

## CORONARY HEART DISEASE NPC1L1 MUTATIONS LOWER CHD RISK

Individuals with a naturally-occurring heterozygous mutation in *NPC1L1*, a gene that encodes the Niemann–Pick C1-like 1 protein, have a lower plasma LDL-cholesterol level and a reduced risk of coronary heart disease (CHD) compared with noncarriers. These findings, from the Myocardial Infarction Genetics Consortium investigators, were published in *The New England Journal of Medicine*.

*NPC1L1* regulates cholesterol transport in the intestine and is targeted by ezetimibe, which lowers LDL-cholesterol levels by ~50%. However, whether ezetimibe actually decreases the risk of CHD in patients is unclear, and has been investigated in the IMPROVE-IT trial. The consortium investigators used a genetic approach to determine whether mutations in *NPC1L1* that decrease the protein's activity by 50% have a similar effect on LDL-cholesterol level to that of ezetimibe, and whether this effect translates into a lowering of CHD risk.

The team sequenced the exons of *NPC1L1* in 7,364 individuals with CHD and 14,728 individuals who did not have the disease, and identified 15 mutations. The investigators then genotyped a further 22,590 patients with CHD and 68,412 control participants for the presence of the most common *NPC1L1*-inactivating variant, p.Arg406X. In individuals for whom plasma lipid levels were available ( $n = 42,813$ ), those who were heterozygous carriers for p.Arg406X had a significantly lower LDL-cholesterol level (mean adjusted difference  $-12$  mg/dl [ $0.31$  mmol/l];  $P = 0.04$ ) than noncarriers.

Interestingly, patients with CHD were less likely to be a heterozygous carrier of an *NPC1L1*-inactivating mutation than healthy individuals (carrier frequency 0.04% versus 0.09%). This difference equates to a 53% reduced risk of developing CHD in carriers of the mutation (OR 0.47, 95% CI 0.25–0.87,  $P = 0.008$ ).

These results mimic the effect of ezetimibe on LDL-cholesterol levels, and suggest that this drug will also lower the risk of CHD. Indeed, the investigators of the IMPROVE-IT trial, who presented data at the AHA Scientific Sessions 2014 in Chicago, IL, USA, confirm that adding ezetimibe to statin therapy does indeed lower the risk of adverse cardiovascular events.

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