By Jennie Dusheck

A team led by researchers at the 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, Evan 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 Science. 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 genetic 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 Stanford faculty. “The Personalis team dropped everything, came in weekends, to carry out in-depth sequencing of Astrea,” Ashley said.

Scientists find how Zika virus affects cranial precursor cells

By Krista Conger

Infection by the Zika virus causes a population of cells in the cranium of a developing embryo to secrete neurotoxic levels of immune signaling molecules called cytokines, according to a new study by researchers at the School of Medicine. Although the study was conducted solely in cells grown in a laboratory dish, it may provide one possible explanation for why babies born to women infected with the virus can suffer from a birth defect called microcephaly, or abnormally small heads.

“Affected babies have small brains and small skulls,” said assistant professor of medicine Catherine Blish, MD, PhD. “Cells in the cranial neural crest give rise to the bones and cartilage of the skull and face, and they also form an important supportive niche for the developing brain. We wondered if the Zika virus could infect cranial neural crest cells, perhaps giving rise to deficits in skull formation and altered neural development.”

The study was published online Sept. 29 in Cell Host & Microbe. Blish is the senior author. Graduate students Nicholas Bayless and Rachel Wachtel co-authored the study. See ZIKA: page 6

Prions, proteins with a bad rap, can pass on beneficial traits

By Rosanne Spector

Prion proteins, best known as the agents of deadly brain disorders like mad cow disease, can help yeast survive hard times and pass the advantageous traits down to their offspring, according to a new study by researchers at the School of Medicine.

The study, published in the Oct. 6 issue of Cell, indicates that in yeast — and possibly other organisms, including humans — protein-based inheritance is more widespread than previously believed, and could play a role in evolution.

“Evolution there’s a paradox,” said Daniel Jarosz, PhD, assistant professor of chemical and systems biology and of developmental biology, who is lead author of the study. “We know that there are an extraordinary number of mechanisms that exist to protect the integrity of the genetic code and to assure that it’s faithfully passed on to future generations. But we also know that evolutionary success requires adaptability. How can you reconcile that need with the fact that the raw material for that innovation is really limited?”

Jarosz had a hunch that prions might be part of the answer. The new study suggests this could be the case.

How prions work

To understand his hunch, you need to know a bit about how prions work. Let’s consider this scenario in a bottle of beer on a hot summer day: When some of the yeast cells floating in your beer get stressed, in this case by the blazing sun, they begin producing large quantities of proteins called molecular chaperones — or proteins that help other proteins fold. These chaperones wrap around prions and fold them into a shape that kicks off a chain reaction of sorts. Other prions of its kind follow suit, using the original as a template.

“I sometimes liken it to a spreading fashion trend among teenagers,” said Jarosz. “Once it catches on with a couple of kids it
“Hello, Houston? This is George.”

“Kate, this is David. It’s good to see you!” Relman said. “I have to say this — because how often do you get to say this? — greetings from Earth.”

Rubins laughed. “I have to say this, because I don’t get to say this often: Greetings from space.”

“Kate spent a significant fraction of her graduate career in a spacesuit,” Relman quipped, referring to her studies of smallpox and Ebola, for which she at times wore a positive-pressure-supplied-air protective suit.

“Scientists are trained to fly and pilots are trained to be scientists,” Rubins said. “I trained under you and Pat [Brown, MD, PhD], which helped prepare you for what you are doing now?”

Rubins replied, “Looking back at graduate school, is there something you think helped prepare you for what you are doing now?”

Rubins said, “We take our coffee in the morning and we turn it into tomorrow’s coffee, as we often say up here. We take every bit of water from the system and we recycle it. … We take the CO2 out of the environment. We are making our own atmosphere. … That, I think, is a proving ground for technology for sustaining life off the planet.”

Relman asked, “Looking back at graduate school, is there something you think helped prepare you for what you are doing now?”

Rubins replied, “Getting the chance to be at Stanford, to do work there, to train under you and Pat [Brown, MD, PhD, professor emeritus of biochemistry] and all of the associated mentors, friends and colleagues there, taught me to be a scientist. I put this to use every day.”

