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Sonia Fernandez

A Confluence of Rare Mutations

Three decades ago, UC Santa Barbara neuroscientist Kenneth S. Kosik first started studying a Colombian family afflicted with a genetic form of early-onset Alzheimer's disease. He and fellow researchers realized that they were only scratching the surface of largely invisible, yet profound, consequences of the colonization carried out by the Spanish almost five centuries in the past.

"When my colleagues were conducting this clinical trial on the individuals in this very large rural family that carried this mutation, they needed as many participants as possible," Kosik said, recalling efforts to recruit people for the study. The family in question, which comprises several thousand people, was unique. Members that carried the so-called Paisa mutation would, like clockwork, begin to develop the hallmark forgetfulness of Alzheimer's — what they called *la bobera* — in their 40s. Working with Colombian neuroscientist Francisco Lopera, the researchers tried to cast as wide a net as they could to find even those in remote parts of the country with early-onset dementia that caused so much undue suffering in Colombia.

The extent of the condition was far more than they anticipated — their investigation yielded genetic results that reach back millennia and span several continents. The researchers' work is published in the journal Genome Medicine.

Far-flung Origins

Juliana Acosta-Uribe remembers the early days of that study. Then a medical student, she was wrapping up her studies en route to becoming a physician scientist

with a year devoted to social service.

“We were getting over a thousand phone calls from people with early-onset dementia in their families,” said Acosta-Uribe, now a project scientist in the Kosik Lab and lead author of the paper. “And we were testing them to see if they were part of family with the Paisa mutation.”

But as they tested these people for the PSEN1 E280 mutation, as it is formally known, the researchers’ assumptions that their new patients were somehow a subset of the original family evaporated. The vast majority of tests came back negative. Further testing revealed that the researchers had a concentration of unrelated families with different mutations that resulted in the same observable characteristics.

“We’ve gotten pretty good at identifying different mutations that lead to neurodegenerative diseases —their genotype.” Kosik said. “But we don’t really understand the relationship between the genotype and their phenotype — that is, what they look like clinically, what type of dementia they get, how it comes on, what mechanisms are affected.”

Genomic testing yielded only part of the story, with information that seemed at first to only deepen the mystery. The famous Paisa mutation, for instance, had been traced back to a single founder from early Habsburg Spain, while another mutation was traced back to West Africa. Yet another was identified with Native American roots. How had they all emerged in the rural countryside of Colombia?

Clues to this phenomenon may be found in Colombia’s history and the movement of people across the globe.

“So many different factors of the demography and the history of the population and its movement shaped the current risk burden of Alzheimers disease,” said Acosta-Uribe. During the time of Spain’s conquest of the Americas, Europeans first showed up on the northern shores of what would become Colombia in the early 16th century, making efforts to settle and colonize the area. Later that century, West Africans would be added into the mix as enslaved labor.

People weren’t the only ones mixing in Colombia at that time, however.

“People do not travel alone,” Acosta-Uribe said. “People travel with their bugs.” According to the researchers, the people traded their bugs with others who had never encountered them before and the population “suffered massive mortality from numerous infectious diseases, including smallpox, influenza, syphilis, hepatitis, measles, encephalitis, tuberculosis, diphtheria, cholera, typhus, scarlet fever and meningitis.”

The collapse of the population caused a narrowing of the gene pool — a genetic bottleneck in which the few remaining survivors, who also happened to possess these rare mutations, became the founders of subsequent populations, passing their mutations to their offspring. A long period of colonization followed in which migration slowed and people mostly stayed put. The lack of new genes, isolated pockets of people and large families helped establish the mutations within the population.

“If they have several generations of large families, those mutations get amplified, and they get amplified locally, because the people are not moving around,” Kosik explained. “And what we begin to see in Colombia is that the genetic map overlaps with the geographic map, because you can actually match people with a mutation to a certain region.”

This mechanism explains how the mutations were able to proliferate in the population over generations. But the researchers’ investigations sparked another question, one that was difficult to ignore.

“When you put a selective pressure, such as pathogens, into a population, the question that arises is, do the survivors have any benefit over the ones who died?” Acosta-Uribe said. Could having these mutations — in particular variants of the PSEN1 (presenilin) gene — have conferred some sort of protection to their carriers against the onslaught of infectious disease in the early days of colonization, thereby ensuring their survival?

