Single gene cause of insulin sensitivity may offer insight for treating diabetes

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People with a rare genetic condition show profound insulin sensitivity.

(Medical Xpress)—The first single gene cause of increased sensitivity to the hormone insulin has been discovered by a team of Oxford University researchers.

The opposite condition – insulin resistance – is a common feature of type 2 diabetes, so finding this cause of insulin sensitivity could offer new opportunities for pursuing novel treatments for diabetes.

Although mutations in the *PTEN* gene cause a rare condition with increased risk of cancer, the biological pathways the gene is involved in could offer promising targets for new drugs.

The Oxford University researchers, along with colleagues at the Babraham Institute in Cambridge, UK, and the Churchill Hospital in Oxford, UK, report their findings in the New England Journal of Medicine. The study was funded by the Wellcome Trust, the Medical Research Council, the National Institute for Health Research Oxford Biomedical Research Centre, and the Biotechnology and Biological Sciences Research Council.

'Insulin resistance is a major feature of type 2 diabetes,' says Dr Anna Gloyn of the Oxford Centre for Diabetes, Endocrinology and Metabolism at the University of Oxford, who led the work. 'The insulin-producing cells in the pancreas may be working hard and pumping out lots of insulin, but the body's cells no longer respond.

'Finding a genetic cause of the opposite – insulin sensitivity – gives us a new window on the biological processes involved. Such understanding could be important in developing new drugs that restore insulin sensitivity in type 2 diabetes.'

The *PTEN* gene encodes for an enzyme that is part of the insulin signalling pathway in the body. It is known to have a role in controlling the body's metabolism, and to play a part in cell growth. The Oxford team was interested in learning more about this dual role.

There is an inherited genetic condition called Cowden syndrome caused by faults in the *PTEN* gene. It is very rare and is thought to affect perhaps one in 200,000 people, with around 300 people with the condition in the UK. *PTEN*'s role in cell growth sees people with Cowden syndrome develop many benign polyps in their skin, mouth and bowel, and have a higher risk than the general population of developing breast cancer, thyroid cancer and womb cancer.

'*PTEN* is a gene that is heavily involved in processes for both cell growth

and metabolism,' says first author Dr Aparna Pal of the University of Oxford. 'Given *PTEN*'s dual role, we were interested in understanding the metabolic profile of people with Cowden syndrome. It was possible that mutations in *PTEN* could improve metabolism.'

The team carried out glucose tolerance tests with 15 people with Cowden syndrome and 15 matched controls. Those with Cowden syndrome had significantly higher insulin sensitivity. In collaboration with their colleagues at the Babraham Institute, the team showed that this was caused by increased activity in the insulin signalling pathway.

The researchers also noticed that the body mass index of those with Cowden syndrome appeared greater than the controls. They carried out a comparison with a much larger control group of over 2,000 individuals from the Oxford Biobank, a data and tissue resource for research established by Professor Fredrik Karpe.

This confirmed that those with Cowden syndrome had higher levels of obesity as a group than the controls. The extra body weight appeared to be caused by extra fat, and there were no differences in where the fat was stored compared to controls.

'This was a surprise. Normally insulin sensitivity goes with being lean,' says Professor Karpe.

Dr Gloyn concludes: 'We now know that mutations that inactivate the *PTEN* gene result in increased cancer risk and obesity, but also increase insulin sensitivity which is very likely to protect against type 2 diabetes.

'The study shows how intimately the biological pathways governing cell growth and metabolism are linked. We need to thoroughly understand these pathways to identify which genes to target in the development of new drugs.'

She adds: 'While there are promising research avenues to pursue here, in the meantime the best way to avoid diabetes remains exercising more and eating less.'

More information: PTEN mutations cause constitutive insulin sensitivity and obesity in humans, *New England Journal of Medicine*, 2012.

Provided by Oxford University