Rubins then addressed the students in the audience: “It’s pretty fun to be a scientist in space, but it’s also incredibly fun to be a scientist on Earth. I hope that some days when the experiments get a little grinding, you think about how incredibly lucky we all are to be able to observe the world around us.”

The event was made possible by the Dean’s Office at the School of Medicine; the Stanford Medicine Alumni Association; and NASA, in particular astronaut Christina Koch and her colleagues in the Astronaut Office at NASA’s Johnson Space Center.
Researchers receive NIH grants for ‘high-risk’ work

Seven researchers at Stanford have received awards totaling $10.25 million from the National Institutes of Health to explore bold approaches to make research challenges.

The Stanford recipients are among 88 scientists nationwide to receive Pioneer, New Innovator, Transformative Research and Early Independence awards from the NIH’s High-Risk, High-Watermark Program. The awards total about $12.7 million and are supported by the NIH’s Common Fund.

“The program continues to support high-caliber investigators whose ideas stretch the boundaries of our scientific knowledge,” said NIH director Francis Collins, MD, PhD. “We welcome the newest cohort of outstanding scientists to the program and look forward to their valuable contributions.”

Six Stanford scientists received New Innovator Awards, and one received an Early Independence Award. Both are members of the School of Medicine, and the seventh is from the School of Humanities & Sciences.

New Innovator Award

The New Innovator Award provides up to $1.5 million over five years to fund innovative research by an investigator who has not yet received a research project grant or the equivalent from the NIH.

JOHN ANDREWS, MD, assistant professor of infectious diseases, plans to use his award to study a new way of detecting tuberculosis by testing air samples in public spaces.

Tuberculosis affects 9.6 million people every year and causes 1.5 million deaths annually, making it the No. 1 cause of death due to infectious disease. Resource-limited countries have traditionally tried to control TB by waiting until people show up in a hospital, clinic or doctor’s office with symptoms, and then treating them for TB.

But infected individuals may be capable of transmitting TB to others for as much as a year before they are diagnosed. Early diagnosis of tuberculosis disease would be ideal, but individual screening is costly and not sustainable in poor countries where the TB burden is greatest.

More than 80 percent of transmissions cannot be linked to close contacts among household members. Andrews intends to use custom-built air-sampling devices and highly sensitive molecular diagnostic techniques to study the utility of testing for TB in the air in public settings, such as schools, churches and public transit, in the hope of locating the “hot spots” where TB transmission occurs.

Andrews is a member of Stanford Bio-X.

SEAN BENDALL, PhD, assistant professor of pathology, will focus his grant on single-cell proteomics—an approach that provides a snapshot of a cell’s protein profile that can yield valuable information about its identity and function.

He will use the technique to study some of the earliest precursors of blood cells called hematopoietic stem cells in an effort to identify those that can customize and broaden hematopoietic stem cell therapy. Currently, 10,000 such stem cells are planted per year to reconstruct the immune systems of cancer patients who have received lethal doses of chemotherapy or radiation to treat their disease. Only about 1 percent of all cells transplanted, however, are true multipotent stem cells.

“Leveraging single-cell proteomic technologies that we have pioneered, we can capture cell identities and functional information on millions of individual cells in a single experiment,” said Bendall. “This will allow us to comprehensively characterize the nature of these most primitive cells and their function in human regenerative medicine, health and disease.”

Bendall is a member of Bio-X and of the Stanford Cancer Institute.

ALIA CRUM, PhD, assistant professor of psychology, will use her award to continue examining the ways in which a person’s mindset alters their physiology and behavior. Her work is intended to explore the presence of the placebo effect and look at the ways in which a person’s mental state can elicit physical changes.

One example is in the study she did examining nutrition labels. She took identical vanilla milkshakes and labelled them in two different ways—once as a calorie and healthy, the other indulgent—and then examined blood levels of a hormone that signals satiety.

“What she found is that if people eat the same thing but think they are eating something very different, their blood hormone states reflect their expectations—not their meals. People who thought they were getting a low-calorie snack had hormone levels indicating that they weren’t done eating. Those who expected to be full felt full,” said Fordyce.

