The man who is aging too fast

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Nobuaki Nagashima was in his mid-20s when he began to feel like his body was breaking down. He was based in Hokkaido, the northernmost prefecture of Japan, where for 12 years he had been a member of the military, vigorously practicing training drills out in the snow. It happened bit by bit—cataracts at the age of 25, pains in his hips at 28, skin

problems on his leg at 30.

At 33, he was diagnosed with Werner syndrome, a disease that causes the body to age too fast. Among other things, it shows as wrinkles, weight loss, graying hair and balding. It's also known to cause hardening of the arteries, heart failure, diabetes and cancer.

I meet Nagashima under the white light of a Chiba University Hospital room, around 25 miles west of Tokyo. A gray newsboy cap covers his hairless head freckled with liver spots. His eyebrows are thinned to a few wisps. Black-rimmed glasses help with his failing eyesight, his hip joints—replaced with artificial ones after arthritis—ache as he stands to slowly walk across the room. These ailments you might expect to see in an 80-year-old. But Nagashima is just 43.

He tells me that he has been in and out of hospital ever since his diagnosis. That his deteriorating health forced him to leave the military. Nagashima has had five or six surgeries, from his toes to hips to eyes, to treat aging-related ailments. He's lost 15 kilograms since he was first diagnosed. He needs a walking stick to do a distance over a few meters, and has a temporary job at the City Hall, going to the office when his body will allow but working from home when it doesn't.

He remembers driving home after his diagnosis, crying to himself. When he told his parents, his mother apologized for not giving birth to a stronger person. But his father told him that if he could endure this disease, he was indeed strong, and maybe scientists would learn from him, gaining knowledge that could help others.

Apart from the X and Y sex chromosomes, we inherit two copies of every gene in our bodies—one from our mother and one from our father. Werner syndrome is what's called an autosomal recessive disorder, meaning it only shows when a person inherits a mutated version

of a gene called WRN from both parents.

Nagashima's parents are aging normally. They each have one functional copy of WRN, so their bodies don't show any symptoms of the disease. But he was unfortunate to have received two mutated copies of WRN. His grandparents are still alive and as well as one might expect for a couple in their 90s, and the family are unaware of any other Werner cases in their family history.

WRN was discovered only in 1996, and since then there have been few examples of Werner. As of 2008, there were only 1,487 documented cases worldwide, with 1,128 of them in Japan.

Lest this seem like a uniquely Japanese condition, George Martin, co-director of the International Registry of Werner Syndrome at the University of Washington, thinks the number of actual cases globally is around seven times higher than the numbers recorded today. He says most cases around the world will not have come to the attention of any physicians or registries.

The huge imbalance in Japanese cases he puts down to two factors. First, the mountains and islands of the Japanese landscape and the isolating effect that's had on the population through history—people in more isolated regions in the past were more likely to end up having children with someone more similar to them genetically. A similar effect is seen in the Italian island of Sardinia, which also has a cluster of Werner cases. Second, the startling nature of the condition, and the higher frequency with which it appears in Japan (affecting an estimated one in a million people worldwide but one in 100,000 in Japan), means the Japanese medical system is more aware than most when Werner syndrome appears.

In Chiba University Hospital, they hold records of 269 clinically

diagnosed patients in total, 116 of whom are still alive. One of them is Sachi Suga, who can only get around in a wheelchair. Her muscles are so weak she can no longer climb in and out of the bath, which makes it difficult to keep up the Japanese practice of ofuro, the ritual of relaxing each night in a deep tub of steaming hot water. She used to cook breakfast regularly for herself and her husband, but now she cannot stand at a stove for more than a minute or two at a time. She's resorted to preparing quicker-to-make miso soup the night before, which he eats before leaving for work at 5.30am.

Waif-like in a short black wig, Suga has tiny wrists as delicate as glass, and she speaks to me in a hoarse, throaty whisper. She tells me of the home aid worker who visits three times a week to help wrap her ulcer-covered legs in bandages. She has terrible back and leg pain. "It hurt so much, I wanted my legs to be cut off." Yet on the positive side, the 64-year-old has long surpassed the average life expectancy of around 55 for people with Werner syndrome.

Only a handful of people with Werner currently attend Chiba. Recently, they started a support group. "Once our conversation started, I forgot about the pain completely," says Suga. Nagashima says the meetings often end with the same question: "Why do I have this disease?"

If you were to unravel the 23 pairs of chromosomes in one of your cells you would end up with about two meters of DNA. That DNA is folded up into a space about a 10,000th of that distance across—far more compacted than even the tightest origami design. This compacting happens with help from proteins called histones.

DNA, and the histones that package it up, can acquire chemical marks. These don't change the underlying genes, but they do have the power to silence or to amplify a gene's activity. Where the marks are put or what form they take seems to be influenced by our experiences and

environment—in response to smoking or stress, for instance. Some seem to be down to random chance, or the result of a mutation, as in cancer. Scientists call this landscape of markings the epigenome. We do not know yet exactly why our cells add these epigenetic marks, but some of them seem to be connected to aging.

Steve Horvath, professor of human genetics and biostatistics at the University of California, Los Angeles, has used one type of these, called methylation marks, to create an "epigenetic clock" that, he says, looks beyond the external signs of aging like wrinkles or gray hair, to more accurately measure how biologically old you are. The marks can be read from blood, urine, organ or skin tissue samples.

Horvath's team analyzed blood cells from 18 people with Werner syndrome. It was as if the methylation marking was happening on fast-forward: the cells had an epigenetic age notably higher than those from a control group without Werner.

