Greenlandic gene could be key to beating obesity

The Inuit people carry a genetic variant, which increases their risk of developing obesity and type 2 diabetes. Among the Greenlandic Inuit, scientists have identified a variation of a gene, which could lead the way to a cure for obesity.

The ADCY3 variant increases the body mass index (BMI) among one in 25 Greenlanders and almost guarantees the development of obesity and type-2 diabetes among those who inherit two copies of the variant.

According to one of the scientists behind the study, the discovery might one day halt the global obesity epidemic.

“When we increase the activity of the gene in mice, they become resistant to obesity. If we can understand how the gene works then we could perhaps also find a way to activate it in people so that we can help severely overweight people,” says senior-author Torben Hansen, scientific director and professor at the Section for Metabolic Genomics at the University of Copenhagen, Denmark.

The study is published in the scientific journal Nature Genetics.

Three separate studies support each other

The study is just one of three to study the ADCY3 gene, published in the same issue of Nature Genetics. All three demonstrate a connection between the damaged version of the gene and the risk of becoming obese and developing type-2 diabetes.

One study also demonstrates that the gene has a role in appetite regulation and metabolism in mice.

The other identifies rare genetic variants in ADCY3 among Pakistani family members, where some individuals developed severe obesity as children.

The results are worth taking notice of, says Thorkild Sørensen, who studies obesity at the Novo Nordisk Foundation Center for Metabolic Research. He was not involved in the new research.

“Recognising these functions can perhaps form the basis for treatments and prevention of obesity,” says Sørensen.

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Genetic variant makes Inuit 15 kilograms heavier

Comparing health data and genetic material of 5,000 Grenlandic Inuit, the scientists showed that four per
cent of them carried a damaged (loss-of-function) variant of ADCY3.

The variant appears to prevent the gene from functioning as it should, and people with a copy of the ADCY3 variant weigh on average two kilograms more than the average and have two centimetres more around their waist. They are also more likely to develop type 2 diabetes.

Those who carry two copies of the gene weigh on average 15 kilograms more, and carry an extra 17 centimetres around their waist.

By studying large genome databases of non-Inuit individuals, scientists discovered eight carriers of the loss-of-function ADCY3 variants. Seven out of eight carriers had type 2 diabetes.

“We find a very severe form of inherited obesity associated with a dysfunctional ACDY3 gene. It’s an entirely new obesity gene that hasn’t been described in humans before,” says Hansen.

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**Obesity treatment for Inuit**

For the Greenlandic Inuit, the new results are immediately relevant, since one in 25 of them carry the gene variant that increases their risk to obesity and type 2 diabetes.

A child born of two carriers of the gene is 25 per cent more likely to carry two copies of the gene and almost guaranteed to develop severe obesity and type 2 diabetes.

“The next step is to see whether some of the current treatment options for severe obesity work for this group of people,” says Hansen.

Read More: Birth weight linked to diabetes and obesity[11]

**Mice with hyperactive gene resistant to obesity**

For everyone else, the new discovery could point towards a future treatment of obesity.

According to Hansen, experiments show that genetically modified mice with a damaged ADCY3 gene develop obesity. While increasing the activity of the intact version of the gene in mice prevented obesity.

While scientists cannot simply modify genes in humans, the discovery does provide new insight into the mechanisms behind obesity, which could be a target for future treatments.

“You might be able to stimulate a signal pathway, which the gene is involved in, and fight obesity in that way. In the long run it could be significant in treating severely overweight people,” says Hansen.

The discovery also highlights that the genetic cause of obesity and type 2 diabetes varies across different populations. Scientists and doctors need to remember this when judging the risk of disease, says Hansen.

“We need more research into the specific causes of obesity and other diseases in different populations,” he says.

Read More: Despite self-governing, Inuit still suffer social and health problems[12]

Next step: study damaged gene in mice brains
Hansen and colleagues are now studying the mechanisms behind the ADYC3 variant.

They suspect that the gene is related to appetite regulation and will test this using mouse models, by damaging the gene in various places in the brain and monitor the effect.

“In this way we can see which regions of the brain depend on the function of this gene,” says Hansen.

The study was a collaboration between scientists from Novo Nordisk Foundation Center for Basic Metabolic Research at the University of Copenhagen, the University of Greenland, The National Institute for Public Health at the University of Southern Denmark and the Steno Diabetes Center Copenhagen.

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Read more in the Danish version of this story on Videnskab.dk [13]