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New biochemical discoveries into developing disease

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Researchers have undertaken the most comprehensive investigation of genetic variance in human metabolism and discovered new insights into a range of common diseases. Their work has revealed 37 new variants that are associated with concentrations of metabolites in the blood. Many of these match variants associated with diseases such as chronic kidney disease, type 2 diabetes and blood clotting.

The team conducted the largest ever study of the human genome for genetic variants associated with metabolites - the biochemical compounds representing the start or end of metabolic reactions - using genome wide association analysis. They were searching for genetic influences on levels of more than 250 compounds in people's blood, including lipids, sugars, vitamins, amino acids and many others. They discovered variants that have a significant effect on the levels of these compounds, and hence on the underlying biological and disease processes.

"Our findings provide new insights for many disease-related associations that have been reported in previous studies, including cardiovascular and kidney disorders, type 2 diabetes, cancer, gout, thrombosis and Crohn's disease," says Dr Nicole Soranzo, one of the study's researchers from the Wellcome Trust Sanger Institute. "Often the effects of variants discovered in genome wide association analyses are modest and we perhaps have a poor understanding of the biologic mechanism behind the association. Our approach can overcome these problems and possibly inform individualized therapy/treatment."

In previous studies, scientists have looked at the levels of one or a few metabolic traits; for example, cholesterol levels, or sugar in the blood, that is investigated in the doctor's surgery to help to diagnose disease. The new approach in this work was to assay a much wider range of smaller biochemical compounds, to give as complete a picture as possible of the molecules that are symptoms of disease and those that might contribute to disease.

The hope was that this more complete picture would allow researchers to better understand the function of genetic variants responsible for driving disease. This was the case.

Among the discoveries made by the team was a previously unknown association of mannose, a natural sugar, with diabetes-associated variants; this link suggests a new line of research to examine the role of mannose in diabetes, both as a diagnostic and as part of the disease process.

They also identified a possible mechanism to detoxify substances, which could affect the risk of developing kidney disease. This followed the discovery of a highly significant association with the NAT8 gene.

"These are remarkable findings powered by our method that enables researchers to identify new and potentially relevant metabolic processes and pathways," says Professor Karsten Suhre. Dr Christian Gieger adds: "To improve effectively treatment through biomedicine, we need to put genetics into its biological context. In trying to do this in our study, we have identified new molecules of interest that could be clinically significant." Both are the lead authors from the Helmholtz Center Munich, German Research Centre for Environmental Health.

Their study also discovered variants associated with blood clotting and thrombosis.

"We were able to show that variants in or near three genes are associated with a biochemical modification to peptides, a small protein that controls blood clotting. These same variants are variously associated with an increased risk for heart disease, thrombosis and other similar conditions," says Professor Tim Spector, Director of the TwinsUK twin cohort at the Department of Twin Research and Genetic Epidemiology, King's College London, which provided one of the two study samples. "We speculate that this is a new example of a mechanism that alters blood clotting. This discovery could one day lead to improved treatments."

Additionally, the researchers investigated the association of metabolite levels with drug response and treatment, including statins and thalidomide. They showed that in one case, a variant in a gene called ACE, associated with blood pressure control, could undermine treatment effects. The novel biochemical basis could help to identify possible side effects in drug trials and support development of new formulations to reduce side effects.

The data will be made publicly available as a knowledge-based resource on the internet to aid future studies, and biological, as well as clinical, interpretation of genome wide association studies.

More information: Suhre K, Shin S-Y, Petersen A-K et al. (2011) Human metabolic individuality in biomedical and pharmaceutical research. Nature Published online 31 August 2011. doi: 10.1038/Nature10354

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