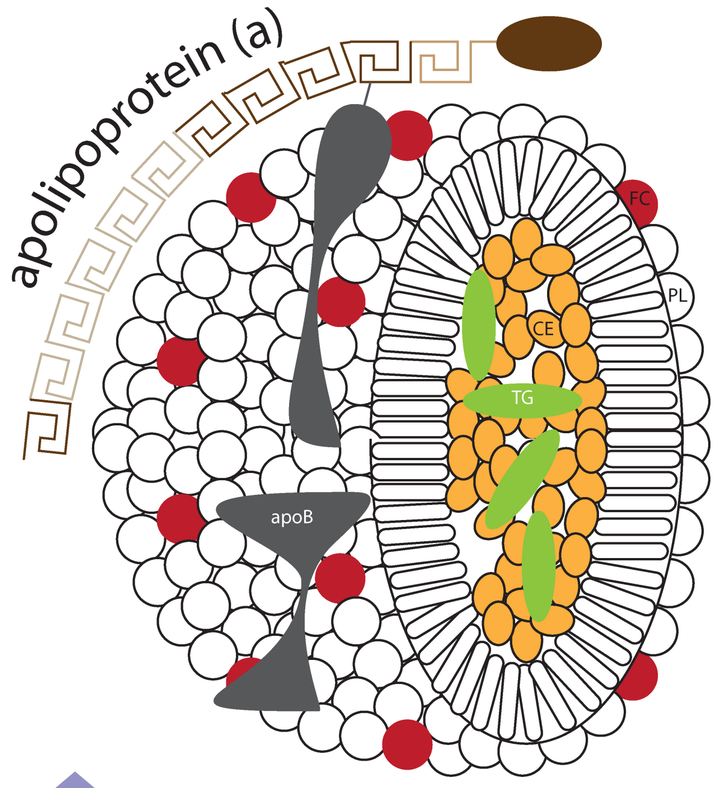
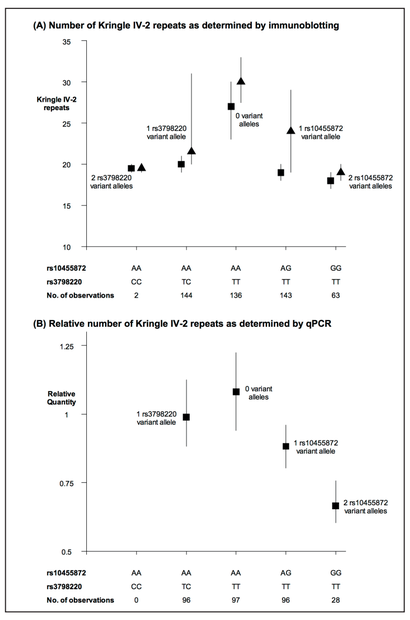
The Wellcome Trust Centre for
Human Genetics

UNIVERSITY OF OXFORD

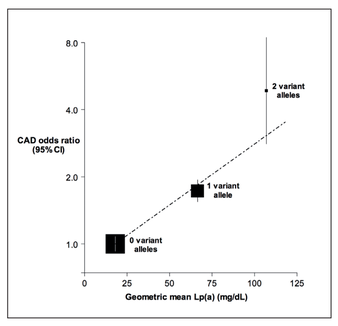
Lipoprotein(a) is a causal risk factor for coronary artery disease



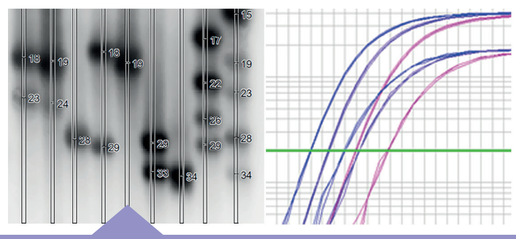
Schematic of a lipoprotein(a) particle coated in phospholipid and with a core packed with cholesterol esters (CE) and triglycerides (TG). The apolipoprotein(a) molecule contains a variable copy number of a kringle repeat domain: here 5 copies are plotted in beige