Nagashima's and Suga's genetic information is part of a database held by Chiba University. There is also a Japan-wide database of Werner syndrome and the International Registry at the University of Washington. These registries are providing researchers with insights into how our genes work, how they interact with the epigenome, and how that fits with aging as a whole.

Scientists now understand that WRN is key to how the whole cell, how all our DNA works—in reading, copying, unfolding and repairing. Disruption to WRN leads to widespread instability throughout the genome. "The integrity of the DNA is altered, and you get more mutations… more deletions and aberrations. This is all over the cells," says George Martin. "Big pieces are cut out and rearranged." The abnormalities are not just in the DNA but in the epigenetic marks around it too.

The million-dollar question is whether these marks are imprints of diseases and aging or whether the marks cause diseases and aging—and ultimately death. And if the latter, could editing or removing epigenetic marks prevent or reverse any part of aging or age-related disease?

Before we can even answer that, the fact is, we know relatively little about the processes through which epigenetic marks are actually added and why. Horvath sees methylation marks as like the face of a clock, not necessarily the underlying mechanism that makes it tick. The nuts and bolts may be indicated by clues like the WRN gene, and other researchers have been getting further glimpses beneath the surface.

In 2006 and 2007, Japanese researcher Shinya Yamanaka published two studies which found that putting four specific genes—now called Yamanaka factors—into any adult cell could rewind it to an earlier, embryonic state, a stem cell, from which it could then be turned into any other type of cell. This method, which earned Yamanaka the Nobel Prize, has become a mainspring for stem cell studies. But what made this all the more interesting was that it completely reset the epigenetic age of the cells to a prenatal stage, erasing the epigenetic marks.

Researchers replicated Yamanaka's experiments in mice with a condition called Hutchinson–Gilford progeria syndrome, which has similar symptoms to Werner but only affects children (Werner is sometimes called adult progeria). Remarkably, the mice rejuvenated briefly, but they died within a couple of days. Totally reprogramming the cells had also led to cancer and loss of the cells' ability to function.

Then in 2016, scientists at the Salk Institute in California engineered a way to partially rewind the cells of mice with progeria using a lower dose of the Yamanaka factors for a shorter period. The premature aging slowed down in these mice. They not only looked healthier and livelier than progeria mice who hadn't had the treatment, but their cells were

also found to have fewer epigenetic marks. Moreover, they lived 30 per cent longer than the untreated mice. When the researchers applied this same treatment to normally aging mice, their pancreases and muscles also rejuvenated.

Separately, the same scientists are also using gene editing technology on mice to add or subtract other epigenetic marks and see what happens. They're also trying to modify the histone proteins to see if that can alter genes' activity. Some of these techniques have already shown results in reversing diabetes, kidney disease and muscular dystrophy in mice. The team are now trying similar experiments on rodents to see if they can reduce the symptoms of arthritis and Parkinson's disease.

The big question remains: is the disappearance of the epigenetic marks related to the reversal of cell development—and possibly the ageing of the cell—or an unrelated side-effect? Scientists are still trying to understand how changes in epigenetic marks relate to ageing, and how Yamanaka factors are able to reverse age-related conditions.

Horvath says that, from an epigenetic point of view, there are clear commonalities in aging across many regions of the body. Epigenetic aging in the brain is similar to that of the liver or the kidney, showing similar patterns of methylation marks. When you look at it in terms of these marks, he says, "aging is actually rather straightforward, because it's highly reproducible in different organs."

There's a feverishness around the idea of resetting or reprogramming the epigenetic clock, Horvath tells me. He sees huge potential in all of it, but says it has the feel of a gold rush. "Everybody has a shovel in their hand."

Jamie Hackett, a molecular biologist at the European Molecular Biology Laboratory in Rome, says the excitement comes from the suggestion that

you can have an influence over your genes. Previously there was a fatalistic sense of being stuck with what you are given, and nothing you can do about it.

Back in the Chiba hospital room, Nagashima removes one of his high-top sneakers, which he has cushioned with insoles to make walking more bearable.

He tells me about his former girlfriend. They had wanted to marry. She was understanding after his diagnosis and even took a genetic test so they could be sure they would not pass the condition on to their kids. But when her parents discovered his condition, they disapproved. The relationship ended.

He has a new girlfriend now. He wants to make her his life partner, he tells me, but to do so he must get up the courage to ask for her parents' permission.

Nagashima slips down a brown sock, revealing a white bandage wrapped around the sole of his swollen foot and ankles. Beneath, his skin is raw, revealing red ulcers caused by his disease. "Itai," he says. It hurts. Then he smiles. "Gambatte," he says—I will endure.

More information: Steve Horvath and colleagues say that the DNAm GrimAge estimator (named after the Grim Reaper) is the best epigenetic predictor of lifespan, time to heart disease, time to cancer and age at menopause. www.ncbi.nlm.nih.gov/pubmed/30669119

Horvath and team find that Werner syndrome is associated with increased epigenetic age of blood cells. www.ncbi.nlm.nih.gov/pmc/articles/PMC5425119/

Researchers at the Salk Institute show how epigenetic editing can

affect the health of mice.
www.cell.com/cell/fulltext/S0092-8674(17)31247-3

A team at the University of Washington review WRN mutations found around the world. www.ncbi.nlm.nih.gov/pubmed/27667302

Erika Hayasaki has written about twin science, which offers a window into current epigenetic research. www.theatlantic.com/science/ar …-epigenetics/560189/

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