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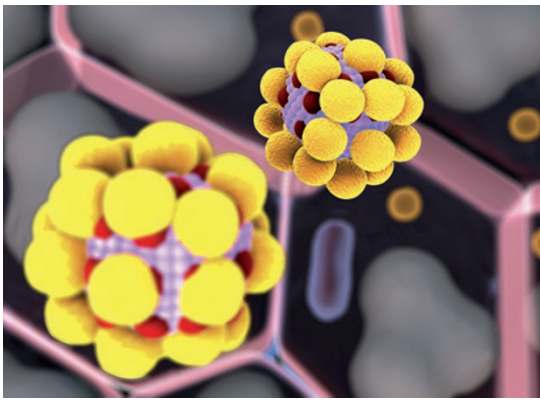
GENETICS

APOC3 mutations lower CVD risk



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High serum triglyceride levels are associated with an increased risk of coronary heart disease (CHD) and ischaemic vascular disease. Now, in two separate papers, investigators from Denmark and a multinational consortium identify heterozygous mutations in the gene encoding apolipoprotein C-III (apo-CIII; *APOC3)* that reduce plasma triglyceride levels, and confer a beneficial cardiovascular effect for carriers.

"Apo-CIII is an important component of triglyceride-rich lipoproteins whose normal function is to inhibit hydrolysis of these lipoproteins in plasma and thereby preserves triglyceride levels," explains Anne Tybjærg-Hansen who led the Danish study. "Therefore, inhibiting apo-CIII is an attractive way of reducing triglyceride levels and hence residual cardiovascular risk."

The team used two independent prospective cohorts of Danish descent that included a total of 75,725 individuals who had completed a health questionnaire, had a physical examination, and provided a blood sample. After sequencing the exons and splice site regions of 10,333 participants from one cohort, three *APOC3* variants—R19X, A43T, and a splice-site mutation IVS2+1G>A—were all associated with reduced nonfasting triglyceride levels. Individuals with a heterozygous mutation for one or more mutations had 44% lower plasma triglyceride levels compared with noncarriers ($P<0.001$).

During follow-up (median 34 years), 10,797 participants from the two Danish cohorts studies developed ischaemic vascular disease and 7,557 ischaemic heart disease. In these patients, an *APOC3* mutation was associated with reduced risk of developing either ischaemic vascular (HR 0.59, 95% CI, 0.41–0.86, $P=0.007$) or heart disease (HR 0.64, 95% CI, 0.41–0.99, $P=0.04$).

The other study, led by Dr Sekar Kathiresan from the Broad Institute and Massachusetts General Hospital in Boston, MA, USA, sequenced the exons from 18,666 genes from 3,734 participants in seven population-based cohorts, who had measurable fasting plasma triglyceride levels. In this study, *APOC3* mutations were also strongly associated with serum triglyceride levels—the three also identified by the Danish team, and a second splice site mutation (IVS3+1G>T).

Individuals who were heterozygous for any *APOC3* mutation had a 39% lower mean plasma triglyceride level compared with noncarriers ($P=6\times10^{-9}$). In a separate, replication group ($n=41,671$) the presence of one or more *APOC3* mutation was associated with a 39% lower serum triglyceride level ($P=<1\times10^{-20}$) compared with noncarriers. Moreover, in another cohort of 110,970 individuals from 14 different studies, those with an *APOC3* mutation had a 40% lower risk of developing CHD than noncarriers (OR 0.60, 95% CI, 0.47–0.75, $P=4\times10^{-6}$).

Finally, to determine if plasma apo-CIII levels were associated with the risk of CHD, the team used data from 2,707 participants from the Framingham Heart Study, for whom plasma apo-CIII levels and genotype data were available. In this group, an *APOC3* mutation was associated with a 46% lower plasma apo-CIII level ($P=8\times10^{-10}$). Moreover, a 1 mg/dl decrease in serum apo-CIII level was associated with a 4% lower risk of incident CHD (HR 0.96, 95% CI, 0.94–0.98, $P<0.001$).

The data from both studies indicate that plasma triglyceride levels have a causal effect on both ischaemic vascular disease and CHD, and the results highlight that naturally occurring mutations could be useful for identifying potential therapeutic targets. "Inhibition of apo-CIII should be tested in large randomized trials," concludes Tybjærg-Hansen.

Tim Geach

Original articles Jørgensen, A. B. *et al*. Loss-of-function mutations in *APOC3* and risk of ischemic vascular disease. *N. Engl. J. Med.* doi:10.1056/NEJMoa1308027 | The TG and HDL Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute. Loss-of-function mutations in *APOC3*, triglycerides, and coronary heart disease. *N. Engl. J. Med.* doi:10.1056/NEJMoa1307095