

THE IMPORTANCE OF LPA GENE POLYMORPHISM IN THE EARLY DEVELOPMENT OF ATHEROSCLEROSIS

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ABSTRACT

Lipoprotein(a) [Lp(a)] is a low-density lipoprotein-like particle in which apolipoprotein B-100 is covalently linked to apolipoprotein(a) [apo(a)], a plasminogen-related glycoprotein encoded by the LPA gene. Plasma Lp(a) concentration is among the most strongly heritable quantitative traits in human biology: variation at the LPA locus explains the large majority of its interindividual variance, and adult-equivalent levels are established in early childhood and remain largely stable thereafter. The kringle IV type 2 (KIV-2) copy number variation, which determines apo(a) isoform size, together with single-nucleotide variants such as rs10455872 and rs3798220 and a growing catalogue of loss-of-function alleles, governs lifelong exposure to Lp(a). Genome-wide association studies and Mendelian randomization analyses have established Lp(a) as a causal, independent risk factor for coronary heart disease, ischemic stroke, peripheral arterial disease and calcific aortic valve stenosis. Because the genetic determinants of Lp(a) operate from birth, high-risk LPA genotypes are particularly relevant to premature atherosclerosis, arterial ischemic stroke in children and young adults, and to the amplified risk observed in familial hypercholesterolemia. In this review, we summarize the structure and genetic architecture of the LPA locus, the mechanisms through which Lp(a) promotes early atherogenesis, including arterial retention, oxidized phospholipid-driven inflammation and impaired fibrinolysis, and the epidemiological evidence linking LPA variation to early-onset disease. We also discuss measurement and screening strategies, the implications of recent outcome data for nucleic acid-based Lp(a)-lowering therapies, and the open questions that must be addressed before genotype-guided prevention can be implemented from youth.

KEYWORDS: lipoprotein(a); LPA gene; apolipoprotein(a); kringle IV type 2; single-nucleotide polymorphism; premature atherosclerosis; Mendelian randomization; oxidized phospholipids; familial hypercholesterolemia; antisense oligonucleotides

1. INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of death worldwide, and although clinical events typically occur in middle and late adulthood, the underlying disease process begins decades earlier. Fatty streaks and early intimal lesions are already detectable in adolescents and young adults, and the cumulative burden of exposure to atherogenic lipoproteins over the life course is a major determinant of when clinical disease becomes manifest. Among the circulating risk factors that act from early life, lipoprotein(a) [Lp(a)] occupies a unique position. First described by Kåre Berg in 1963 as a novel antigenic serum variant [1], Lp(a) was later shown to consist of an apolipoprotein B-100 (apoB)-containing low-density lipoprotein (LDL)-like particle to which a large, highly polymorphic glycoprotein, apolipoprotein(a) [apo(a)], is covalently attached [2,3].

Unlike LDL cholesterol, plasma Lp(a) concentration is minimally influenced by diet, physical activity or most conventional lipid-lowering drugs, and is determined predominantly by genetic variation at a single locus, *LPA* [4,5]. Concentrations span more than three orders of magnitude between individuals and differ markedly between ancestries [6]. Large prospective cohorts and individual-participant meta-analyses have demonstrated a continuous, graded association between Lp(a) concentration and the risk of coronary heart disease and stroke [7,8], and genetic studies have provided compelling evidence that this relationship is causal [9,10]. Approximately one in five individuals of European ancestry has a concentration above 50 mg/dL, a level at which ASCVD risk is clinically meaningful [11,12].

Because the *LPA* genotype is fixed at conception and Lp(a) levels reach adult-equivalent values in early childhood, exposure to Lp(a) is essentially lifelong. This property makes *LPA* variation particularly relevant to the early stages of atherogenesis and to premature clinical disease. The aims of this review are to summarize the genetic architecture of the *LPA* locus, to examine the molecular mechanisms through which Lp(a) promotes atherosclerosis from an early age, to evaluate the epidemiological and genetic evidence linking *LPA* polymorphism to early-onset vascular disease, and to discuss implications for screening and therapy.