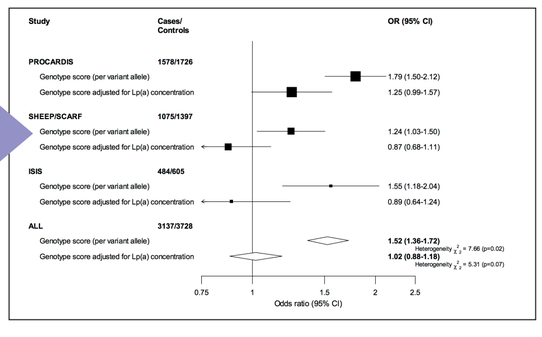
Two SNPs define a genotype score that shows a striking pattern of association with higher CAD risk and Lp(a) levels



The two SNPs in apolipoprotein(a) tag relatively short isoforms containing 18-20 kringle repeats (panel A). This tagging pattern is confirmed by qPCR analysis



Measuring isoform sizes by immunoblots (left hand panel) is labour intensive and reveals diffuse isoform banding patterns that can be hard to resolve. The quantitative PCR analysis of genomic DNA (right hand panel) provides an alternative estimate of the total copy number of kringle repeats across the diploid genome



The association of the apolipoprotein (a) genotype score with CAD risk is attenuated by adjustment for Lp(a) concentrations. This indicates a causal relationship between SNP, biomarker and disease

WHAT WAS KNOWN

- Lipoprotein(a) is a unique type of low-density lipoprotein particle where an apolipoprotein(a) molecule is covalently bound to apolipoprotein B
- Levels of these cholesterol-rich Lp(a) particles are highly heritable and a risk factor for coronary artery disease (CAD)
- The kringle domain of the apolipoprotein(a) molecule shows striking copy-number variation (CNV) and isoform size is negatively correlated with Lp(a) levels
- Isoform assays are technically challenging, expensive and with limited resolution which limits their application in large-scale epidemiological studies
- The genetic determinants of Lp(a) levels and of isoform size were incompletely understood, as was their causal relevance for CAD

WHAT WE DID

- Patients with premature CAD and ancestry-matched controls were assembled from four European countries (Germany, Italy, Sweden and UK) through the PROCARDIS collaboration
- Lp(a) levels were measured in patients and controls and apolipoprotein(a) isoform sizes were estimated using proteomic (immunoblot) and genomic (qPCR) methods
- Fifty-thousand single nucleotide polymorphisms (SNPs) were genotyped to systematically scan for CAD associations in two-thousand candidate genes across the genome

WHAT THIS ADDS

- We identified two SNPs that individually and when combined into an apolipoprotein(a) genotype score, showed strong associations to CAD risk and Lp(a) levels
- The SNPs tagged short (low copy number) isoform alleles that jointly confer a 50% increase in CAD risk to one-sixth of the population
- The pattern of SNP associations to Lp(a) levels and CAD risk was consistent with a causal relationship between biomarker and disease
- The genotype score has subsequently revealed novel risk associations with ischemic stroke, peripheral vascular disease and aortic aneurysms
- The study refocused attention on Lp(a) as an emerging risk factor and validates Lp(a) as a novel drug target for CAD prevention

REFERENCES

Genetic variants associated with Lp(a) lipoprotein level and coronary disease.

R Clarke*, J F Peden*, J C Hopewell*, T Kyriakou, A Goel, S C Heath, S Parish, S Barlera, M G Franzosi, S Rust, D Bennett, A Silveira, A Malarstig, F R Green, M Lathrop, B Gigante, K Leander, U de Faire, U Seedorf*, A Hamsten*, R Collins*, H Watkins *& M Farrall* on behalf of the PROCARDIS Consortium.

The New England Journal of Medicine 2009 361(26): 2518–28.