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Insights into the genetic causes of coronary artery disease and heart attacks

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In the largest genetic study of Coronary Artery Disease (CAD) to date, researchers from the CARDIoGRAMplusC4D Consortium report the identification of 15 genetic regions newly associated with the disease, bringing to 46 the number of regions associated with CAD risk.

The team identified a further 104 independent genetic variants that are very likely to be associated with the disease, enhancing our knowledge of the genetic component that causes CAD.

They used their discoveries to identify biological pathways that underlie the disease and showed that lipid metabolism and inflammation play a significant role in CAD.

CAD and its main complication myocardial infarction (heart attack) are one of the most common causes of death in the world and approximately one in five men and one in seven women die from the disease in the UK. CAD has a strong inherited basis.

"Our research strengthens the argument that, for most of us, genetic risk to CAD is defined by many genetic variants, each of which has a modest affect," says Dr Panos Deloukas, co-lead author from the Wellcome Trust Sanger Institute. "We went beyond traditional genetic association studies to explore likely genetic signals associated with the disease and to use the information to identify biological pathways underlying CAD.

"Our next step is to design new analyses to also test rarer variants to

provide a full catalogue of disease associations that in the future, could identify individuals most at risk of a heart attack."

The Consortium spanning over 180 researchers from countries across Europe (UK, Germany, Iceland, Sweden, Finland, the Netherlands, France, Italy, Greece), Lebanon, Pakistan, Korea, USA and Canada analysed DNA from over 60,000 CAD cases and 130,000 apparently unaffected people. The researchers integrated the genetic findings into a network analysis and found the metabolism of fats being the most prominent pathway linked to CAD.

The second most prominent pathway, however, was inflammation which provides evidence at the molecular level for the link between inflammation and heart disease.

"The importance of the work is that while some of the genetic variants that we have identified work through known risk factors for CAD such as high blood pressure and cholesterol, many of the variants appear to work through unknown mechanisms," says Professor Nilesh Samani, co-lead author from the University of Leicester. "Understanding how these genetic variants affect CAD risk is the next goal and this could pave a way to developing new treatments for this important disease."

This study provides a useful framework for future projects to elucidate the biological processes underlying CAD and to investigate how genes work together to cause this disease.

Professor Peter Weissberg, Medical Director at the British Heart Foundation, which co-funded the research, said: "The number of genetic variations that contribute to heart disease continues to grow with the publication of each new study. This latest research further confirms that blood lipids and inflammation are at the heart of the development of atherosclerosis, the process that leads to heart attacks and strokes.

"These studies don't take us any closer to a genetic test to predict risk of heart disease, because this is determined by the subtle interplay between dozens, if not hundreds, of minor genetic variations. The real value of these results lies in the identification of biological pathways that lead to the development of heart disease. These pathways could be targets for the development of new drug treatments in the future."

More information: 'Large-scale association analysis identifies new risk loci for coronary artery disease'. Published online in *Nature Genetics* on December 2, 2012. DOI: 10.1038/ng.2480

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