She carried out similar work with exercise. Simply by telling hotel maids their work counted as exercise was enough to elicit some of the benefits of an active lifestyle. Women who considered their work exercise worked longer, had lower blood pressure and had smaller hip-to-waist ratios.

ELIZABETH EGAN, MD, PhD, assistant professor of genetics and of bioengineering, specializes in developing new instrumentation and assays for making quantitative, systems-scale biophysical measurements of molecular interactions.

Egan is a member of the Stanford Child Health Research Institute.

POLLY FORDYCE, PhD, assistant professor of genetics and of bioengineering, specializes in developing new instrumentation and assays for making quantitative, systems-scale biophysical measurements of molecular interactions.

Egan and his team will use a concept known as forward genetic screening. They will generate many blood-forming stem cells with different genetic changes, then reduce them to many red blood cells, and test how well the various cells can be infected by the malaria parasite. Their studies will then explore exactly what mechanisms in the red blood cells enable infection by the parasite, ultimately aiming to provide insights for creating new antimalarial medications.

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Early Independence Award

AASHISH MANGLIK received an Early Independence Award, which supports promising young investigators with up to $1.25 million over five years. The awards are meant to allow exceptional early career scientists to more quickly assume independent research positions by eliminating or shortening the traditional postdoctoral training period.

Manglik, MD, PhD, instructor of molecular and cellular physiology, focuses on decoding the molecular basis of transmembrane signaling and transport in order to understand how cells recognize and respond to their extracellular environment.

He intends to direct his NIH funding toward the study of ferroportin, the key transporter in the body responsible for regulating iron levels in the blood. Ferroportin, in turn, is regulated by a hormone called hepcidin, which previous research has shown binds to and degrades ferroportin in the presence of high serum iron levels. Ferroportin or hepcidin dysfunction can result in hemochromatosis, also known as iron overload, or various anemias.

There are no approved therapies that work by inhibiting ferroportin or hepcidin levels, activities or interactions. Manglik’s work aims to understand how ferroportin works at the most basic level in order to produce new knowledge and new reagents that may lead to drugs capable of treating hemochromatosis or anemia by inducing favorable changes in the ferroportin-hepcidin pathway.
New bioscience students welcomed as ‘partners in discovery’

By Tracie White

Dirk Spencer, future plant scientist, sat grinning nervously with his new white lab coat draped carefully across his knees, waiting for his life as a Stanford graduate student in biology to officially begin.

“We are here to celebrate a very important milestone,” said Will Talbot, PhD, professor and chair of developmental biology, and the School of Medicine’s senior associate dean for graduate education and postdoctoral affairs. Talbot addressed the crowd of first-year bioscience students, their families, friends and colleagues, seated in Berg Hall at the Li Ka Shing Center for Learning and Knowledge. “We are here to welcome our new partners in discovery.”

Spencer, a 22-year-old from Brooklyn, was one of 122 new bioscience students chosen from an applicant pool of 1,959 who began classes Sept. 26. On Sept. 28, the students were awarded crisp, white lab coats during an annual ceremony welcoming them to their graduate-level studies at Stanford.

“All I know about the ceremony is I’m not supposed to put on the lab coat until I walk across the stage,” said Spencer, chatting before the start of the event about how his research interests in plant biology could have relevance for human health by solving problems related to nutrition and food security. “I just wasn’t quite sure how yet.”

‘A formal start’

“It’s like a formal start to everything,” said another new graduate student, Ron Shanderson, an Atlanta native whose childhood love of dinosaurs morphed over time into an interest in cancer biology.

The students, who sat grouped together according to their departments, listened as Talbot welcomed them and introduced Lloyd Minor, MD, dean of the School of Medicine.

“The key is this: Don’t become discouraged,” Minor said. “This is a game of the long haul. … What may seem like a small advance later may be one of the most impactful things that you’ve done in your life.”

Minor shared a quote by School of Medicine faculty member Michael Levitt, PhD, reflecting on his career after winning the Nobel Prize in chemistry in 2013: “‘You never really have a single “Eureka” moment. There are a lot of small steps. Each time you solve a step, that’s great — but there’s another step. It’s really important not to give up.’”

