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Scientists discover new genetic variation that contributes to diabetes

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Scientists have identified a genetic variation in people with type 2 diabetes that affects how the body's muscle cells respond to the hormone insulin, in a new study published today in *Nature Genetics*. The researchers, from Imperial College London and other international institutions, say the findings highlight a new target for scientists developing treatments for diabetes.

Previous studies have identified several genetic variations in people with type 2 diabetes that affect how insulin is produced in the pancreas. Today's study shows for the first time a genetic variation that seems to impair the ability of the body's muscle cells to use insulin to help them make energy.

People with type 2 diabetes can have problems with the body not producing enough insulin and with cells in the muscles, liver and fat becoming resistant to it. Without sufficient insulin, or if cells cannot use insulin properly, cells are unable to take glucose from the blood and turn it into energy. Until now, scientists had not been able to identify the genetic factors contributing to insulin resistance in type 2 diabetes.

In the new research, scientists from international institutions including Imperial College London, McGill University, Canada, CNRS, France, and the University of Copenhagen, Denmark, looked for genetic markers in over 14,000 people and identified four variations associated with type 2 diabetes. One of these was located near a gene called IRS1, which makes a protein that tells the cell to start taking in glucose from

the blood when it is activated by insulin. The researchers believe that the variant they have identified interrupts this process, impairing the cells' ability to make energy from glucose. The researchers hope that scientists will be able to target this process to produce new treatments for type 2 diabetes.

Professor Philippe Froguel, one of the corresponding authors of today's study from the Department of Genomic Medicine at Imperial College London, said: "We are very excited about these results - this is the first genetic evidence that a defect in the way insulin works in muscles can contribute to diabetes. Muscle tissue needs to make more energy using glucose than other tissues. We think developing a treatment for diabetes that improves the way insulin works in the muscle could really help people with type 2 diabetes.

"It is now clear that several drugs should be used together to control this disease. Our new study provides scientists developing treatments with a straightforward target for a new drug to treat type 2 diabetes," added Professor Froguel.

The researchers carried out a multistage association study to identify the new gene. First, they looked at genome-wide association data from 1,376 French individuals and identified 16,360 single-nucleotide polymorphisms (SNPs), or genetic variations, associated with type 2 diabetes. The researchers then studied these variations in 4,977 French individuals.

Next, the team selected the 28 most strongly associated SNPs and looked for them in 7,698 Danish individuals. Finally, the researchers identified four SNPs strongly associated with type 2 diabetes. The most significant of these variations was located near the insulin receptor substrate 1, or IRS1, gene.

To test their findings, the team analysed biopsies of skeletal muscle from Danish twins, one of whom had type 2 diabetes. They found that the twin with diabetes had the variation near IRS1 and this variation resulted in insulin resistance in the muscle. They also noted that the variation affected the amount of protein produced by the gene IRS1, suggesting that the SNP controls the IRS1 gene.

Source: Imperial College London (news : web)

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