular weekly clinical meeting of Stanford Medicine's Center for Inherited Cardiovascular Disease, Euan Ashley, FRCP, DPhil, a professor of medicine and of genetics, and James Priest, MD, an instructor in pediatric cardiology, heard about the case and knew they

could help. "We realized how sick this child was," Priest said, "and we had a new tool—rapid whole-genome sequencing—that could make a faster and more comprehensive diagnosis than the available clinical genetic testing. So that night I went and talked to the parents and the rest of the team, collected a blood sample and we started the test."

A paper describing the case was published online Sept. 26 in *Proceedings of the National Academy of Sciences*. Priest is the lead author, and Ashley is the senior author.

While Astrea Li began a six-week stay in the hospital, Priest looked in her blood cells for any of several gene variants known to cause long QT syndrome. He found a suspicious mutation, but he immediately ran up against two problems. First, he wasn't positive that the mutation was capable of causing such serious heart problems.

Second, the ratio between normal and mutated gene variants was unusual. Because of that odd ratio, Priest wondered if Astrea might be a mosaic of two kinds of cells. It was possible for a mutation to have occurred when her cells were first dividing as an early embryo, within hours after conception, leaving a small lineage of related cells marked for a separate fate.

Connecting the dots

Connecting all the dots was a huge hurdle. "It was two to three weeks of high-intensity work and about as dramatic as it gets," said Ashley, who directs the Stanford Center for Inherited Cardiovascular Disease and co-directs Stanford Health Care's Clinical Genomics Service.

First they had to confirm that the variant was real. They did this by turning to colleagues at a sequencing firm called Personalis that Ashley had co-founded with other Stanford faculty. "The Personalis team

dropped everything, came in weekends, to carry out in-depth sequencing of Astrea and her parents," said Ashley. The company's scientists established that the gene variant was real and present in Astrea but not her parents, indicating it was a new mutation.

To find out if the particular mutation they had identified could cause long QT syndrome, Priest and Ashley gave the sequence to a team of collaborators at Gilead, a company that designs drugs to treat the disease. Gilead reported that the gene variant would cause long QT syndrome. Moreover, they said, this mutation was especially deadly.

Next the Stanford team wanted to be sure that Astrea really was a mosaic individual; they needed to show that individual cells actually had different genomes, some carrying the deadly mutation, some healthy. Each cell's genome would have to be individually mapped. "That field was founded by Stephen Quake," said Ashley, "so having him here at Stanford, I called him and asked if he could help." Quake, PhD, a professor of bioengineering and of applied physics who is also a co-author of the paper, and his team looked at individual cells from Astrea's blood sample and showed that most of her cells had normal genes, but 8 percent carried the mutation for long QT syndrome. Astrea's blood cells were definitely mosaic.

But another question remained. It wasn't yet clear if the baby's heart tissue was also a mosaic of normal and damaged cells.

Despite treatment with two drugs and the implantation of defibrillator and a pacemaker, Astrea developed an enlarged heart when she was about 7 months old. To her parents, she looked healthy, but assessments showed that she was in great danger; during a visit to the hospital, her heart stopped again. Astrea needed a heart transplant, and her name was quickly added to a waiting list for a donor heart. "I thought it would be at least a year of waiting," said Tsoi. But after just five weeks, someone

from Stanford called and asked if she was driving. "Are you in a safe place?" the voice asked. It was news of a donor.

On the day of Astrea's transplant, her parents took their two older daughters and picnicked on the Stanford campus, waiting patiently to hear how the surgery went. In the evening, they went to see Astrea. "The first thing I saw was the monitor," said Tsoi. "That was the first time I'd ever seen the green line—the heart beat line—so stable and regular."

The tissue from Astrea's original heart allowed researchers to determine that, indeed, 8 percent of the heart cells carried the deadly mutation they believed had been causing her long QT syndrome.

The team still wondered, though, if a heart with 8 percent mutant cells could really have caused Astrea's severe long QT syndrome. The team contacted colleagues in the Computational Cardiology Laboratory at Johns Hopkins University, experts in computer modeling of cardiac electrical activity. The biomedical engineers' eventual computer model of a heart with a mosaic of healthy and mutant cells in the organ's electrical tissue acted exactly the way Astrea's real heart did. "It was an important moment: a mosaic heart really could cause heart block and cardiac arrest," said Ashley.

"We'd thrown everything we had at diagnosing the baby," said Ashley, "but still we wanted to know, how common is this?"

Broader analysis

To find out how often mosaicism might explain undiagnosed arrhythmia, the team partnered with a genetic testing company with a database of arrhythmia cases. "We asked them, 'How many cases of mosaicism have you seen when you looked at genes that cause arrhythmia?' The answer was about 0.1 percent," Priest said.

The team's work may offer a new way to finally determine the cause of arrhythmias that previously had been a mystery, said Priest. About 30 percent of heart arrhythmia patients don't have a genetic diagnosis. "Maybe," he said, "there are additional mutations that are in the heart only. Genetic tests are nearly always done on blood or other easily acquired tissues. So it's easy to imagine a mosaic gene variant that occurs only in the heart and doesn't show up in the blood. Really, the same reasoning could apply to genetic diseases that affect other parts of the body.

"And that really is a brand new phenomenon," Priest added. Until recently, he said, no one has thought of looking for mosaic gene variants as the cause of these kinds of diseases.

"What we are uncovering is a phenomenon that is much more common than we had ever anticipated," said Ashley. In fact, he said, "I think there's enough evidence now to suggest that a large number of people have some level of mosaicism," although the genetic differences are probably harmless in most of us.

The team's approach to this case is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

Astrea's mother said that when her daughter was first born, "we asked, 'Is she safe now? Is she stable now?' and one of the doctors told me, 'We don't know. But even for your two older girls, there's no guarantee they'll be healthy tomorrow. So treat Astrea like a normal kid and make every day count.'"

Tsoi said this advice inspired her to become a different kind of mother. "I used to be very strict, but since that day whenever I want to do something with the kids, I just do it as soon as possible." She advises

other parents, "Don't think too much about the future, don't wait. Just do it."

Earlier this month, Astrea celebrated her third birthday. She does cartwheels with her older sisters and loves to listen to the music from Frozen. Coming home in the car with her mother recently, Astrea said, "I don't want to go home. I want to play outside."

"And so we did," said her mother.

Provided by Stanford University Medical Center