Minus a gene, mice bulk up

Muscles: Hopkins researchers, tinkering with mouse DNA, hope to help humans who have wasting diseases.
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Known for being tiny and fast, hundreds of mice in labs at Johns Hopkins are adjusting to a new self-image: a brawny bod.

By erasing one gene from their DNA, researchers enabled the mice to grow muscles two to three times the normal size.

The rodents, nicknamed "Arnold Schwarzenegger mice" by Hopkins lab workers, lumber around their cages with bulked-up shoulder and hip muscles.

People hoping to get larger muscles without exercising will have a long wait, for it will take years to translate the new knowledge into a drug or other treatment.

But the finding, published in this week's edition of the journal Nature, has implications for millions of elderly people who lose muscle mass, for athletes with hamstring pulls and for meatier chickens and turkeys.

Most importantly, it may eventually lead to treatments for people with muscle-wasting diseases such as muscular dystrophy.

"They do look a little strange. We just made a normal mouse that just happens to have twice as much muscle," said Alexandra McPherron, a Hopkins doctoral student and lead author on the study. McPherron and a research team at the Johns Hopkins School of Medicine led by Dr. Se-Jin Lee, a molecular biologist and geneticist, first identified a gene, called GDF 8, one member of a powerful family of genes that control how cells grow and develop for specific functions.

The scientists discovered that the gene regulates the growth of skeletal muscles -- the ones that cover legs, arms and extremities.

When scientists eliminated the gene from the mice's genetic code, their muscles grew dramatically.

Lee's group has been following the mice for about a year. Their offspring, born without the gene, also develop a husky form. "They potentially have stumbled upon something that can have major impact down the road," said Dr. Vince Caiozzo, an assistant professor in the Department of Orthopedics at the University of California at Irvine, where he studies muscles.

Skeletal muscle, which contracts to make the body move, makes up about 40 percent of human body weight.

One question that researchers have long wanted to answer is what governs the growth of a particular muscle.

Finding at least one of the control switches, even in mice, gives researchers much to work with.

Gene in other animals

The Hopkins group also found the gene in humans, and many animals, from birds and cows to pigs, sheep and dogs. If the same genetic alteration was made in livestock, for instance, it could create more food from the same number of animals.

Scientists cautioned that the ramifications of turning off the gene aren't clear. Lee's group also has to determine whether the gene plays the same role in humans.

Although possible treatments are years away, the Hopkins work offers hope to patients with muscle-destroying diseases, from muscular dystrophy to cancer.

Muscle-wasting conditions have never been well understood. They cross several disciplines, from neurology to rheumatology, which has fragmented research.

Muscular dystrophy is the name for a group of about 40 of these disorders, which vary in age of onset, inheritance pattern and rate of progression.

A few can be treated, but for most, doctors can't alter the disease's destructive course. Many patients will ultimately die.

Children with one form of muscular dystrophy, known as Duchenne's, need leg braces at age 11 or 12, and a wheelchair by their mid-teens.

By their late teens, they need help eating, and eventually, help breathing. They are expected to die by their early 20s.

"Those children know that tomorrow will always be worse than yesterday," said Dr. Leon Charash, pediatric neurologist at Cornell University Medical School and chairman of the national medical advisory committee for the Muscular Dystrophy Association.

Benjamin Cumbo, 9, has just started to go down that road. The Upper Marlboro fourth-grader can't keep up with his friends running at recess, although he still has been able to earn an orange belt in karate and play sports.

"It's not really sad or anything, but I just wish I could really run that fast," Benjamin said.

Dr. Marinos Dalakas, chief of the neuromuscular disease section at the National Institute of Neurological Disorders and Stroke, said the study is significant, but he was skeptical about how much it may help patients.

"Too much muscle is not always good," said Dalakas. In muscular dystrophy, for instance, if the disease is killing the muscles, having more muscle won't stop the illness.

"There is no evidence at the moment that hypertrophy {enlarged muscles} will be good for humans or safe."

Hopkins' Lee agrees that the finding doesn't mean a cure, but he believes that the extra muscle would help delay certain stages of disability in patients, possibly even extending life for some. Other implications The gene is also relevant for people without serious diseases, from people who tear muscles playing sports to astronauts who lose muscle mass in space.

The elderly, who have about a 30 percent decrease in muscle mass, are not as able to prevent falls. Death after a fall is a major cause of mortality in the elderly.

Dr. James E. Wood, an orthopedic surgeon who specializes in sports medicine at Sinai Hospital, said the dark side of the Hopkins finding is that any future drug would be pursued by healthy people who simply want to bulk up.

He often has to tell gym members to stop building so much muscle. If a muscle becomes too large, it can overpower the ability of the tendon to hold it to the bone.

In the genetically altered mice, scientists have observed no other physical differences except that they're a little sluggish. Some researchers suggested that might stem from the added weight the mice were carrying around.

One of the buffed-out mice even got beaten up by a skinny, normal one when they were put in the same plastic container for a news conference. Chasing the larger one, the smaller mouse repeatedly bit the other's back.

Lee, a slight man, observed the conquest. "It is my opinion," he said, "that skinny guy's going to take over the world."

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[Illustration]
PHOTO; Caption: Mighty and mousy: Mouse at left lacks a key gene and so has unusually large shoulder and hip muscles. Normal mouse is at right, in undated handout photo from Johns Hopkins.; Credit: ASSOCIATED PRESS

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