2. Structure and Genetic Architecture of the *LPA* Locus

2.1. Apolipoprotein(a) Structure and Lp(a) Assembly

The *LPA* gene is located on chromosome 6q26–q27 within a cluster that also contains the plasminogen gene (*PLG*) and the related pseudogene *LPAL2*. Cloning of the apo(a) cDNA revealed a striking homology to plasminogen:

apo(a) contains multiple copies of a domain resembling plasminogen kringle IV, a single copy resembling kringle V, and an inactive protease-like domain [2]. The kringle IV-like domains are subdivided into ten types (KIV-1 to KIV-10) on the basis of amino acid sequence; all are present as single copies except KIV-2, which is present in a variable number of identical repeats [3,13]. Lp(a) assembly occurs at or near the hepatocyte surface in a two-step process: an initial non-covalent interaction between lysine-binding sites in KIV-7 and KIV-8 and lysine residues of apoB-100 is followed by the formation of a single disulfide bond between a cysteine in KIV-9 and apoB-100 [14]. The lysine-binding site in KIV-10 mediates binding to fibrin, cell-surface receptors and oxidized phospholipids and is critical for several of the pathogenic properties of the particle [15,16].

2.2. The KIV-2 Copy Number Variation and Apo(a) Isoform Size

The KIV-2 region is one of the most variable copy number polymorphisms in the human genome. Each repeat unit spans approximately 5.6 kb and contains two exons, and the number of repeats ranges from one to more than forty per allele, generating more than forty apo(a) isoforms of different molecular mass [13]. Early family studies established that apo(a) phenotypes are inherited in a codominant manner and that isoform size is inversely related to plasma Lp(a) concentration [17]. The molecular basis of this relationship lies in hepatocellular processing: larger apo(a) isoforms are retained longer in the endoplasmic reticulum and are more extensively degraded before secretion, whereas smaller isoforms are secreted more efficiently [18]. Analyses using sibling pairs and pulsed-field gel electrophoresis demonstrated that sequence variation at the *LPA* locus accounts for more than 90% of the variance in plasma Lp(a) concentration, with KIV-2 copy number alone explaining roughly 30–70% depending on the population [4].

The clinical relevance of isoform size has been confirmed in large epidemiological studies. A systematic review of 40 studies including approximately 58,000 participants showed that individuals carrying small apo(a) isoforms (generally defined as 22 or fewer KIV repeats) have approximately twice the risk of coronary heart disease and ischemic stroke compared with carriers of large isoforms [19]. Mendelian randomization analyses subsequently indicated that the effect of isoform size on coronary risk is mediated mainly by its impact on Lp(a) concentration, rather than by an independent property of small isoforms [20]. The broad size heterogeneity of apo(a) also has important analytical consequences: immunoassays based on antibodies directed against the repetitive KIV-2 epitope may overestimate concentrations in carriers of large isoforms and underestimate them in carriers of small isoforms, a problem that motivated the development of isoform-insensitive assays and reporting in molar units [21].

2.3. Single-Nucleotide Variants and Loss-of-Function Alleles

Beyond KIV-2 copy number, numerous single-nucleotide variants (SNVs) modulate Lp(a) concentration. A landmark study using a gene-centric array identified two common *LPA* variants, rs10455872 (intronic) and rs3798220 (a missense variant, I4399M, in the protease-like domain), that were strongly associated with both Lp(a) level and coronary disease [9]. Together these variants explained approximately one third of the variance in Lp(a) concentration, and carriage of one or both was associated with a 1.5- to 2.5-fold increase in coronary risk; much of their effect reflects strong linkage disequilibrium with small KIV-2 alleles. Genome-wide association studies (GWAS) consistently identified the *SLC22A3–LPAL2–LPA* cluster as one of the strongest coronary artery disease loci [22,23], and GWAS of Lp(a) concentration conditioned on isoform size have revealed additional independent signals across the region [24].

