Lipoprotein-Associated Phospholipase A₂ Loss-of-Function Variant and Risk of Vascular Diseases in 90,000 Chinese Adults

Lipoprotein-associated phospholipase A₂ (Lp-PLA₂) produces the proinflammatory mediators lysophosphatidylcholine and oxidized free fatty acids through hydrolysis of oxidized phospholipids carried on low-density lipoproteins in atherosclerotic plaques. Although increased Lp-PLA₂ activity has been associated with higher risks of occlusive vascular diseases, recent phase III trials of the Lp-PLA₂ inhibitor darapladib, which reduces Lp-PLA₂ activity by 60%, failed to establish a protective role of darapladib for prevention of major vascular events in patients with stable coronary heart disease (CHD) or acute coronary syndrome (1,2).

A V279F loss-of-function variant in the PLA2G7 gene encoding Lp-PLA₂ results in 50% lower activity for each copy of the variant, is common in East Asians (3) and allows an unbiased assessment of the causal effects of lifelong lower Lp-PLA₂ activity, analogous to randomized trials of Lp-PLA₂ inhibition (4). We genotyped PLA2G7 V279F (rs76863441) in 91,428 individuals randomly selected from the China Kadoorie Biobank prospective cohort of 0.5M participants recruited in 2004 to 2008 from 10 regions of China (5). Follow-up for International Statistical Classification of Diseases and Related Health Problems 10th Revision–coded incident events continued to January 1, 2014, through linkage with morbidity and mortality registries and a nationwide health insurance system. The pre-specified primary endpoint was major vascular events (MVE) (vascular death, myocardial infarction, stroke), with >90% power to detect a 20% lower relative risk at p < 0.01. As a context, the trials were powered to detect 15% risk reductions, and differences in lifelong exposure associated with genetic variants would be expected to have greater effects than intervening for a few years in later life (4). Secondary endpoints, for which power was lower, included major coronary events (CHD death, myocardial infarction), major occlusive events (CHD death, myocardial infarction, ischemic stroke), and stroke subtypes.

The mean baseline age of participants was 51 years and 40% were men. History of CHD was reported by 3%, stroke or transient ischemic attack by 2%, diabetes by 6%, and hypertension by 12% of participants. Antihypertensive or statin use was reported by 5% and 0.2% of participants, respectively. The frequency of PLA2G7 V279F was 5% overall, but varied from 3% to 7% by region (p<0.0001) and 10.6% of participants had at least 1 loss-of-function variant. There were no differences in blood pressure, adiposity, or other baseline characteristics by genotype. There was no significant association of PLA2G7 V279F with MVE, either overall (odds ratio: 0.98; 95% confidence interval: 0.90 to 1.06; p=0.63) as assessed among 7,141 cases and 81,489 controls who had no prior history of vascular disease, or in specific population subgroups defined by sex, 10-year age group, region, or smoking status. Nor was PLA2G7 V279F associated with any of the components of MVE (Figure 1).

This is the largest single study to investigate the associations of PLA2G7 V279F with risk of vascular diseases, and the results exclude any protective effect on MVE >10% in this general population. These findings are consistent with a previous meta-analysis of PLA2G7 V279F involving 3,611 East Asian CHD cases (3), and with the recent findings from randomized trials of Lp-PLA₂ inhibition (1,2). In contrast with the trials, MVE in this study predominantly involved stroke, reflecting the differences in cardiovascular disease rates between East Asian and European populations.

In conclusion, genetically determined lower Lp-PLA₂ activity appeared to have no substantial causal effects on major vascular diseases, consistent with findings from randomized trials of Lp-PLA₂-lowering therapy. These findings indicate that it may be valuable to use functional genetic variants in large-scale prospective studies with follow-up of a range of health outcomes to help predict any beneficial and adverse effects of novel therapeutic strategies (as well as to identify any potential...
alternative indications) prior to undertaking costly clinical trials.

Iona Y. Millwood, DPhil
Derrick A. Bennett, PhD
Robin G. Walters, PhD
Robert Clarke, MD
Dawn Waterworth, PhD
Toby Johnson, PhD
Yiping Chen, DPhil
Ling Yang, PhD
Yu Guo, MSc
Zheng Bian, MSc
Alex Hacker, BA
Astrid Yeo, PhD
Sarah Parish, DPhil
Michael R. Hill, DPhil
Stephanie Chissoe, PhD
Richard Peto, MSc
Lon Cardon, PhD
Rory Collins, FMedSci
Liming Li, MD
*Zhengming Chen, DPhil
on behalf of the China Kadoorie Biobank Collaborative Group
*Clinical Trial Service Unit & Epidemiological Studies Unit
Nuffield Department of Population Health
University of Oxford

Old Road Campus
Oxford OX3 7LF
United Kingdom
E-mail: zhengming.chen@ctsu.ox.ac.uk
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