This would not be an unusual situation, according to Acosta-Uribe.

“There are many examples of selection for people who have a genetic variant that in other conditions could be detrimental,” she said. For example, she pointed out, people who are heterozygous (one copy of a mutated gene from one parent and one normal copy from the other) for sickle cell anemia are resistant to severe malaria. The mutation that leads to the sickle-shaped cells also “interferes with the reproductive cycle of the malaria parasite.”

Unfortunately, the notion that having these PSEN1 mutations helped their carriers fend off deadly infectious diseases might forever be in the realm of speculation, Kosik said.

“We can’t replay the tape of life,” he said. “We can’t replay everything that happened there to prove it, but it’s fairly credible.” Two tantalizing bits of circumstantial evidence in this mystery: a total of 13 mutations to the PSEN1 gene found in the Colombian cohort alone (a “statistically unusual” concentration of these rare mutations for a country of Colombia’s size and population), and antimicrobial properties of the peptides that cause the sticky insoluble plaques that are characteristic of Alzheimer’s disease.

“It turns out that the amyloid beta peptide may have an antimicrobial function; there’s this very ancient system of protection against invading organisms in which an antimicrobial peptide gloms onto the invading organism and walls it off from the rest of the body,” Kosik said. The speculation is that this particular mutation may have been positively selected perhaps because it protected people from disease. His lab is investigating this effect with an even deeper look at the genomes in their cohort, but at best it may remain a statistical argument, Kosik added.

As the Kosik Lab continues its work, with the results of a major clinical trial just around the corner, it’s clear that the huge genomic dataset they’ve generated is only the tip of the iceberg when it comes to the genetics of illnesses in the global population.

“We’ve generated a unique dataset that can help us understand the genetics of illnesses in non-white populations,” Acosta-Uribe said. The majority of genomic data concentrates on European genomes, which can obscure much of the picture when it comes to gene-related diseases in the human population, she added. This is especially true of the connections between mutations and their physical outcomes.

For instance, in her survey of the genomes for this project, Acosta-Uribe found that the same mutations and pathologies that present themselves in the European context as ALS (also known as Lou Gehrig’s disease) present in the Native American lineage as frontotemporal dementia. Additionally, tracing the Native American mutation backward through time, she found that it originated with the first population of the Americas.

“We compared the Colombian carriers of these variants with the Asian carriers of this variant,” Acosta-Uribe said, “and we identified that indeed Colombians had gotten it back from their ancestors who migrated through the Bering Strait and populated the Americas more than 30,000 years ago.”

Back in the present, this new knowledge can provide some clues to members of the Colombian cohort as to why the genetic form of Alzheimer’s disease is so prevalent in their families. It also underscores the value of collaboration in the effort to understand and potentially treat this as-yet-incurable disease. One bright spot: One woman in the family with the Paisa mutation lived her entire life without developing Alzheimer’s, possibly because a second copy of the rare genetic mutation decoupled the two hallmark signs of the disease: amyloid beta plaques (which were found in her brain after her death), and tau tangles (which were not found).

“This paper led us to develop tight bonds with the scientific community and with the families in Colombia,” Acosta-Uribe said. “We were able to explain to the families why this was happening to them and tell them that while we may not yet be able to cure them, we will be there with them.”

Research in this project was also conducted by Bradley W. Killingsworth, Rijul Singhal, Sarah Labib and Nithesh Perumal at UCSB; David Agillón, Margarita Giraldo, Lucía Madrigal, Diana Alzate, Lina Velilla, Sonia Moreno, Gloria P. García, Amanda Saldarriaga, Francisco Piedrahita, Liliana Hincapié, Hugo E. López, Dionis Vallejo, Juan Marcos Solano and Andrés Villegas-Lanau at Universidad de Antioquia; Ezquiel I. Surace, Tatiana Itzcovich and Ricardo Allegri at Fleni-CONICET; Eric M. Reiman at Banner Alzheimer's Institute; Raquel Sánchez-Valle at University of Barcelona; Charles L. White III at University of Texas Southwestern Medical Center; Diana Matallana at Pontifical Xaverian University; Richard Meyers at HudsonAlpha Institute for Biotechnology; and Sharon R. Browning at University of Washington.

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