Ten new diabetes gene links offer picture of biology underlying disease

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(Medical Xpress) -- Ten more DNA regions linked to type 2 diabetes have been discovered by an international team of researchers, bringing the total to over 60.

The study provides a fuller picture of the genetics and biological processes underlying type 2 diabetes, with some clear patterns emerging.

The international team, led by researchers from the University of Oxford, the Broad Institute of Harvard and MIT, and the University of Michigan, Ann Arbor, used a new DNA chip to probe deeper into the

genetic variations that commonly occur in our DNA and which may have some connection to type 2 diabetes.

Their findings are published in the journal *Nature Genetics*.

'The ten gene regions we have shown to be associated with type 2 diabetes are taking us nearer a biological understanding of the disease,' says principal investigator Professor Mark McCarthy of the Wellcome Trust Centre for Human Genetics at the University of Oxford. 'It is hard to come up with new drugs for diabetes without first having an understanding of which biological processes in the body to target. This work is taking us closer to that goal.'

Approximately 2.9 million people are affected by diabetes in the UK, and there are thought to be perhaps a further 850,000 people with undiagnosed diabetes. Left untreated, diabetes can cause many different health problems including heart disease, stroke, nerve damage and blindness. Even a mildly raised glucose level can have damaging effects in the long-term.

Type 2 diabetes is by far the most common form of the disease. In the UK, about 90% of all adults with diabetes have type 2 diabetes. It occurs when the body does not produce enough insulin to control the level of glucose in the blood, and when the body no longer reacts effectively to the insulin that is produced.

The researchers analysed DNA from almost 35,000 people with type 2 diabetes and approximately 115,000 people without, identifying 10 new gene regions where DNA changes could be reliably linked to risk of the disease. Two of these showed different effects in men and women, one linked to greater diabetes risk in men and the other in women.

With over 60 genes and gene regions now linked to type 2 diabetes, the

researchers were able to find patterns in the types of genes implicated in the disease. Although each individual gene variant has only a small influence on people's overall risk of diabetes, the types of genes involved are giving new insight into the biology behind diabetes.

Professor Mark McCarthy says: 'By looking at all 60 or so gene regions together we can look for signatures of the type of genes that influence the risk of type 2 diabetes.

'We see genes involved in controlling the process of cell growth, division and ageing, particularly those that are active in the pancreas where insulin is produced. We see genes involved in pathways through which the body's fat cells can influence biological processes elsewhere in the body. And we see a set of transcription factor genes – genes that help control what other genes are active.'

While gene association studies have been successful in finding DNA regions that can be reliably linked to type 2 diabetes, it can be hard to tie down which gene and what exact DNA change is responsible.

Professor McCarthy and colleagues' next step is to get complete information about genetic changes driving type 2 diabetes by sequencing people's DNA in full.

He is currently leading a study from Oxford University that, with collaborators in the US and Europe, has sequenced the entire genomes of 1400 people with diabetes and 1400 people without. First results will be available next year.

'Now we have the ability to do a complete job, capturing all genetic variation linked to type 2 diabetes,' says Professor McCarthy, a Wellcome Trust Senior Investigator. 'Not only will we be able to look for signals we've so far missed, but we will also be able to pinpoint which

individual DNA change is responsible. These genome sequencing studies will really help us push forward towards a more complete biological understanding of diabetes.'

More information: 'Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes', *Nature Genetics*. DOI: 10.1038/ng.2383

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