

HEALTH

The Secret to Long Life? It May Lurk in the DNA of the Oldest Among Us

James Clement has scoured the globe for supercentenarians, aged 110 and older, willing to contribute their genomes to a rare scientific cache.

By AMY HARMON NOV. 13, 2017

As one of the exceedingly rare members of her species to live beyond age 110, Goldie Michelson had divulged her secrets to longevity countless times before dying last year at 113.

“Morning walks and chocolate,” the Gloucester, Mass., resident and onetime oldest living American told the steady stream of inquisitors that marked her final years.

Unlike the growing ranks of nonagenarians and centenarians, those who breach a 12th decade, known as supercentenarians, rarely face protracted illness or disability before they die, a boon that many of them have ascribed to personal habits.

“I try to live the truth,” said Shelby Harris, who threw out the first pitch of the local minor league baseball team’s 2012 season a few months before he died at 111 in Rock Island, Ill. Emma Morano of Verbania, Italy, still cooking her own pasta until a few years before she died last April at 117, prescribed raw eggs, and no husband.

But even as they indulged the notion that exceptionally healthy longevity can be explained by lifestyle, each agreed to donate DNA to a private effort to find the secrets in supercentenarian genes.

The full genetic sequences of Ms. Michelson, Mr. Harris and Ms. Morano are among some three dozen genomes of North American, Caribbean and European supercentenarians being made available this week by a nonprofit called Betterhumans to any researcher who wants to dive in.

A few additional genomes come from people who died at 107, 108 or 109. If unusual patterns in their three billion pairs of A's, C's, G's and T's — the nucleobases that make up all genomes — can be shown to have prolonged their lives and protected their health, the logic goes, it is conceivable that a drug or gene therapy could be devised to replicate the effects in the rest of us.

“I hope you find something that does someone some good,” said Clarence Matthews, 110, who allowed his blood to be drawn as a final contribution to the database last year at his Indian Wells, Calif., home while I watched at his side.

One in Five Million

The rare cache of supercentenarian genomes, the largest yet to be sequenced and made public, comes as studies of garden-variety longevity have yielded few solid clues to healthy aging. Lifestyle and luck, it seems, still factor heavily into why people live into their 90s and 100s.

To the extent that they have a genetic advantage, it appears to come partly from having inherited fewer than usual DNA variations known to raise the risk of heart disease, Alzheimer's disease and other afflictions.

That is not enough, some researchers say, to explain what they call “truly rare survival,” or why supercentenarians are more uniformly healthy than centenarians in their final months and years.

Rather than having won dozens of hereditary coin tosses with DNA variations that are less bad, scientists suggest, supercentenarians may possess genetic code that actively protects them from aging.

But the effort to find that code has been “challenged,” as a group of leading longevity researchers put it in a recent academic paper, in part by the difficulties in acquiring supercentenarian DNA.

The New England Centenarian Study, one of a handful of longevity research groups around the world focusing on supercentenarians, now turns down prospective DNA donors under age 103: “We tell them they're too young,” said Dr. Thomas Perls, the study's director.

The DNA sequences being released this week were acquired almost single-handedly by James Clement, 61, the founder of a company advised by the prominent Harvard geneticist George Church.

A professed citizen-scientist, Mr. Clement collected blood, skin or saliva from supercentenarians in 14 states and seven countries over a six-year period. Many were still gardening, arguing, driving and flirting. Ms. Michelson, for one, was fond of reading and reciting Shakespeare.

The usefulness of such a small group for a genetic study is unclear, which is one reason Mr. Clement's company, now defunct, has turned into a crowdsourcing project.

Complex traits like height, body mass index and disease risk — phenotypes, as they are known in genetics-speak — typically arise from a combination of hundreds of places in the genome where the DNA alphabet differs between individuals.

Zeroing in on which variations affect which phenotypes requires the statistical power of tens of thousands of DNA samples — almost certainly a dealbreaker when it comes to supercentenarians, whose verified number, worldwide, hovers at around 150.

On large swaths of the planet, where birth records are sketchy or nonexistent, identifying verified supercentenarians is virtually impossible. In the United States, researchers say supercentenarians account for about one in five million people.

Amateur genealogists dedicated to validating the ages of the world's oldest people estimate that even the unverified total comes to only about 1,000.

Still, some researchers hope that despite the limited number of available genomes, it will be possible to identify the secret sauce of supercentenarians with methods used to uncover the genetic basis for other rare conditions. No one quite knows how many genomes might be necessary.

“This is what we call an ‘extreme phenotype,’ ” said Dr. Church, who ultimately arranged for the genomes to be sequenced so that Mr. Clement could release them through a nonprofit. “The farther out you go on the bell curve, the more likely you are to find something, even with a small sample size.”

