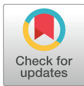

commentary

Lipoprotein(a): the common, likely causal, yet elusive risk factor for cardiovascular disease[1]

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Lipoprotein(a) [Lp(a)], first described in 1963 by the Norwegian Kaare Berg, consists of a low density lipoprotein (LDL)-like particle with an additional apolipoprotein covalently bound to apolipoprotein B; apolipoprotein(a) [apo(a)] (1). Lp(a) plasma concentrations are highly heritable with >50% of the variation in levels attributable to genetic variation in the *LPA* gene locus coding for apo(a) synthesized by hepatocytes. Of particular importance is the so-called kringle-IV type 2 (KIV-2) *LPA* copy number variant (CNV) determining the number of kringle-shaped protein structures in apo(a), thus determining apo(a) isoform size, which correlates inversely with plasma Lp(a) levels (1).

Over the years, numerous epidemiologic studies have documented an association of elevated Lp(a) levels with increased risk of cardiovascular disease, although the enthusiasm for Lp(a) was severely dampened in the early nineties with the publication of the first two large prospective studies, both yielding null findings (2). Notably, both studies used long-term frozen samples and questionable assays, underscoring the importance of using appropriate sample material and validated Lp(a) assays to yield reliable results (3). In the past decade, however, several large epidemiologic and genetic epidemiologic studies have confirmed the importance of elevated Lp(a) levels in cardiovascular disease including coronary heart disease, to some extent peripheral atherosclerosis and ischemic stroke, and most recently also aortic valve stenosis and heart failure (4–10). Thus, at present, strong genetic evidence exists to support a causal role for Lp(a) in the development of cardiovascular disease (1, 2, 11). This was most recently demonstrated in a large genetic study where a gene risk score based on just 4 *LPA* single nucleotide polymorphisms (SNPs), all strongly associated with low plasma Lp(a) levels, predicted decreased risk of coronary heart disease, peripheral arterial disease, stroke, aortic valve stenosis, and heart failure (12). Currently, and largely motivated by findings from the genetic epidemiologic studies on Lp(a) levels, *LPA* gene variants, and risk of cardiovascular disease of later years, efforts are undertaken to develop effective drugs targeting elevated Lp(a) levels found in 1 in 5 individuals in the general population (13) and representing one of the strongest genetic risk factors for cardiovascular disease (11). This despite the fact that to this day, Lp(a) is still associated with many unanswered questions with regards to production, catabolism, normophysiological function, and pathophysiological mechanism of action (1), the latter which may include both proatherosclerotic, prothrombotic, and proinflammatory effects (1, 2, 11).

In this issue of the *Journal of Lipid Research,* Mack et al. (14) report on their efforts to identify genetic loci associated with Lp(a) concentrations by conducting a large hypothesis-free meta-analysis of data from five genome-wide association studies (GWASs) supplemented with a gene-based test of association for candidate genes for possible Lp(a) receptors and regulators. Altogether, 13,781 individuals were included and ~10 million SNPs analyzed. Notably, for all individuals, apo(a) isoforms were determined using Western blot analyses, enabling adjustment of GWAS findings for apo(a) isoform size (determined by the *LPA* KIV-2 CNV), the most influential factor in determining plasma Lp(a) levels. The authors identified 48 independent SNPs in the *LPA* gene region and 1 SNP in the *APOE* gene region to be associated with Lp(a) concentrations. A weighted [by effect on Lp(a) levels] SNP-score based on the 48 identified SNPs in the *LPA* gene region could explain 36% of the total variability in Lp(a) levels in the study participants. The identified SNP in the *APOE* gene region is identical to the SNP that defines the APOE2 allele, explained 0.5% of the total phenotypic Lp(a) concentration variance, and each *APOE2* copy decreased Lp(a) concentrations by 3.3 mg/dl. In analyses adjusted for apo(a) isoform size, 31 independent SNPs were identified (30 in the *LPA* gene region and again the *APOE* rs7412 SNP); for the *LPA* SNPs, most of them were different from the SNPs found in the unadjusted analyses. In the gene-based test of association for candidate genes, evidence of the involvement of the *TLR2* gene in the regulation of Lp(a) levels was provided.

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In additional analyses using data retrieved from the CARDIoGRAMplusC4D consortium, seven of the identified SNPs in the *LPA* gene region were found to be significantly associated with CAD on a genome-wide scale (14). The highest effect, corresponding to an odds ratio of 1.73 ($P = 3.35 \times 10^{-30}$) for coronary artery disease per minor allele copy, was found for SNP rs186696265, where each copy of the minor allele increased Lp(a) levels by 48 mg/dl in a model adjusting for other SNPs independently associated with Lp(a) levels. As noted by the authors, the rs186696265 SNP is located between two intergenic enhancer regions suspected to regulate *LPA* expression. Overall, the authors observed a direct proportional relationship of the Lp(a)-associated variants with CAD risk increase for Lp(a)-increasing variants and a corresponding decrease in risk for Lp(a)-decreasing variants, thus further adding to the present strong genetic evidence of elevated Lp(a) levels as a causal factor in cardiovascular disease development.

The finding by Mack et al. concerning the *APOE* rs7412 SNP is consistent with findings from (most) previous studies on *APOE* genotypes and Lp(a) levels, including a very large recent study in 431,239 patients (15), and as summarized by the authors (14). Interestingly, the *APOE2* Lp(a)-lowering effect has recently been demonstrated to be independent of plasma apoE levels and to not modify Lp(a) associated risk of myocardial infarction or of aortic valve stenosis after subjects are stratified for Lp(a) levels (16). Indeed, Lp(a) levels may be a determinant of the apparent protective effect of *APOE2* in cardiovascular disease. However, the underlying biologic mechanism between the *APOE*-Lp(a) associations still has not been elucidated and merits further research, as do the findings in the present study of an association between the *TLR2* genotype and Lp(a) levels.

The study by Mack et al. (14) represents a timely and valuable effort to gain further insights into the regulation of Lp(a) levels. Importantly, the authors undertook the laborious effort of determining apo(a) isoform size to control for the well-known effect of the *LPA* KIV-2 CNV on levels, thus increasing power to detect other genes that may affect Lp(a) levels. Of note, the adjustment for apo(a) isoform size was carried out by adjusting for only the predominantly expressed isoform in heterozygous individuals, whereas the contribution of the second isoform was not taken into account, which constitutes a partial and not a complete adjustment for apo(a) isoform size, which the authors also rightly point out. Although one might have hoped that the apo(a) isoform adjustment approach of the present study would have yielded more genetic hits outside of the *LPA* gene locus to ultimately guide new strategies for clarification of Lp(a) production, catabolism and (patho-) physiology, the findings nonetheless underscore the importance of the *LPA* gene locus in determining Lp(a) levels. Thus, the results of the present timely and important study by Mack et al. support a treatment strategy for elevated Lp(a) levels targeting Lp(a) production at the *LPA* gene [i.e., apo(a) mRNA] level, as, for example, by use of antisense specific oligonucleotides, which have resulted in mean Lp(a) lowering of >80% in early clinical trials (17). Data from outcome clinical trials are needed to provide final evidence of a direct causal association of Lp(a) with cardiovascular disease risk and to provide treatment options for individuals at high risk of cardiovascular disease due to high Lp(a) levels.

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