The genetic heart of the lipids

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A new study presages a real aim of genetics: to look at whole populations to in order determine the significance of individual genetic variants for individual health. The research team, whose work is published in *Nature Genetics*, find six novel genetic variants that are associated with lipid levels, a common indicator of heart or artery disease.

The power of 'genetic microscopes' has increased because the methods are in place to study many thousands of DNA samples. This study, involving over 20,000 samples and researchers from a dozen European countries, is the first to find such lipid–gene links by looking at the general population, rather than patients. The study is has been funded by an EU project, ENGAGE.

A search for a lipid–gene link through such large numbers of unselected people has not been published before. The findings increase hopes for improved predictive diagnosis, which could lead to improved public health measures and early prescription of effective treatments.

"Since 2007, human genetics has achieved results that would have been unimaginable only five years ago," explains Professor Leena Peltonen, Head of Human Genetics at the Wellcome Trust Sanger Institute and senior author on the study, "but this is merely the dawn of new understanding. New, more powerful studies, such as our work on lipid levels, will illuminate the areas and the variants of our genome that play an important part in human disease."

Human geneticists often carry out case-control studies: researchers

examine the genetics of people with a given disease (the 'cases') and compare them to the genetics of apparently unaffected people (the 'controls'). Such studies have been hugely successful in trailblazing discovery of genetic variants associated with common disease. However, because the people participating are not drawn at random, researchers are cautious about extrapolating their findings. If we wish to understand the real impact of the identified gene for a disease risk at the population level for disease risk we need to study population cohorts.

A population-based study, in which no selection is made, should address most of the concerns over case-control studies. However, in these studies, scientists are searching for signs of a genetic effect in a much wider group, most of whom will not have any susceptibility to a particular disease.

"It was important that we should be able to find previously known genetic associations with lipid levels: of the 22 regions we describe, 16 have been described previously," explains Cornelia van Duijn, from Erasmus University in Rotterdam, the Netherlands. "This impressive result shows that not only can we find the known genetic associations, but we can also find novel associations in this large-scale collaboration of very diverse population-based cohort studies spanning populations from Lapland to the Dalmatian Islands.

"We will be able to move forward much more quickly if we can look at other diseases in studies such as ours, pooling resources across European populations."

The team were also able to show differences between the sexes: lipid values are known to differ for males and females, as does the prevalence of cardiovascular diseases. The team found significantly different sex-specific effects for some genome regions: the two strongest signals were in near HMGCR and NCAN. HMGCR produces an important enzyme

involved in cholesterol synthesis and is the drug target for statins, commonly used for treating high values of 'bad cholesterol', LDL. The region around NCAN gene has previously been associated with both LDL and triglyceride levels, associated with coronary heart disease.

The results are part of an emerging portrait of genes determining lipid levels: a major aim is to predict more efficiently those at risk of coronary heart disease. The profiles developed using the new genetic variants are better at identifying those at risk of increased lipid levels, but do not yet improve the prediction of artery or heart disease.

Screening for a person with high lipid levels and early treatment with statins is one of the major strategies in the prevention of cardiovascular risk in clinical practice while a healthy diet, weight control and physical activity is the major population level prevention strategy.

"We can be confident that the increased understanding of the control of lipid levels that will come from these genetic discoveries, will, in time, lead to improved ways of treating and preventing heart disease and stroke" explains Mark McCarthy, Robert Turner Professor of Diabetes at the University of Oxford. "In addition, as we become better at identifying those individuals who are at most at risk of these diseases, we should be able to target our therapeutic and preventative efforts more efficiently, perhaps focusing on changing lifestyles in those most likely to benefit".

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