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# Ecuadorean Villagers May Hold Secret to Longevity

By NICHOLAS WADE

People living in remote villages in [Ecuador](#) have a mutation that some biologists say may throw light on human longevity and ways to increase it.

The villagers are very small, generally less than three and a half feet tall, and have a rare condition known as [Laron syndrome](#) or Laron-type [dwarfism](#). They are probably the descendants of conversos, Sephardic Jews from Spain and Portugal who were forced to convert to Christianity in the 1490s but were nonetheless persecuted in the Inquisition. They are also almost completely free of two age-related diseases, [cancer](#) and [diabetes](#).

A group of 99 villagers with Laron syndrome has been studied for 24 years by Dr. Jaime Guevara-Aguirre, an Ecuadorean physician and diabetes specialist. He discovered them when traveling on horseback to a roadless mountain village. Most such villages are inhabited by Indians, but these were Europeans, with Spanish surnames typical of conversos.

As Dr. Guevara-Aguirre accumulated health data on his patients, he noticed a remarkable pattern: though cancer was frequent among people who did not have the Laron mutation, those who did have it almost never got cancer. And they never developed diabetes, even though many were obese, which often brings on the condition.

“I discovered the population in 1987,” Dr. Guevara-Aguirre said in an interview from Ecuador. “In 1994, I noticed these patients were not having cancer, compared with their relatives. People told me they are too few people to make any assumption. People said, ‘You have to wait 10 years,’ so I waited. No one believed me until I got to Valter Longo in 2005.”

Valter D. Longo, a researcher on aging at the [University of Southern California](#), saw the patients as providing an opportunity to explore in people the genetic mutations that researchers had found could make laboratory animals live much longer than usual.

The Laron patients have a mutation in the gene that makes the receptor for [growth hormone](#). The receptor is a protein embedded in the membrane of cells. Its outside region is recognized by growth hormone circulating through the body; the inside region sends signals through the cell when growth hormone triggers the receptor.

The Laron patients' mutation means that their growth hormone receptor lacks the last eight units of its exterior region, so it cannot react to growth hormone. In normal children, growth hormone makes the cells of the liver churn out another hormone, called insulinlike growth factor, or IGF-1, and this hormone makes the children grow. If the Laron patients are given doses of IGF-1 before [puberty](#), they can grow to fairly normal height.

This is where the physiology of the Laron patients links up with the longevity studies that researchers have been pursuing with laboratory animals. IGF-1 is part of an ancient signaling pathway that exists in the laboratory roundworm as well as in people. The gene that makes the receptor for IGF-1 in the roundworm is called DAF-2. And worms in which this gene is knocked out live twice as long as normal.

The Laron patients have the equivalent defect — their cells make very little IGF-1, so very little IGF-1 signaling takes place, just as in the DAF-2-ablated worms. So the Laron patients might be expected to live much longer.

Because of their striking freedom from cancer and diabetes, they probably could live much longer if they did not have a much higher than usual death rate from causes unrelated to age, like [alcoholism](#) and accidents.

Dr. Longo said he believed that having very low levels of IGF-1 was the critical feature of the Laron patients' freedom from age-related diseases. In collaboration with Dr. Guevara-Aguirre, he exposed human cells growing in a laboratory dish to serum from the Laron patients. The cells were then damaged with a chemical that disrupts their DNA. The Laron serum had two significant effects, [the two physicians reported on Wednesday in Science Translational Medicine](#).

First, the serum protected the cells from genetic damage. Second, it spurred the cells that were damaged to destroy themselves, a mechanism the body uses to prevent damaged cells from becoming cancerous. Both these effects were reversed when small amounts of IGF-1 were added to the serum.

Dr. Longo said that some level of IGF-1 was necessary to protect against heart disease, but that lowering the level might be beneficial. A drug that does this is already on the market for

treatment of [acromegaly](#), a thickening of the bones caused by excessive growth hormone. “Our underlying hypothesis is that this drug would prolong life span,” Dr. Longo said. He said he was not taking the drug, called pegvisomant or Somavert, which is very hard to obtain.

A strain of mice bred by John Kopchick of Ohio University has a defect in the growth hormone receptor gene, just as do the Laron patients, and lives 40 percent longer than usual.

Dr. Longo said that his report had first been submitted to *Science*, a better-known journal, which turned down the paper because of an adverse report from one reviewer.

Andrzej Bartke, a gerontology expert at Southern Illinois University, said that the new result was “very important” and that the authors had done a fine job in following the patients and generating high-quality data. “This fits in with what we are learning from studies in animals about the relationship of growth hormone to aging, because both cancer and diabetes are related to aging,” Dr. Bartke said.

The longest-lived mouse on record is one studied by Dr. Bartke. It had a defect in its growth hormone receptor gene, just as do the Laron patients. “It missed its fifth birthday by a week,” he said. The mouse lived twice as long as usual and won Dr. Bartke a [prize presented by the Methuselah Foundation](#) (which rewards developments in life-extension therapies) in 2003.

Dr. Guevara-Aguirre said he had been struggling to get sufficient IGF-1 to treat 30 of his patients before they reached puberty, at which point it will be too late. He said his group of Laron patients, the largest in the world, had provided essential data for drug companies making IGF-1, and he chided the companies for not reciprocating by providing the drug for his patients.

Dr. Arlan Rosenbloom, a pediatric endocrinologist at the [University of Florida](#) who has worked with Dr. Guevara-Aguirre, took a similar position. “Considering that the drug companies needed the initial studies to determine dosage and efficacy, it seems ironic that we should have so much difficulty getting the drug,” he said.

Ownership of the drug has passed through several companies’ hands, so any initial obligation may have been weakened. Dr. Guevara-Aguirre also said he believed that the government of Ecuador should do more to help get the drug for his patients.

Dr. Harry Ostrer, a geneticist at [New York University](#) who is exploring the Laron patients’ degree of Sephardic ancestry, said that he had seen several of Dr. Guevara-Aguirre’s patients in Quito, Ecuador’s capital, and that they were “remarkably youthful in appearance.”