Minor added, “In fact it was only in looking back at his science in his early years that he could understand how every step mattered. … His research in the early 1980s directly led to a $40-billion industry in anticancer drugs.”

Receiving lab coats

As the speeches ended, the students lined up to receive their coats. Biochemistry students came first, followed by those in bioengineering, then biology, and so forth. Like all the other students, Spencer folded his white coat across his left arm and got in line, then walked across the stage, put on his new lab coat with help from Talbot, and shook the dean’s hand.

The crowd cheered as each student walked across the stage. Family members and friends took photos.

The new graduate students — 56 women and 66 men — are entering 14 different bioscience programs, such as biochemistry, neurosciences and genetics. Eighteen already have advanced degrees, and 26 are considered underrepresented minorities in the biosciences. Twenty-six were born in countries outside the United States, including Panama, Hong Kong and Venezuela.

Spencer’s father, a plumber, and his mother, a babysitter, weren’t able to make it to the ceremony. Both his parents, who immigrated to the United States from the West Indies, were back home in New York. He said his grandfather made him promise he’d visit him in the West Indies when he graduated.

“When I told my parents I might be a plant scientist, my father wasn’t quite sure about it,” Spencer said. He said he’s both excited and overwhelmed by the opportunity to improve the future of human health through plant research.

As each of the various faculty members introduced their new students, and watched them put on their coats, they offered words of welcome.

“We look forward to seeing what you can do,” said Tony Ricci, PhD, professor of otolaryngology, who introduced the neurosciences students.

Students chatted and laughed as they left the building, heading out to take a group photo and join the dean for a reception and dinner on the Alumni Lawn.

They adjusted their new coats, some too big, some too small, some just right.

“We’re in now,” one student said as she walked outside. “They can’t take it back, right?”
Community advisory board new resource for Stanford researchers

By Ruth Schechter

Ryan Marlow, PhD, a Stanford instructor of psychiatry and behavioral sciences, was conducting a study on mental health education and interventions in local schools. He wanted children to participate in the three-year project, as well as retain them, was becoming a challenge. He also was having trouble developing relationships with community teachers and families up to date on his study's progress.

So Marlow decided to present his study to the Community Advisory Board for Clinical Research for feedback and assistance.

"The board had some really good ideas on engagement and retention, and gave me some specific recommendations on how to restructure the multi-phase partnerships of the project," he said. "Presenting to an impartial audience also helped confirm to me that my basic assumptions about the right approach were correct.

Help reaching diverse participants

The board is made up of 23 Bay Area residents from diverse backgrounds and communities who are involved in health care, education, law, public service, community groups, business and religious organizations. In goal is to provide insights and advice to Stanford investigators on recruiting study participants from a broad range of ethnicities, cultures, ages and economic backgrounds. The board also offers advice on ways to appeal to those who might not normally sign up for a research study.

The board was established in March by the Stanford Center for Clinical Research, in partnership with the Office of Community Engagement in the Stanford Center for Population Health Sciences. The board is one of only a handful of such enterprises in the country focused on clinical research engagement in the community. Members were carefully selected and received training in research fundamentals, as well as their roles and responsibilities for their volunteer service.

"Researchers often struggle to engage diverse communities in their projects. The solution is to encourage them to participate as partners, which also means going back to the very roots or resources," said board member Nancy Brown, PhD, a clinical investigator and education projects manager at the Palo Alto Medical Foundation.

"The idea here is to bring to the table different people to share different perspectives. It's a resource to help researchers think about their stakeholders so they don't go it alone," she said.

At one recent presentation, for example, board members suggested that a research team include more detail about its methodology. After further discussion they recommended including information for children to make them feel more involved in the research, providing travel vouchers to help with transportation costs and creating video testimonials for a registration website.

"Study design involves all phases, from concept to dissemination. Refinements can be incorporated at any stage," Prochaska said.

Giving presentations

Investigators are asked to provide a project overview to board members in advance of meetings and discuss questions they have about the organization's processes or pending strategies. Current research is reviewed on a monthly basis.

