The Washington Post
Democracy Dies in Darkness

A new, more diverse human genome offers hope for rare genetic diseases

The first draft of the pangenome is based on the full genetic blueprints of 47 people from around the world

By Mark Johnson

May 10, 2023 at 11:00 a.m. EDT

The landmark deciphering of the human genome more than two decades ago allowed doctors to solve thousands of medicine's cruelest mysteries, including the reason 10-year-old Celia Steele has never walked or talked, and now needs tubes to deliver oxygen and food. Deep in the genetic blueprint of the Wichita girl, doctors discovered the cause: two mutations in PDE2A, one of the 20,000 genes in the body. Just four people in the world share her condition.

The answer mattered deeply, but it came with disappointment. Doctors have yet to find a treatment. As powerful and transformative as the sequencing of the human genome has been, the medical revolution it kick-started still falls short, often delivering explanations for illness but no solution.

But hope for Celia and millions of other people with hereditary diseases rose on Wednesday with the announcement of a second scientific landmark: a new, more detailed version of our genetic code that finally begins to account for human diversity — a factor of critical importance to medicine.

Until now, doctors have been comparing their patients to a genetic yardstick heavily weighted toward people of White European ancestry. The first draft of the human genome, released in 2001, relied on one man in Buffalo for about 70 percent of the code.

"There is so much frustration in medicine about how we are operating with such a lack of fundamental knowledge," said Eric Green, director of the National Human Genome Research Institute. "We will look back on how we practiced medicine, and we will be astonished at how barbaric it was."

The pangenome, unveiled in the journal Nature, is based on the full genetic blueprints of 47 people who were sequenced between 2008 and 2015 for another study, including some of African, Asian, Caribbean, American and European ancestries. Scientists hope to expand the new tool over the next two years to incorporate 350 genetic blueprints from around the world.

While the human genome is like a single road, the pangenome resembles a subway map, converging in parts of the sequence that are common to most people and branching out in areas where we differ.

"We can see human variation as if through a new microscope. We'll now be able to make new associations to predict diseases and disease outcomes," said Evan Eichler, a professor of genome sciences at the University of Washington, and one of more than 120 scientists who worked on the five-year, $40 million pangenome project.

Eichler stressed that the pangenome ("pan" comes from the Greek word for "whole") still needs far greater representation from the Middle East, Africa and Oceania, which includes Australia, New Zealand and Papua New Guinea.

This broader version of humankind's genetic architecture builds on previous drafts of the genome. The most complete version yet, unveiled last year, uncovered the mysterious final 8 percent of our code, including millions of new genetic variants — 622 of them linked to disease.

It is likely to be years before many Americans benefit directly from the pangenome. Even if scientists do not find a cure, Celia's mother, Teresa Cruz-Steele, dreams that the pangenome will help experts discover better ways to treat the girl's seizures: "I'm kind of hoping for that, so I can get back my happy child."

Among its early results, the project has aided groundbreaking research into the genetic underpinnings of autism, a disorder estimated to affect 5.4 million adults in the United States.

Eichler, who is one of the researchers on the autism project, said the pangenome helped scientists separate genetic variants that appear in the general population from those that are specific to autism. It also led to the discovery of 150 genes that had not previously been linked to the disorder.

The idea for the pangenome came from bacteria researchers, who realized that they needed multiple genomes to capture true diversity within a species. The human project, carried out by an international consortium of institutions in the United States and Europe, delved deeply into some of the most difficult regions of our genetic code, areas made of long repeating sequences that were devilishly hard to tease apart.

“You realize that there was a degree of genetic complexity that we were completely blind to,” said Eimear Kenny, one of the pangenome researchers and director for the Institute for Genomic Health at Icahn School of Medicine at Mount Sinai. “We just didn’t have the microscope to see it.”

Dramatic improvements in sequencing and computational technology fueled the pangenome research, in part by bringing down the cost of the process.

