Mice Show How a Human Height Gene Works

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(PhysOrg.com) -- A gene linked to greater height and later puberty in large population studies shows a true biological effect, according to a new study from Children's Hospital Boston that finds mice with this variant are larger and have delayed sexual maturity. The mouse model, published online May 30 in *Nature Genetics*, provides a new tool to study metabolism, growth and developmental timing.

The gene, called Lin28, has long been studied in the lab of senior author George Daley, MD, PhD, a Howard Hughes Medical Institute investigator in Children's Stem Cell Program, but for a different reason: it is important in both stem-cell generation and cancer.

"It wasn't our original intent, but we now have a mouse model of genetically controlled human height and puberty onset," Daley said. "I can't watch a basketball game without thinking I'm looking at a team of Lin28 phenotypes," he said, referring to the gene's height-boosting effects.

Many of the common genes identified in large studies of common diseases are only guilty by association and may not even have a major role in disease. Even those that do usually have almost no power to predict individual health outcomes, but they can reveal profound new biological mechanisms that can be harnessed for insights and potential new therapies.

"When you identify a gene in a genome-wide association study, you

don't know how that gene is working," said first author Hao Zhu, MD, a researcher in the Daley lab and an oncologist at Dana-Farber Cancer Institute. "You don't even know that it is involved. You only know it is in the right place to be a suspect, but you don't know how."

The bigger mice came from an attempt to make a mouse model of cancer with an extra Lin28 gene that researchers could turn on to study how it influences cancers when produced at high levels. Instead, Zhu found, the Lin28 gene was expressed at low levels. The mice grew faster, had broader faces, had less body fat, and were heavier and longer in adulthood.

The mice also have an altered metabolism that takes up glucose more efficiently, possibly through an increase in glycolysis, an ancient metabolic pathway used preferentially by tumors. Their larger organs and other tissues are composed of more cells, rather than larger cells. The researchers speculate that the mice burn off more blood sugar, may be less prone to diabetes, and use metabolic processes exploited by cancer cells.

In humans, Lin28 is thought to be one of many genes that work together to determine adult stature and to set pubertal timing. In some people, Lin28 variants may add an extra quarter inch of height and may delay puberty by about a month, according to recent findings from other researchers at Children's and elsewhere.

"This is a nice example of how you can put human and mouse studies together and use the mouse to learn what's going on in human biology," said co-author Joel Hirschhorn, MD, PhD, associate professor of genetics at Children's and Harvard Medical School, who was also part of teams that linked Lin28 and other genes to human height and to puberty timing in other studies in the last two years. "The human genetic studies give us confidence that we're working on biological pathways relevant to

humans."

Less obviously, the mouse model might provide insights into a cancer growth pathway, which was the original intention of the researchers when they began the study. Zhu and his colleagues first developed the Lin28 mice to delve deeper into the role of this growth-related gene. Lin28 is active in cancer cells and is also part of one recipe used to turn ordinary cells into the embryonic-like stem cells known as induced pluripotent stem cells. Scientists believe that cancer hijacks many of the tools that normal embryos use to grow.

But the mouse model did not work as intended. "It was a screwy model," Zhu said. "In this case, there was a slight over-expression of the gene, because it leaked. It was producing the gene when we didn't want it to."

The mice were obviously bigger, and Zhu was interested in how the gene may be regulating body size. "A lot of cancer-causing genes affect the size of mice," Zhu said. "When they're mutated, they become oncogenes. There is a new stream of thinking in cancer to try to figure out how cancer genes are altering metabolism so they can convert nutrients to mass more quickly."

Muscle tissue from the Lin28 mice showed less of the normal fat-burning oxidative process and more of the sugar-burning system, known as glycolytic metabolism. "We're speculating that the shift toward more glycolytic metabolism is allowing the animal to put on mass in a similar way as cancer," said Zhu. "Our next step is to figure out how this gene mechanistically affects glucose uptake and nutrient processing and how that might affect cancer function and growth."

More information: www.nature.com/ng/index.html

Provided by Children's Hospital Boston