Variants that lower Lp(a) are equally informative. A splice-site mutation in the KIV-8 region (rs41272114) was identified as a frequent cause of "null" apo(a) alleles in individuals of European ancestry [25], and population-genetic analyses in Finland identified further loss-of-function variants associated with low Lp(a) concentrations [26]. Individuals carrying genetically lowered Lp(a) showed a reduced risk of coronary heart disease without an apparent excess of adverse phenotypes in a broad phenome-wide scan, an observation that supports the safety of therapeutic Lp(a) reduction [27]. Sequencing of the hypervariable KIV-2 region, previously inaccessible to standard genotyping, uncovered a frequent splice variant (4925G>A) carried by approximately one in five Europeans that markedly reduces Lp(a) concentration and is associated with lower coronary risk, but whose effect is masked when it occurs on a short isoform background [28]. A comprehensive map of single-base polymorphisms in the KIV-2 region has since been published, demonstrating that this region harbors a large reservoir of functional variation that is invisible to conventional arrays [29]. Deep whole-genome sequencing in individuals of European and African ancestry further showed that the genetic determinants of Lp(a) differ substantially between populations [30].

2.4. Ancestral Differences

The distribution of KIV-2 alleles and the effect of a given isoform on Lp(a) concentration vary considerably between ancestries [31]. Individuals of African ancestry have median Lp(a) concentrations two- to threefold higher than individuals of European or East Asian ancestry, and in African populations Lp(a) concentration is less tightly linked to isoform size [31]. The INTERHEART study demonstrated that elevated Lp(a) was associated with myocardial infarction across seven ethnic groups, although the absolute concentrations and population-attributable risk differed substantially [6]. In the Multi-Ethnic Study of Atherosclerosis, the association between Lp(a) and carotid atherosclerosis was also modified by race [32]. These differences imply that genetic risk scores derived in one population cannot be transferred directly to another and that ancestry-specific reference ranges are required.

3. Mechanisms Linking Lp(a) to Early Atherogenesis

3.1. Arterial Wall Retention

Lp(a) shares with LDL the capacity to cross the endothelium and accumulate in the intima, carrying cholesterol into the vessel wall. Studies in rabbits demonstrated preferential influx and reduced fractional loss of Lp(a) in atherosclerotic compared with non-lesioned aorta, indicating that Lp(a) is selectively retained in diseased arterial segments [33]. The lysine-binding properties of apo(a) facilitate binding to extracellular matrix components such as fibrin, fibronectin and proteoglycans, and apo(a) has been localized within human atherosclerotic plaques [34]. On a per-particle basis, Lp(a) is estimated to be substantially more atherogenic than LDL, which may explain why even moderate elevations contribute to lesion initiation in young individuals.

3.2. Oxidized Phospholipids and Vascular Inflammation

A major advance in understanding Lp(a) pathogenicity was the discovery that Lp(a) is the preferential carrier of pro-inflammatory oxidized phospholipids (OxPL) in human plasma [35]. OxPL are bound both in the lipid phase and covalently to the KIV-10 lysine-binding site of apo(a) [15]. Plasma OxPL-apoB levels closely track Lp(a) concentration and isoform size and predict coronary artery disease and cardiovascular events independently of conventional risk factors [36]. Mechanistically, Lp(a)-associated OxPL activate endothelial cells, increase monocyte adhesion and transendothelial migration, and induce a pro-inflammatory monocyte phenotype [37]. Positron emission tomography studies showed that individuals with elevated Lp(a) have increased arterial wall inflammation, and that their circulating monocytes display enhanced migratory capacity that can be reproduced by OxPL in vitro [37]. Elevated Lp(a) also increases endothelial glycolysis via 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3, thereby facilitating inflammation and leukocyte extravasation [38]. These observations support the concept that OxPL constitute a unifying mechanism for the atherogenic, inflammatory and calcific properties of Lp(a) [16]. The same OxPL-mediated pathways promote osteogenic differentiation of valvular interstitial cells, accounting for the strong association between *LPA* variants and calcific aortic valve disease [39].