“There were announcements just this year that we will soon have a $100 human genome,” Kenny said. “That’s an extraordinary leap forward from the 3 billion or so dollars it cost to sequence the first human genome.”

Even with its limitations, the basic ability to map a person’s unique genetic blueprint has had a profound effect on medicine.

“Oh, it’s night and day,” said Tom Curran, executive director and chief scientific officer of the Children’s Mercy Kansas City Research Institute.

Consider cystic fibrosis. Children with the disease often died because doctors lacked the precise molecular diagnosis required to match them to the right treatment, Curran said. The number of children saved by getting the right treatment, he said, meant “we had to invent adult clinics for cystic fibrosis. There is now a cohort of [cystic fibrosis] patients who would never have lived before.”

Then there’s cancer, which will kill an estimated 610,000 Americans this year.

“Cancer is fundamentally a disease of the genome,” said Andrew Futreal, chairman of the department of genomic medicine at MD Anderson Cancer Center in Houston. Measuring patients’ genetic blueprints and comparing them with the altered versions found in their tumors allows doctors to see what has changed, and helps drug developers to target specific points where they can prevent change, or lessen its effects.

Beyond its impact on any single illness, the human genome marked “a tectonic shift in the way we think about health and diseases,” said Stanley Crooke, the chairman and CEO of n-Lorem Foundation, a Carlsbad, Calif.-based nonprofit that helps people with the rarest of mutations, those that cause diseases affecting fewer than 30 people worldwide. “It’s teaching really important lessons about human life.”

One such lesson is that while Celia Steele’s disease is extraordinarily rare, her predicament is not. There are about 10,000 rare diseases, most of them hereditary; all told, they afflict 30 million Americans, or roughly 1 person in 10.

For many of the affected families, the pain and doubt of not knowing what caused an illness can feel overwhelming. Finding an answer — even one that comes without cure or treatment — often has great meaning.

Jean-Baptiste Le Pichon, professor of pediatrics in the Division of Neurology at Children’s Mercy Kansas City, recalled explaining to a mother that a genetic mutation was to blame for her son’s autism.

“She dissolved into tears because she finally had an answer and she had a relief,” he said. “She knew it wasn’t something she did. Her entire life — she told me this on the phone — she had wondered what she had done wrong while she was pregnant to cause this child to have autism.”

For much of Celia’s life, her family has struggled to understand why her twin bother, Corbin, born just one minute and one second after her, shared none of her symptoms.

Corbin hit all his developmental milestones on schedule: rolling over, crawling, sitting, standing, walking, talking.

“He was doing those things, and she wasn’t,” Celia’s mother said.

Celia had strange jerking arm movements. She would tense up suddenly. Teresa and her husband, Cornell, used pillows to prop up Celia whenever she tried to sit; otherwise she fell backward. She didn’t start crawling until she was 2.

At 5, Celia was still crawling and had learned the words, “Mama” and “what.” Then her progress unraveled. About age 7, she began to lose the ability to crawl and say the occasional word. She had trouble breathing. She experienced seizures, sometimes more than 100 in a day. Her eyes would roll back. Her hands would jerk up at her sides as if in surrender.

In 2020, after the family returned from a Make-A-Wish trip to Walt Disney World in Florida, Celia’s condition suddenly grew dire.

“We just couldn’t keep her oxygen up,” Teresa said. “Whatever we tried, we just couldn’t do it.”

Celia wound up in the pediatric intensive care unit at Children's Mercy Kansas City, where a machine had to breathe for her. It was not her first trip to the emergency room, nor her last. Celia's parents estimate there have been somewhere between 15 and 20.

Running on little sleep after nights spent listening for the warning beeps from Celia's ventilator and oximeter, Teresa would tell her four other children: "I go to battle for you guys, but I am in a war for Celia."

Over the years, doctors tested Celia, seeking a genetic explanation for her condition. Always the tests came back with no answer. Her mother felt defeated.

