# New advances in lipid genetics lead to better detection and prevention of major diseases

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Amsterdam, The Netherlands: Studying the genetic make-up of different varieties of lipids (fatty molecules) in the blood plasma of an individual can lead to a better and earlier prediction of diseases such as diabetes, atherosclerosis, and heart disease, two researchers will tell the annual conference of the European Society of Human Genetics today (Monday 30 May). In the first study, Dr. Joanne Curran from the Texas Biomedical Research Institute, San Antonio, USA, will tell the conference that lipidomic profiling will become a more reliable early indicator of individuals likely to develop diabetes than the more commonly used predictors such as blood glucose and insulin levels.

Dr. Curran and colleagues from the US and Australia measured 356 different lipid varieties from about 1100 Mexican American members of large extended families who were part of the San Antonio Family Heart Study. The Mexican American population is at high risk of diabetes with about 25% of this population ultimately becoming diabetic. At the start of the research, 861 of the individuals studied did not have diabetes. However, over the 10 year follow-up examined in the study, 110 individuals did develop the disease.

The scientists were able to isolate 128 different varieties of lipids that predicted the progression to diabetes by measuring the the lipidomic profiles of each individual at multiple timepoints during the follow-up period. "The single best predictor we found was a novel component called dihydroceramide (dhCer). This was substantially increased in people with diabetes. It is also heritable, and appears to be an

independent risk factor unconnected to blood sugar and insulin levels," says Dr. Curran.

After uncovering the link between dhCer and diabetes, the team searched the genome to find locations that harboured genes that influence dhCer levels. They identified a region on chromosome 3 that appeared to contain a gene with substantial importance for the production of dhCer. "Through whole genome sequencing, we are now attempting to identify this causal gene in the hope that it will be informative in the understanding of the pathogenesis of diabetes, and also suggest new avenues for treatment," Dr. Curran says.

In the future, the researchers say, measurement of dhCer levels could become routine in the prediction of individuals likely to become diabetic. One of the difficulties of the current predictive methods is that they do not function until a patient is near to developing the disease. Being able to identify those at risk at the earliest stage would mean that individuals have plenty of time to make the lifestyle changes that could help them avoid the disease – through a change in diet, or increasing physical activity, for example.

"Currently one in ten US adults suffers from diabetes and recently the Centers for Disease Control has predicted that this will increase to one in three by 2050", says Dr. Curran. "We are optimistic that our discovery will lead to new treatments, but in the short-term the importance of finding out at an early stage whether any individual is likely to develop it cannot be overstated. A test based on dhCer levels will help to avoid the serious health effects that diabetes has in its own right, such as kidney failure, amputations, and blindness. It is, of course, also a risk for cardiovascular disease, so the health burden of this condition is enormous", she concludes.

In the second study, Dr. Sara Willems, from the Erasmus Medical

Centre, Rotterdam, The Netherlands, will describe to the conference research carried out on the influence of common genetic lipid variants on atherosclerosis and related heart disease. "A recent genome-wide meta-analysis of more than 100,000 individuals identified a large number of genetic variants associated with levels of LDL (bad) cholesterol, HDL (good) cholesterol and triglycerides. These molecules are, at increased levels of LDL and triglycerides and decreased levels of HDL, important risk factors for cardiovascular disease", says Dr. Willems.

The researchers used risk scores from these genetic variants to test the hypothesis that their cumulative effects were associated with cardiovascular disease. For this purpose they used genetic data from more than 8000 individuals from the population-based Rotterdam Study and more than 2000 individuals participating in the Dutch family-based Erasmus Rucphen Family study.

They found an association between the LDL risk score and arterial wall thickness, and a strong association of this risk score with carotid plaque. These conditions can cause arterial blockage which leads to stroke. The same risk score was also associated with coronary heart disease.

"Our findings show that an accumulation of common genetic variants with small effects on lipid levels can have a significant effect on clinical and sub-clinical outcomes", says Dr. Aaron Isaacs, who led the project. "In the future, as our knowledge of genetic variation increases, effective pre-clinical genetic screening tools may be able to enhance the prediction and prevention of diseases such as cardiovascular disease."

New genetic variants influencing lipid levels are being identified all the time, the researchers say. "As new variants are discovered, we would like to be able to continue to test them, both singly and combined, for association with cardiovascular disease. The cost of these diseases to

individuals, families, society and healthcare systems is immense", says Dr. Willems.

"Cardiovascular disease is the main cause of death in Europe, killing over 4 million people per year. It also represents 23% of the total disease burden (illness and death) across the continent. Managing cholesterol levels is important for prevention. This can be done early in life by effective treatment. We hope that our study, showing that common genetic variants play an important role in the occurrence of cardiovascular disease, marks a starting point for early prediction and prevention and may thus reduce the burden of disease," she concludes.

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