Using human genetics to reveal fundamental processes involved in type 2 diabetes

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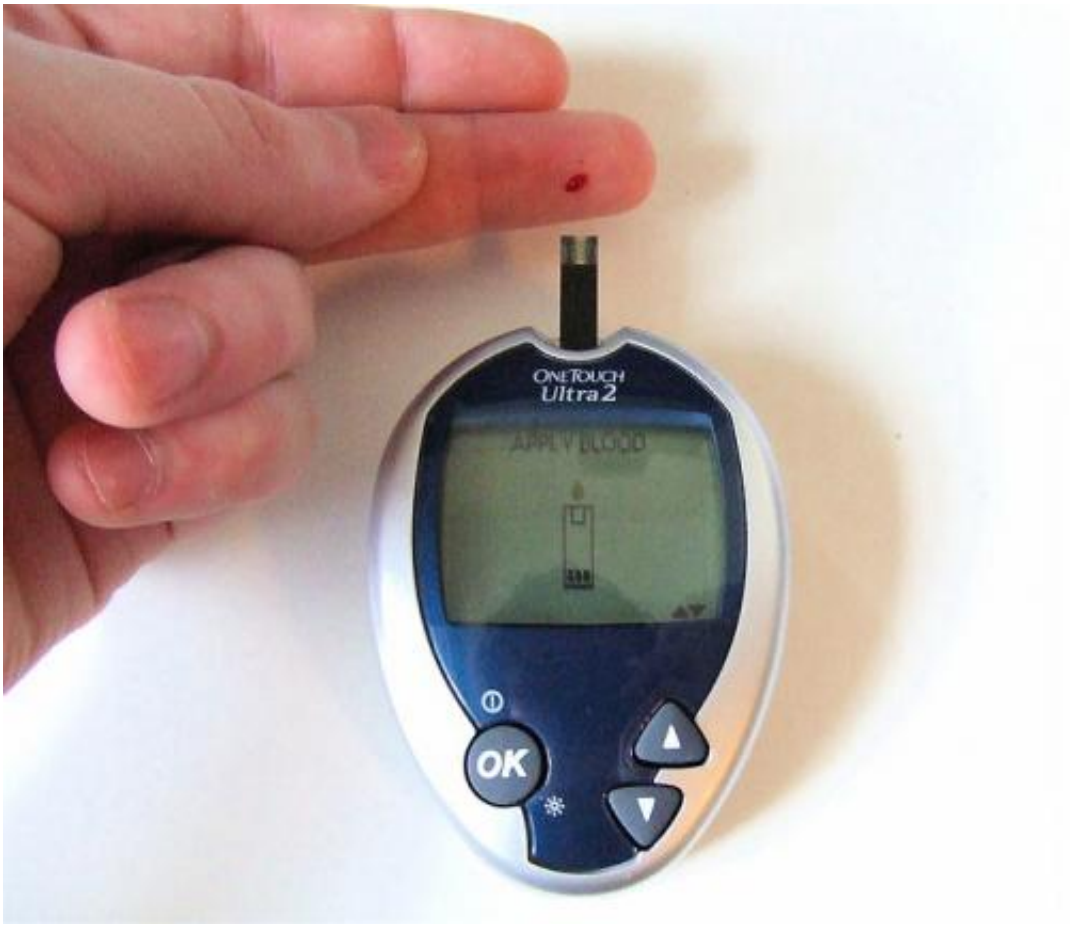

Blood glucose monitoring. Credit: Wikipedia

Researchers at Oxford and Liverpool universities have identified genetic markers that could be used to understand people's risk of developing

type 2 diabetes. Their work is published in *Nature Genetics* today.

Type 2 diabetes is a major contributor to illness and death worldwide, with rates of the disease rising despite current prevention approaches. Many of those affected will go on to develop the complications of diabetes, such as kidney failure and blindness, as current treatments can only do so much. Developing new approaches to disease prevention and treatment is likely to depend on an improved understanding of the genes, proteins and processes which, when disrupted, lead to diabetes.

The Oxford and Liverpool researchers worked with colleagues across a total of 17 countries to address this deficiency in our understanding of diabetes.

The research first involved analysis of large-scale genetic data from over 200,000 people, one quarter of whom had diabetes. The analysis focused on 39 regions of the genome that have been highlighted previously as important for type 2 diabetes risk. Having homed in on the specific DNA sequence changes that were most likely involved in mediating that risk, the researchers went on to determine what was 'special' about those variants. They were able to find a strong signal for the positions in the genome that interact with a regulatory protein called FOXA2 which has an important role as a switch of gene expression.

Wellcome Trust Senior Investigator Professor Mark McCarthy from the University of Oxford said: 'For most regions of the genome associated with type 2 diabetes, it has not been clear how genetic variants affect disease risk. By getting closer to many of the specific genetic changes that influence diabetes risk, we could for the first time detect signals that point to molecules that are key to type 2 diabetes development.'

At one of these regions, near the MTNR1B gene (which codes for one of the receptors for the circadian hormone, melatonin), it was possible to

narrow the list of possible causal sites to a single variant. The researchers were then able to reconstruct the entire mechanism of action leading from that variant to changes in the expression of the melatonin receptor in the insulin-producing cells in the pancreas.

First author Kyle Gaulton said: 'We were able to identify specific signatures of DNA variants that influence individual risk of type 2 diabetes: this is an important step forward in our ability to connect genetic findings to molecular events in key organs, and to understand the biological processes involved.'

Wellcome Trust Senior Research Fellow Professor Andrew Morris from the University of Liverpool said: 'Our study demonstrates how localisation of likely causal variants and assessment of their likely impact in disease-relevant tissues can further our understanding of the biological processes underlying type 2 diabetes and other complex human diseases, offering a promising avenue for translation into clinical utility.'

More information: Genetic fine mapping and genomic annotation defines causal mechanisms at type 2 diabetes susceptibility loci, *Nature Genetics*, nature.com/articles/doi:10.1038/ng.3437

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