From biological basics to diabetes discovery

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In two major studies published in *Nature Genetics* today, researchers use biological understanding to dissect the genetics of diabetes. An international team comprising researchers from more than 100 institutions analysed vast suites of genetic data from more than 100,000 people of European descent to uncover the associations.

In the first study, the team identified ten novel genetic markers for biological traits underlying type 2 diabetes. In a companion paper the same consortium identified three new variants that are associated with raised levels of glucose seen in a common test for type 2 diabetes. The results help to unravel the complex biological story of type 2 diabetes: as well as revealing five new associations that influence directly the risk of diabetes, this research will drive studies to understand the biology of disease and to search for treatments to alleviate the burden caused by the disease.

The team are working to understand the normal metabolism of glucose as well as diseases of glucose metabolism, such as diabetes. They seek to uncover new genetic variants that are risk factors for the development of diabetes, as well as identifying genes that influence variation in the healthy range. Diabetes occurs when our bodies fail to produce sufficient insulin or when our cells fail to recognise and react to the insulin produced, resulting in abnormally high blood glucose or sugar levels.

The research was done by the Meta-Analyses of Glucose and Insulin-related Traits Consortium (MAGIC) who examined several commonly used measures including levels of fasting glucose and insulin and blood

sugar levels two hours after an oral sugar challenge.

They searched data from population studies of people without diabetes to examine the links between glucose levels and SNPs - single letter changes in the genome that can act as markers for particular physical traits or disease. They found nine new genetic regions associated with fasting glucose, 16 regions associated with insulin production but only a single region associated with insulin resistance.

"We were delighted that we were able to find so many SNPs associated with raised levels of glucose," says Dr Inês Barroso, from the Wellcome Trust Sanger Institute, "but amazed that we found only one strong association with levels of insulin. We don't think this is a technical difference, but that the genetics is telling us that the two measures, insulin and glucose, have different architectures, with fewer genes, rarer variants or greater environmental influence affecting insulin resistance."

The team have strong evidence that other genetic factors remain to be found: their study explains about ten per cent of the genetic effect on fasting glucose. They believe that there will be rarer variants with a larger impact that would not be found by a study such as this.

Many of the diabetes-risk loci had not previously been identified in case-control studies, which compare patients with apparently healthy people. The genome-wide approach used here is a valuable complementary method to find variants that influence disease risk. Importantly, the participants were apparently healthy people, rather than patients, which suggests that important genetic determinants can be found in larger groups of unaffected people, rather than the sometimes restricted groups of patients.

This study not only provides further information about new loci that are associated with glucose levels and diabetes risk, but provides light into

the different biological pathways that lead to diabetes. Professor Mark McCarthy of Oxford University says "Our knowledge of type 2 diabetes is slowly being added to with these genetic studies as we are beginning to unravel the complex pathways that lead to the common endpoint of disease."

In the detailed analysis of the glucose challenge, the team found three novel genetic associations, the most prominent of which was with a gene called GIPR-A. Normally, this gene produces a protein that is part of the normal hormone response to feeding, acting to stimulate release of insulin and thus control levels of glucose. The variant is associated with impaired response to the glucose meal and elevated levels of glucose. GIPR sits at a key decision point in glucose metabolism.

"Today's findings are the result of a tremendous group effort involving hundreds of scientists including large consortia in the UK in major institutions working together," says Professor Nick Wareham of the MRC Epidemiology Unit at the University of Cambridge Institute of Metabolic Science. "Traits associated with diseases like type 2 diabetes are so common that it becomes exceptionally difficult to find the genetic regions underlying the physical features and to make that connection solidly. In the face of common diseases, we need to work together in large teams to share and analyse the vast suites of data available. The availability of funding for such consortia from the Wellcome Trust, Medical Research Council and other funders including Diabetes UK has made such work possible and allowed the UK to be at the forefront of these efforts."

More information:

-- Dupuis J, Langenberg C, Prokopenko I, Saxena R, Soranzo N et al. (2010) New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk. Nature Genetics. Published online before print as doi:10.1038/ng.520