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Could a rare mutation that causes dwarfism also slow ageing?

People with Laron syndrome have a low risk of heart disease and a number of other age-related disorders, hinting at strategies for new treatments.

By Mariana Lenharo

Jaime Guevara-Aguirre (back left) and Valter Longo (back right) pose with several of the Laron study participants. Credit: Courtesy Jaime Guevara-Aguirre & Valter Longo

A rare form of dwarfism that affects only 400–500 people worldwide has caught the interest of scientists who study ageing and metabolic diseases. This is because a series of studies have associated the condition with a number of positive health effects, including protection against diabetes, cancer[1] and cognitive decline[2]. Mice with a similar condition live for about 40% longer than do control animals[3].

Although it is unclear whether people with the condition, known as Laron syndrome or growth-hormone-receptor deficiency, live longer on average than those without it, a study published today in *Med* shows that they do seem to be at lower risk of developing cardiovascular disease[4]. They have lower blood pressure, reduced artery fat build-up and a less thick carotid artery wall than do relatives who do not have the syndrome.

"In some sense, this was the most important of all studies," says Valter Longo, a biogerontologist at the University of Southern California in Los Angeles and a co-author of today's paper. "It was the last piece missing in showing that they seem to be protected from all the major age-related diseases." Studying the details of the syndrome, he adds, might inspire the development of drugs or diets with similar protective effects.

From Ecuador to the world

The study examined 24 people with Laron syndrome and 27 of their relatives, all of whom live in Ecuador, which is home to about one-third of all people with the condition, says Jaime Guevara-Aguirre, an endocrinologist at the University of San Francisco in Quito, Ecuador, and a co-author of the study. He has been following this group for more than 30 years, since he identified a cluster of cases in a few secluded villages in the Andes Mountains.

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People with Laron syndrome have a deficiency in the growth hormone receptor that prevents their bodies from properly using the hormone. These individuals have normal or high levels of growth hormone but low levels of insulin-like growth factor-1 (IGF-1), which

Dwarfism may stymie diseases of old age

normally helps growth hormone to promote the growth of bones and tissues.

Because having low IGF-1 levels has been associated with a higher risk of cardiovascular disease[5], "everybody assumed that people with Laron probably had a lot of heart and cardiovascular problems, too", says Longo. A previous study by the same group found that people with Laron syndrome had a normal rate of death from cardiovascular disease[1]. But when Guevara-Aguirre investigated some of the deaths attributed to heart attacks, he found inconsistencies. "People in those little towns sometimes attribute any death without an explanation to myocardial infarction because it's the easiest thing," he says.

The researchers performed a series of tests that showed that people with Laron syndrome actually had normal or improved levels of cardiovascular-disease risk compared with their relatives without the disorder.

"These are preliminary results from a very small number, but they're interesting observations," says Ravi Savarirayan, a clinical geneticist and researcher at Murdoch Children's Research Institute in Melbourne, Australia. "And I think they will need to be replicated in much larger cohorts." Savarirayan and his colleagues found similar results[6] in patients with another type of dwarfism called achondroplasia. "It was just really interesting when I looked at this paper and saw a lot of similarities between the two," he says.

Endocrinologist Manuel Aguiar-Oliveira at the Federal University of Sergipe in Brazil, who studies another rare mutation that causes short stature, also found similar cardiovascular protective effects[7] in a group of people he has been following for more than 30 years in Brazil. "The data are very similar," he says.

Researchers are intrigued by the possibility that people with Laron syndrome might live longer than average. So far, Longo, Guevara-Aguirre and their colleagues have found no sign of this, but they still hope to find a longevity signal if they compare

people with the syndrome with their unaffected siblings. “I’m still trying to get the funds to do this study,” says Guevara-Aguirre.

Drug inspiration?

Haim Werner, a geneticist at Tel Aviv University in Israel who studies the protective effects of Laron syndrome against cancer, says that the current work is important in helping to characterize genes and pathways that might confer protection against cardiovascular disease. “Delineation of these genes is of crucial importance for future nutritional or pharmacological interventions,” he says.

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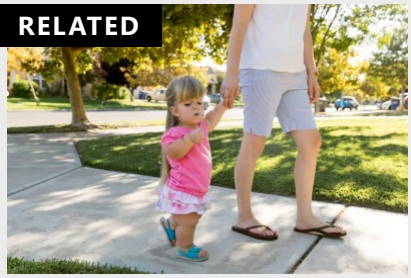

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Longo hopes that the recent results might inspire the development of new strategies to prevent cardiovascular disease in people without the condition, perhaps an oral drug to bring IGF-1 levels down by targeting the growth hormone receptor. “We just have to find out how to do it safely, so that we don’t make things worse,” he says. Aguiar-Oliveira is less enthusiastic about blocking hormones to mimic the positive effects in unaffected people. “I think this type of intervention may be risky,” he says.

The researchers also want to help people with Laron syndrome. Longo and Guevara-Aguirre have been advocating for pharmaceutical companies and the Ecuadorian government to provide IGF-1 to children and adolescents with the syndrome to promote growth, which some research suggests might have benefits for people with dwarfism. The researchers have also begun testing a dietary approach that they hope will improve the growth of children with the syndrome. And Guevara-Aguirre has been providing free medical care to the group. “They still call me every week with one problem here or there,” he says. “Fortunately, they don’t have many.”

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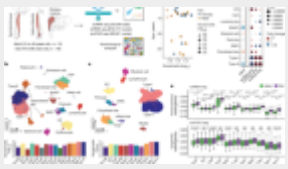

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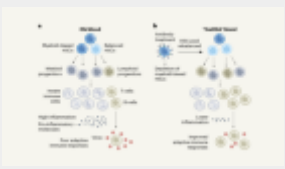

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