3.3. Antifibrinolytic and Prothrombotic Properties

The structural homology between apo(a) and plasminogen suggested early on that Lp(a) might interfere with fibrinolysis. Lp(a) binds fibrin and competes with plasminogen, reducing plasmin generation [40]. Detailed biochemical studies identified the domains of apo(a) required for inhibition of plasminogen activation on fibrin and degraded fibrin surfaces [41]. Although epidemiological evidence linking Lp(a) to venous thromboembolism in adults is weak, an antifibrinolytic effect may be particularly relevant in children and young adults, in whom arterial ischemic events frequently have a thrombotic component (see Section 5.4).

4. Genetic Evidence for Causality

The causal role of Lp(a) in ASCVD has been established by Mendelian randomization, which exploits the random allocation of alleles at conception. In the Copenhagen City Heart Study, genetically elevated Lp(a), indexed by KIV-2 genotype, was associated with an increased risk of myocardial infarction of a magnitude consistent with that predicted from observed concentrations [10]. The concordance between genetic and observational estimates was confirmed for rs10455872 and rs3798220 [9] and in large consortia combining genetic data from hundreds of thousands of participants [42,43]. These analyses have also been used to estimate the magnitude of Lp(a) lowering required to achieve clinical benefit: Burgess and colleagues estimated that an absolute reduction of approximately 100 mg/dL would be needed to produce a risk reduction comparable to lowering LDL cholesterol by 1 mmol/L [42], whereas a subsequent analysis with isoform-adjusted estimates suggested a required reduction of approximately 66 mg/dL [43]. Genetic studies have likewise implicated Lp(a) causally in calcific aortic valve stenosis [39] and peripheral arterial disease [27].

5. *LPA* Variation and Early Development of Atherosclerosis

5.1. Lp(a) from Birth to Adulthood

A defining feature of Lp(a) is that its concentration is genetically programmed and expressed early in life. In the population-based COMPARE study, Lp(a) concentrations were low at birth but rose rapidly during the first months of life, approaching adult-equivalent values in early childhood [44]. In nearly 3,000 children followed at a pediatric lipid clinic, Lp(a) concentrations were largely stable into adulthood, with modest increases in some individuals, indicating that a single childhood measurement provides a reasonable estimate of lifelong exposure [45]. These data form the rationale for considering Lp(a) measurement in youth, particularly in children with a family history of premature ASCVD, familial hypercholesterolemia or a history of ischemic stroke [11,46].

5.2. Prospective Evidence from Youth Cohorts

The most direct evidence that high Lp(a) in youth predicts adult disease comes from the International Childhood Cardiovascular Cohort Consortium. In this analysis of participants whose Lp(a) was measured in childhood or adolescence and who were followed for several decades, elevated Lp(a) in youth was associated with a higher risk of major cardiovascular events in adulthood, and the risk was greatest when high Lp(a) coincided with elevated LDL cholesterol [47]. These findings indicate that the atherogenic effects of Lp(a) accumulate over a lifetime and that risk stratification can begin long before clinical disease.

5.3. Premature Coronary Artery Disease

High Lp(a) is consistently over-represented in patients with premature coronary artery disease. In the Copenhagen City Heart Study, individuals with extreme Lp(a) levels (above the 95th percentile) had an approximately two- to threefold higher risk of myocardial infarction than those with levels below the 22nd percentile [8]. In a case-

control study of patients with acute coronary syndrome before the age of 35 years, Lp(a) concentrations above 50 mg/dL were markedly more frequent than in controls and were independently associated with premature events [48]. Because conventional risk factors are often modest in young patients, elevated Lp(a) may account for a substantial proportion of otherwise unexplained early events. Genetic risk scores built from *LPA* variants improved discrimination modestly beyond measured Lp(a) and conventional risk factors in the UK Biobank [49].