"We understand how difficult it is to get people to participate in a study, and we really want to help," said Prochaska and the board co-chairs plan to evaluate the board's role on a regular basis, using feedback from both researchers and board members after each session, and surveying presenters to determine what kind of feedback would best aid their projects.

Many of the board members are well-connected in their community and can network to help publicize research recruitment efforts. "The goal is to get away from the standard marketing and recruitment approach, and be creative in how we reach people," said Prochaska.

In the meantime, Matlow has incorporated some of the board's suggestions on how to better coordinate the multiple administrators, schoolteachers and families involved in his three-year research project.

"They're the perfect group to go to, and they are a great resource for Stanford Medicine researchers," she said.

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"They're the perfect group to go to, and they are a great resource for Stanford Medicine researchers," she said. "It's a neutral and confidential setting to process how to manage some of the complexities of designing and refining a research project. And there's a foundation there if I want to go back."

More information is available on the Stanford Center for Clinical Research website.
The Zika virus, which is spread by the mosquito genus *Aedes*, is of the virus are currently occurring in multiple countries and in three American territories: American Samoa, Puerto Rico and the U.S. Virgin Islands. Local mosquito-borne transmission has also been identified in two areas of Miami, and the World Health Organiza- tion has designated the disease a public health emergency of international concern. “Our study brings attention to the possibility that other infected embryonic cell types in the developing head can influence Zika-associated birth defects, including microcephaly, perhaps through signaling to neighboring cells or by serving as a viral replication reservoir,” said Wysocka. “Formation of the cranial neural crest cells and a cross-talk between brain and craniofacial development occurs during the first three months of human fetal development, which is when epidemiological studies have suggested that Zika infection correlates with poor birth outcomes.”

The researchers said that although the findings are intriguing and merit further study, their studies were conducted only on cells grown in a laboratory and it is possible that other factors related to Zika infection may affect brain size and outcomes in affected infants. Tomok Sugi, PhD, a senior scientist in Wysocka’s lab, is also a co-author of the study. The research was supported by the National Institutes of Health, the Tadjoa and John Mortagage Faculty Scholar Program from the Stanford Child Health Research Institute, the March of Dimes Birth Defect Foundation, the Howard Hughes Medical Institute, a seed grant from the Stanford Center for Systems Biology and two Ruth L. Kirschstein awards.

Stanford’s Department of Medicine also supported the work. 

Air-bag helmet could reduce impact of head in bike crashes

By Taylor Kubota

David Camarillo knows all too well that bicycling is the leading cause of sports-related chemical fusion and brain injury in the United States. He’s had two concussions as the result of bicycling accidents. While he doesn’t doubt that wearing a helmet is better than no helmet at all, Camarillo thinks that traditional helmets don’t protect riders sufficiently.

“Foam bike helmets can and have been proven to reduce the likelihood of skull fracture and other, more severe brain injury,” said Camarillo, PhD, an assistant professor of bioengineering at Stanford University. But I firmly believe that a bike helmet is there to protect against a concussion. That’s not true.”

Knowing what he does about traditional bike helmets, Camarillo, whose lab works on understanding and preventing concussion, decided to test a new type of helmet that is starting to be available in some European countries.

A paper describing the results was published Sept. 27 in the *Annals of Biomedical Engineering*. Camarillo is the senior author, and postdoctoral scholar Mehmet Kurt, PhD, is the lead author.

Reduced acceleration

The helmet Camarillo tested comes in a stocker worn around the neck. It pops up, like an air bag, around a person’s head when it senses a potential collision. It was originally designed to address the fact that people don’t like to wear helmets for aesthetic reasons. The researchers computed this air-bag helmet directly to traditional foam bike helmets.

Their results were striking.

Conducted drop tests, which are typical federal tests to assess bicycle helmets, and we found that air-bag helmets, with the right initial pressure, can reduce head accelerations five to six times com- pared to a traditional bicycle helmet,” Kurt said.