As the goal of slowing aging to extend human “health span” has gained traction in the scientific mainstream, research has largely been limited to animal studies.

A secretive Google spinoff called Calico, for California Life Company, is said to be scrutinizing the genome of the naked mole rat, celebrated for a life span 10 times longer than that of most of its rat cousins. Federally funded scientists are testing a drug on monkeys based on an experiment that doubled the lives of roundworms.

And in laboratories across the world, the markers of age in over-the-hill mice, rats and turquoise killifish are, sometimes, being reversed.

But what works in shorter-lived organisms often does not translate to humans, whose average life span in developed countries is approaching 80 years. So despite the limitations of Mr. Clement's database, several prominent researchers have already expressed interest in it.

"This could show the utility of starting a bigger collection," said Paola Sebastiani, a longevity researcher at Boston University.

An account of what Mr. Clement calls the Supercentenarian Research Project offers a glimpse at what that might entail, including perseverance, compassion and a sense of humor that trends toward dark.

Life or Death

It was an inauspicious start, Mr. Clement admitted in an email to a friend in January 2011. The first supercentenarian Mr. Clement had lined up to visit, Mississippi Winn, had died at 113 before he could get from his home in San Jose, Calif., to hers in Shreveport, La.

"RIP Miss Winn," he posted on the Facebook page that family members had set up for Ms. Winn, believed to be the last living child of African-Americans born into slavery.

Such condolences would become a familiar refrain. Of the 70,000 or so Americans who live to be 100, only some two dozen are typically alive at 110.

Once that milestone is reached, as Mr. Clement quickly learned, the chance of dying within the next year is roughly 50 percent. After 113, the odds are closer to 66 percent. The oldest person on record, Jeanne Calment, was 122 when she died in 1997; only one other person is known to have lived beyond age 118.

"Even while you're packing the car, the person may fall ill and say they're not up to it," Mr. Clement said, after the first of several plans for me to observe a DNA donation was abruptly canceled.

Mr. Clement could extract DNA from post-mortem samples, with permission from the family and assuming he could reach the funeral home in time. Exhumation is also possible, in theory, to obtain samples.

But for understandable reasons, he said, family members most often ended communications with him at the time of a supercentenarian's death. To improve the odds of getting samples —

and the gender balance, since supercentenarians are nearly all women — he lowered his target age from 110 to 106.

“It’s better to get there when they’re alive,” he said.

Guided by the World’s Oldest People email list, whose moderator, Robert D. Young, verifies ages on behalf of Guinness World Records and tracks supercentenarians for the Gerontology Research Group, Mr. Clement placed decal dots designating the locations of prospective participants on a map pinned to the wall of his home office.

He created Google alerts for the phrases “109th birthday,” “110th birthday,” and “111th birthday,” and for the obituaries of known supercentenarians.

Unlike so-called blue zones, where centenarians are said to cluster, there is no geographical shortcut for netting supercentenarians. So he called, emailed and sent Facebook friend requests to whatever contacts he could find, wherever he could find them.

A Birthday Invitation

There was, nominally, the prospect of making money.

But with a business plan that, even to some of his investors, sounded more like a research project, Mr. Clement seems to have undertaken the task largely because it provided the chance to act on a longstanding interest in human longevity, including his own.

A self-described transhumanist who eats mostly low-glycemic vegetables and nuts and walks seven miles a day, Mr. Clement has accumulated an eclectic résumé that includes starting a brew pub, practicing international tax law and cofounding a futurist magazine.

He harbors what he prefers to call a “healthy love of life,” rather than an aversion to death, and he is possessed of an apparently genuine conviction that longer lives would make humans more humane.

“My hat was off to someone who was willing to take the time out of his life to go get these precious specimens,” said Dr. Church, the Harvard geneticist, who has devoted a portion of his laboratory to research into the reversal of aging.

The kind of ultrarare mutations that supercentenarians might harbor, Dr. Church believed, were not likely to be detected with standard techniques, which scan only the places in the genome where DNA is already known to vary between individuals.

To look for as-yet-uncataloged variations would require sequencing all of the supercentenarians' six billion genetic letters, a far more expensive procedure. When he and Mr. Clement first discussed the idea in 2010, the cost was about \$50,000 per genome.

But the price was falling. And with the financial support of a handful of like-minded wealthy individuals who agreed to invest in the exploratory phase of the project, "it just seemed," Mr. Clement said, "like something I could do."

Even with the Harvard name as a calling card, several of the families he contacted over the next few years did not respond to his inquiries. A few, Mr. Clement knew, had already been approached by laboratories at Stanford and Boston University, which were collecting their own stashes of supercentenarian DNA.

"She already did her DNA donation," Paul Cooper, the grandson of Besse Cooper, a 116-year-old former suffragist, told Mr. Clement, who had driven several hundred miles to her Monroe, Ga., nursing home in 2012.