5.4. Arterial Ischemic Stroke in Children and Young Adults

The association between Lp(a) and ischemic stroke appears to be particularly strong in the young. In a German multicentre study, elevated Lp(a) was one of the main risk factors for spontaneous ischemic stroke in childhood [50]. A meta-analysis of observational studies in neonates and children confirmed that elevated Lp(a) is among the thrombophilic traits that significantly increase the odds of a first arterial ischemic stroke [51]. In North American children, elevated Lp(a) and small apo(a) isoforms were both associated with arterial ischemic stroke [52]. In adults, a meta-analysis showed that the association between Lp(a) and ischemic stroke was stronger in younger individuals [53]. The contribution of antifibrinolytic properties of apo(a) to these early thrombotic events remains to be established.

5.5. Interaction with Familial Hypercholesterolemia

The combination of familial hypercholesterolemia (FH) and high Lp(a) is particularly atherogenic. Because standard laboratory methods for LDL cholesterol include the cholesterol content of Lp(a), a substantial fraction of individuals with a clinical diagnosis of FH may actually have high Lp(a) as the primary cause of their phenotype [54]. In genetically confirmed FH, elevated Lp(a) further increases coronary risk, and cascade testing that includes Lp(a) measurement identifies additional relatives at high risk [55]. Children with FH accumulate LDL exposure from birth and benefit from early statin therapy [56]; in those with concomitant high Lp(a), the cumulative atherogenic burden is even greater, which strengthens the case for Lp(a) testing in pediatric FH clinics.

5.6. Subclinical Atherosclerosis and Plaque Progression

Imaging studies have linked Lp(a) to subclinical disease and plaque progression. In patients undergoing serial coronary computed tomography angiography, elevated Lp(a) was associated with accelerated progression of low-attenuation, necrotic-core plaque [57]. Lp(a) and coronary artery calcification provide independent and additive prognostic information [58]. Associations between Lp(a) and carotid atherosclerosis have also been described, with differences between ancestries [32]. Together, these data support a model in which genetically elevated Lp(a) drives both early lesion formation and the development of high-risk plaque features.

5.7. A Life-Course Model of *LPA*-Driven Atherogenesis

Taken together, the data reviewed above support a life-course model in which *LPA* genotype sets the level of a lifelong atherogenic exposure that begins within the first years of life [44,45]. In carriers of small KIV-2 alleles, of the rs10455872 or rs3798220 risk alleles, or of combinations of these variants, high Lp(a) concentrations deliver cholesterol and OxPL to the arterial intima continuously from childhood [9,35]. During this period the particle is preferentially retained at sites of early lesion formation [33], and its OxPL cargo activates endothelial cells and primes circulating monocytes toward a pro-inflammatory, pro-migratory phenotype [37,38]. The antifibrinolytic properties of apo(a) may add a thrombotic component that becomes clinically apparent as arterial ischemic stroke in childhood or as premature acute coronary syndrome in young adults [41,48,52]. When high Lp(a) coexists with other risk factors that also act from early life, most notably genetically elevated LDL cholesterol in FH, the cumulative burden rises sharply and clinical disease is brought forward by years or decades [47,54,55].

Conversely, carriers of large isoforms or of loss-of-function variants such as the KIV-2 4925G>A splice variant or the rs41272114 null allele experience a lifelong reduction in exposure that is associated with lower coronary risk [25,27,28]. This natural experiment provides the strongest argument that the timing of intervention matters: genetic variants act for an entire lifetime, whereas pharmacological lowering in late adulthood may not recapitulate the same benefit [42,43]. The principal *LPA* variants discussed in this review and their effects are summarized in Table 1.

Table 1. Principal genetic variants at the *LPA* locus and their relevance to early atherosclerosis.