The drop test consisted of putting the helmets on a dummy head containing accelerometers and dropping it, neck-side up, from various heights onto a metal platform. The head form was tilted at two different angles, simulating hits to the rear of the crown in the brain. Researchers dropped the helmets from as low as 0.8 meters to as high as 2 meters and measured concussion metrics before each drop in order to get these results.

“As our paper suggests, although air-bag helmets have the potential to reduce the acceleration levels that you experience during a bicycle accident, it also suggests that the initial pressure that your air-bag helmet has is very critical in reducing these acceleration levels,” Kurt said.

Without the maximum amount of air, the air-bag helmet could bottom out, causing the head to hit the ground with much more force than if it were wearing a traditional foam helmet. In current versions of the air-bag helmet, a chemi- cal process triggers expansion, which doesn’t seem to guarantee maximum air pressure.

Linear acceleration and concussion

In this study, the researchers measured linear acceleration of a head upon impact to determine the risk of skull fracture and head injury. Linear acceleration does not directly relate to risk for concussion. Concussion is a rapidly evolving area of research, but experts currently think that it may be related to angular stretching of the brain, which is more likely caused by a rotating motion rather than linear motion.

“There are many theories as to why concussion happens, but the predomin- ant one is that, as your head rotates very quickly, the soft tissue within your brain contorts and, essentially, what you get is a stretching of the asons, which are the wiring of the brain,” Camarillo said.

The drop test used in this study is cur- rently the standard test for bicycle helmets. Testing the abilities of the helmets to reduce rotational forces would better reveal how they could protect against concussion, Camarillo said. However, given the large advantage of the air-bag helmet in this research, there is a good chance it would reduce the likelihood of concussion compared to a foam helmet, he said.

Better helmet testing

The air-bag helmet is not available in the United States but is sold in some Eu- ropean countries.

“If our research and that of others begins to provide more and more evi- dence that this air-bag approach might be significantly more effective, there will be some major challenges in the U.S. to legally have a device available to the public,” Camarillo said. Even for

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Mosaic
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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 would help out.” 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 other daughters and picnic on the Stanford campus, waiting patiently to hear how the surgery went. In the evening, they went to see Astrea. “The first thing she said was, ‘I’m in a station wagon,’” 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 re-sealing of 96 percent of the hole, which would raise additional testing issues, including the fact that helmets are generally tested on a head dummy without a neck, which couldn’t wear the air-bag helmet. “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 had 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 listens 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.

Other Stanford-affiliated co-authors are former graduate student Charles Gawad, MD, PhD; assistant professor of pediatric cardiology Scott Ceresnak, MD; postdoctoral scholar Frederick Dewey, MD, PhD; former pediatric electrophysiology fellow Lindsey Malloy-Walton, DO, MPH; genetic counselors Kyla Dunn, MS, and Megan Grove, MS; assistant professor of medicine Marco Perez, MD; senior research scientist Norma Neff, PhD; clinical associate professor of cardiothoracic surgery Katsuhide Maeda, MD; professor of pediatrics Anne Dubin, MD; and professor of cardiovascular medicine Thomas Quertermous, MD.

This work was supported by grants from the National Institutes of Health.

Stanford’s Department of Medicine also supported the work.

Co-authors Ashley and John West are co-founders of Personalis Inc., which performs clinical genetic testing, and performed sequencing for the study.

Helmet
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conventional foam helmets, the standard testing doesn’t address some elements that science indicates matter when it comes to brain injury and head trauma, including assessment of rotational forces and drop tests of parts of the helmet other than the crown. The air-bag helmet would raise additional testing issues, including the fact that helmets are generally tested on a head dummy without a neck, which couldn’t wear the air-bag helmet.

Future air bag helmet research

The researchers plan to test how the air-bag helmet affects rotational accelerations and forces on the head during impact, and how it could reduce tissue-level strains in the brain. The researchers also want to more thoroughly understand how the air cushioning holds up.

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.

“Well 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 genetics 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 arhythmia?’ 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.