Walter Breuning, of Great Falls, Mont., one of just a handful of men known to have lived to 114, replied in late 2010 that it was his preference not to risk winter meetings. He died early the next spring.

An invitation to the 111th birthday party of James Sisnett in Barbados finally served as Mr. Clement's entree in February 2011. He died two years later.

Mr. Sisnett, who grew his own food until he was 105, was "still fascinated by seeing a nice-looking backside" when he was in his 110s, his daughter, Everine Carter, 88, recalled in a telephone interview.

Losing Precious Samples

The best time to get DNA from a supercentenarian, Mr. Clement found, is midmorning. By lunchtime, they would prefer to be eating. After lunch, they might be groggy or napping.

Most, like Dorothy Peel of London, then 108, had sharp minds. Ms. Peel inspected the informed consent form through her reading glasses and peppered him with questions about other supercentenarians he had met.

Crisscrossing Europe in 2011, Mr. Clement hit his collecting stride. But there were some bumps.

He had ordered an inexpensive kit that allowed him to prick a supercentenarian's finger and deposit a drop of blood on a card to preserve it, often used by geneticists in the field.

Within a few months he had blood drops from 15 donors, including Ralph Tarrant of Sheffield, England, who at 108 completed the London Times crossword puzzle every afternoon.

Not until he had switched to hiring a phlebotomist to perform blood draws with a needle did he learn that the cards with the original 15 samples were defective. “We could not detect any DNA,” read a 2011 email from the laboratory.

Mr. Clement confessed the news to Dr. Church in a meeting at his Harvard office. “You didn’t test the cards?” the geneticist asked him gently.

Still, Mr. Clement had 23 good samples in hand, and the cost of sequencing by this time had fallen to some \$15,000 per genome. With his remaining funds, he sequenced 15, leaving the rest in cold storage.

Mr. Clement quickly discovered 2,500 differences between the supercentenarian DNA and those of controls. But even with help from graduate students in Dr. Church’s lab, it was hard with such a small group to know which, if any, were significant.

So over the next few years, Mr. Clement, working without a salary, collected samples whenever he could, adding another dozen from supercentenarians across the United States.

In the spring of last year, a company Dr. Church had co-founded, Veritas Genetics, announced that it would sequence human genomes for \$1,000 each. Dr. Church told Mr. Clement that Veritas would sequence the remaining samples, and so he set out to collect a few more.

Advice From America’s Oldest Man

In July 2016, I was invited to accompany Mr. Clement to Mr. Matthews’s home in California. As much as I looked forward to meeting my first supercentenarian, I was not prepared to envy his win in the genetic longevity lottery.

I had feared he would be lonely, a concern echoed by several of the Facebook viewers who watched me ply him with questions over a live video stream the morning we met. “I don’t want to outlive my friends and family,” one typed. “That’s no fun.”

The prospect of shifting today’s average life span to that of the known limit of all humanity is disorienting. An average life expectancy of 80 in some ways seems generous — it was just 48 when Mr. Matthews was born in 1906. Most of us expect around 80 years on the planet, assuming nothing horrendous happens.

“When you have children the first time, it don’t come with a manual, and it don’t come with a manual when your dad gets to be 100, then 105, then 110,” said Mr. Matthews’s son, Steve, 75, who also gave blood the day we visited.

But Mr. Matthews asserted without hesitation that he still enjoyed life. Pleasures included his lunchtime smoothie, his family, the kindness of his caregiver, and — this with a nod to a New York Times photographer and a rakish grin — “having my picture taken.”

He reminisced fondly about his second wife, Katherine, who died in 1980 and with whom he had loved to dance.

At 110, he said he had never been diagnosed with a serious illness. The younger Mr. Matthews recalled that his father had played a one-under-par, 18-hole golf game on his 99th birthday. Having built a successful real estate business, he provided financial support to his last surviving sibling, a sister who was 105.

Talking to him, it was hard not to fantasize about the possibility that, as another Facebook participant suggested, “by the time we get to that age, we may all be living to 110.”

At the time the oldest man in America, Mr. Matthews sometimes strained to hear, but his sense of humor and perspective were intact. If that was what we wanted, he advised, “Keep breathing.”

Mr. Matthews died this summer. His DNA was sequenced a few weeks later, and last month Mr. Clement uploaded it to the database. Like all normal human genome sequences, the beginning of his first chromosome reads like this:

TAACCCTAACCCCTAACCCCTAACCCCTAACCCCTAACCCCTAACCCCTAACCCCTAACCCCTAACCCCTAACCCCT

Whether, in combination with the genomes of his fellow supercentenarians, the rest contains the secret to a long, healthy and happy life remains to be seen.