Metabolic MAGIC: Meta-analyses reveal new genetic regions influencing blood glucose traits

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Researchers have identified 38 new genetic regions that are associated with glucose and insulin levels in the blood. This brings the total number of genetic regions associated with glucose and insulin levels to 53, over half of which are associated with type 2 diabetes.

The researchers used a technology that is 100 times more powerful than previous techniques used to follow-up on genome-wide association results. This technology, Metabochip, was designed as a cost-effective way to find and map genomic regions for a range of cardiovascular and metabolic characteristics on a large scale. Previous approaches were not cost effective and tested only 30-40 DNA sequence variations, but this chip allowed researchers to look at up to 200,000DNA sequence variations for many different traits at one time. The team hoped to find new variants influencing blood glucose and insulin traits and to identify pathways involved in the regulation of insulin and glucose levels.

"We wanted to use this improved Metabochip technology to see whether we could find additional genomic associations that may have been previously missed," says Dr Claudia Langenberg, co-lead author from the Medical Research Council Epidemiology Unit, Cambridge. "Our earlier work identified 23 genetic regions associated with blood glucose levels, highlighting important biological pathways involved in the regulation of glucose. At that stage, and before the design of the Metabochip, we were still limited by our capacity to quickly follow-up

and afford parallel genotyping of promising, but unconfirmed genetic regions associated with glucose levels in many different studies across the world."

The team combined data from new samples typed on the Metabochip with data from a previous study to discover genetic regions associated with blood glucose and insulin levels. They identified 38 previously unknown regions for three different quantitative traits associated with blood glucose levels; fasting glucose concentrations, fasting insulin concentrations and post-challenge glucose concentrations.

"Our research is beginning to allow us to look at the overlap between genomic regions that influence insulin levels and other metabolic traits," says Dr Inga Prokopenko, co-lead author from the University of Oxford. "We observed some overlap between the regions we identified and genetic regions associated with abdominal obesity and various lipid levels, which are a hallmark of insulin resistance. We hope that these studies will help to find gene networks with potential key modifiers for important metabolic processes and related diseases, such as type 2 diabetes."

The team also found many more, less significant, genetic regions that may be associated with blood glucose and insulin levels but currently don't have the available data to definitively establish them as genome-wide significant. This supports previous evidence that there is a long tail of many other genetic regions that add up to quite small genetic effects but may increase the risk of such diseases as diabetes.Collectively, these less significant associations may represent important blood glucose and insulin level associations.

"In addition to these top signals there is statistical evidence that many other regions that appear to be biologically plausible also influence these traits, but what's limiting is that we don't have large enough sample sizes

to have the power to validate them," explains Dr Inês Barroso, co-lead author from the Wellcome Trust Sanger Institute. "Nevertheless, studying these functionally would be extremely beneficial if we want to fully understand the biology of blood glucose levels and the origin of diabetes."

"What we've found in this study is a number of genomic regions that influence blood glucose and insulin traits. Further analysis such as genetic mapping or 'fine-mapping' and functional analysis will expand and improve our understanding of the control of glucose and insulin levels in healthy persons and what goes wrong in type 2 diabetes patients."

More information: Robert Scott, Vasiliki Lagou, Ryan P. Welch et al 'Large-scale association study using the Metabochip array reveals new loci influencing glycemic traits and provides insight into the underlying biological pathways'. Published in *Nature Genetics* online on 12 August: DOI: 10.1038/ng.2385

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