Celia was enrolled in the Genomic Answers for Kids program at Children's Mercy, which has analyzed the genetic blueprints of about 6,000 patients, boys and girls for whom all other tests had failed.

In September 2020, a genetic counselor phoned Teresa with the results from Celia's test. Her condition had a name: PDE2A-related disorder. The gene involved carried the instructions for making an enzyme linked to other neurological disorders. To cause harm, the mutation must come from both parents. Teresa and Cornell were carriers. Each had one copy of the mutation.

"I literally felt the blood just rush down my body," Teresa said, recalling the phone call with Celia's test results. "I had to sit down. I was sitting there with my hands on my face listening to her, shaking and shaking, crying and crying. It was like a sense of relief."

Although doctors don't fully understand how the mutations cause Celia's symptoms, they know the genetic changes destroy the function of an enzyme that helps cells throughout the body receive, process and transmit signals. Some of the signals come from the brain and direct movement in parts of the body, "so when those signals aren't transmitted correctly, the body doesn't move and function as it would typically," said Rose Gelineau-Morel, a pediatric neurologist at Children's Mercy who has treated Celia and specializes in movement disorders.

There is no clear prognosis for Celia, Teresa said. "We don't know for sure if it's fatal, if it'll get worse or stay the same. We are hopeful because there is an adult who has this condition, so we know at least maybe it's not fatal. But we cannot say 100 percent."

The much more detailed pangenome fuels hope for families like Celia's because there already have been cases in which better understanding of the human genome has led to viable treatments.

The National Institutes of Health's Undiagnosed Diseases Program has searched the genetic sequences of about 2,700 patients, diagnosing around 300 through the tests. Of those, roughly 100 have received treatment for a specific disease; about 250 have been able to get treatments that provide some relief from symptoms.

In March 2022, Melissa Evans received news about her son, Logan, whose genome was sequenced after years of illness climaxing in a cardiac arrest when he was 9.

"Melissa," the doctor said, "this rarely happens, but I know what Logan has, and there's a treatment."

Melissa and her husband, Jason, adopted Logan from foster care when he was 3. He was not talking at that point, struggled with walking and showed signs of autism and attention-deficit/hyperactivity disorder. From an early age, he displayed behavioral problems.

"He got kicked out of every preschool he ever attended," said Melissa, who lives with her husband in Quinton, Va. "In second grade, he had nine suspensions. He'd throw furniture. I was getting a phone call every single day. 'Hey can you calm Logan down?'"

On the evening of Dec. 14, 2021, he began vomiting and had to be taken to the emergency room of a local hospital. His blood sugar level was at 7; it should have been around 120. Logan was then taken by helicopter to MedStar Georgetown University Hospital. There he flailed away at his intravenous and medication lines, as well as at the tubes in his chest that helped remove the fluid accumulating around his lungs. Hospital staff placed his arms and legs in restraints and administered the antipsychotic drug Haldol.

Shortly afterward, the Evans were told that their son had suffered a cardiac arrest, a rare side effect of the medication. When they entered the room a nun was already there. Jason remembers telling her, "Your being here terrifies us. It's a sign he is not going to make it."

Doctors were able to stabilize Logan, who was later transferred to Children's National Hospital. While there, his genome was sequenced.

A few months later, medical geneticist Seth Berger discovered a harmful mutation in the gene SLC6A8, which had impaired the body's ability to transport an important source of energy called creatine. Logan's condition, which is known to have affected about 300 people around the world, could be treated.

Since starting on supplements that boost his creatine levels, Logan has changed dramatically. He takes about 50 pills a day, but he is able to work with his parents on vocabulary assignments. He no longer lashes out at school, and for the first time in years he can ride the bus to school with the other children.

"It's groundbreaking, and it completely changed the course of his life," said Kyle Moser, his former assistant principal. "If we can do this for one child, we should continue the research."