Eating, drinking and being merry at staff BBQ

Alberto Louvet, Nghi Le and Natalia Kassouleva attend a School of Medicine Staff Appreciation Barbecue, featuring a catered lunch and live music, on Oct. 4. This year, the barbecues were held at five different campus locations on five different days. At each, Lloyd Minor, MD, dean of the School of Medicine, and Marinia Cohen, senior associate dean of finance and administration, thanked the staff for all they do to support students, advance research and keep the medical school humming.
Gene could help explain insulin resistance, researchers say

By Jennie Dusheck

Health researchers have known for decades that Type 2 diabetes results from a phenomenon called insulin resistance, but what causes insulin resistance has remained a mystery.

Now, researchers at the School of Medicine and the University of Wisconsin-Madison have begun to untangle a web of connections that includes a gene; mitochondrial DNA, which produce energy for cells; insulin resistance; and how well the body’s metabolism functions.

“We’ve identified a mechanism for insulin resistance that involves a gene that ties insulin resistance to mitochondrial dysfunction,” said Joshua Knowles, MD, PhD, an assistant professor of cardiovascular medicine at Stanford.

A paper describing the work was published in the Oct. 1 issue of Cell. Knowles is the senior author, and Indhumathi Chennamsetty, MD, a postdoctoral scholar at Stanford, is the lead author.

Insulin is a hormone secreted by the pancreas that helps fat and muscle cells take glucose from the blood. When a person’s cells stop responding to insulin, the person has insulin resistance and glucose builds up in the blood, signaling the pancreas to produce ever more insulin.

Insulin resistance severe enough to damage body tissues is a problem. One 2015 study estimated that nearly 35 percent of all U.S. adults are sufficiently insulin resistant to be at greater risk of diabetes and cardiovascular disease. The environmental causes of the skyrocketing rate of insulin resistance in the United States include poor diet and sedentary habits, but the molecular mechanisms have been unknown, said Knowles.

Suspect gene

Previous work by Knowles and his team linked a variant of a human gene called NAT2 with insulin resistance in humans. In mice, suppressing a similar gene, called Nar1, caused metabolic dysfunction, including decreased insulin sensitivity and higher levels of blood sugar, insulin and triglycerides.

The new study shows that suppressing the expression of the Nar1 gene in mice interferes with the function of mitochondria—cell structures that make ATP, the energy currency of cells. Without ATP, cells cannot live and function.

In 2011, mice whose Nat1 gene had been eliminated gained more weight and had larger fat cells than mice with the Nat1 gene.

Exactly why the Nat1-free mice have trouble running is something Knowles and his colleagues are still working out. “Is that physically an effect on muscle, skeletal muscle? Is that an effect on the heart? We don’t know exactly yet,” he said. Upcoming work will focus on identifying a factor that links all these metabolic effects.

A team led by Joshua Knowles has begun to untangle the cause of insulin resistance, which can increase the risk of developing Type 2 diabetes.

By Jennie Dusheck

Researchers at the University of Wisconsin-Madison also are co-authors of the study.

This research was supported by an American Heart Association Fellow-to-Faculty Transition Award, the LeDucq Foundation and the National Institutes of Health.

Stanford’s Department of Medicine also supported the work.

CARLA SHATZ, PhD, the Sapp Family Provostial Professor, the David Starr Jordan Director of Bio-X and a professor of biology and of neurobiology, was awarded the 2016 Antonio Champa l i m a r d Vision Award, which recognizes groundbreaking research on how eyes send signals to the brain. Shatz shared the price of $1.1 million with Elena Marin-Bejerano, a molecular biologist at the University of California, San Francisco.

Previous winners of the award have included Nobel Prize winners. Shatz’s lab is working on the mechanisms that control neuronal development and are investigating molecular mechanisms that control the development of the nervous system.

Aimee Hersh, MD, an assistant professor of oncology, and her colleagues at Intermountain Healthcare were awarded a $75,000 grant focused on improving patient care for survivors of cancer.

The one-year, $75,000 award is part of the $482,000 Intermountain-Stanford-Collaboration Grant Program, which will support research to improve bone and heart health in people with chronic kidney disease.

This research is supported by the National Institute of Diabetes and Digestive and Kidney Diseases, the National Heart, Lung, and Blood Institute, and the Patient-Centered Outcomes Research Institute.