Variant	Type	Effect on Lp(a)	Clinical association
KIV-2 copy number (1 to >40 repeats)	Copy number variation	Inverse relationship between repeat number and concentration; main determinant of isoform size	Small isoforms associated with approximately twofold higher coronary and ischemic stroke risk
rs10455872	Intronic SNV	Strong increase; tags small KIV-2 alleles	Higher coronary heart disease risk; aortic valve calcification
rs3798220 (I4399M)	Missense SNV, protease-like domain	Strong increase; tags small isoforms	Higher coronary heart disease risk
rs41272114	Splice-site SNV (null allele)	Loss of expression from affected allele	Lower Lp(a) and lower coronary risk
4925G>A (KIV-2)	Splice SNV within KIV-2 repeat	Marked reduction, masked on short isoforms	Lower coronary risk

Population-specific loss-of-function variants	Nonsense/splice SNVs	Reduced or absent Lp(a)	Lower coronary risk without evident adverse phenotypes
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SNV, single-nucleotide variant; KIV-2, kringle IV type 2.

6. Clinical Implications: Measurement and Risk Stratification

Recognition of Lp(a) as a genetically determined, causal risk factor has prompted major guidelines and consensus statements to recommend its measurement. The 2019 European Society of Cardiology/European Atherosclerosis Society guidelines recommended measuring Lp(a) at least once in each adult's lifetime [59], a position expanded in the 2022 European Atherosclerosis Society consensus statement, which proposed thresholds of below 30 mg/dL (75 nmol/L) to rule out and above 50 mg/dL (125 nmol/L) to rule in increased risk, and endorsed cascade testing and testing of youth with a family history of high Lp(a) or premature ASCVD [11]. The National Lipid Association and the American Heart Association have issued similar statements [12]. Because Lp(a) concentration is stable, repeat measurement is generally unnecessary, and reporting in molar units with isoform-insensitive assays is preferred [21].

From a genetic standpoint, direct genotyping of *LPA* variants offers the possibility of identifying high-risk individuals at birth. However, the complexity of the locus means that a small number of SNVs captures only part of the genetic variance, and ancestry-specific effects limit transferability [29,30]. Measured Lp(a) concentration therefore remains the clinical standard, whereas *LPA* genetic scores may be useful in research settings and for interpreting Mendelian randomization analyses [49]. Notably, the risk associated with Lp(a) appears to be modulated by other risk factors: in a primary prevention cohort, the excess risk attributable to high Lp(a) was attenuated at low LDL cholesterol levels [60], suggesting that intensive control of modifiable factors is warranted in individuals with high genetic Lp(a).

7. Therapeutic Perspectives

Conventional lipid-lowering therapies have limited effects on Lp(a). Statins do not lower and may modestly increase Lp(a) [61], and in an individual-participant meta-analysis of statin trials, elevated baseline and on-treatment Lp(a) remained associated with residual cardiovascular risk [62]. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors reduce Lp(a) by approximately 20–30%, and a secondary analysis of the FOURIER trial suggested that patients with higher baseline Lp(a) experienced greater absolute benefit from evolocumab [63]. However, these agents act primarily on LDL particles and cannot normalize the very high concentrations observed in carriers of small apo(a) isoforms.

The genetic specificity of Lp(a) makes it an attractive target for nucleic acid-based therapies acting on *LPA* transcripts in hepatocytes. The antisense oligonucleotide (ASO) targeting apo(a) mRNA reduced Lp(a) in a dose-dependent manner in phase 1 and 2 studies [64], and its N-acetylgalactosamine-conjugated successor, pelacarsen, reduced Lp(a) by up to approximately 80% in patients with established cardiovascular disease [65]. Small interfering RNAs (siRNAs) have produced even greater and more durable reductions: olpasiran lowered Lp(a) by more than 95% at higher doses [66], and both SLN360 (zerlasiran) and lepodisiran produced deep reductions sustained for months after single doses [67,68]. An oral small-molecule inhibitor of apo(a)–apoB interaction, muvalaplin, also substantially lowered Lp(a) in a phase 1 study [69].

The first cardiovascular outcome trial of an Lp(a)-targeted therapy, Lp(a)HORIZON, which randomized more than 8,300 patients with established cardiovascular disease and elevated Lp(a) to pelacarsen or placebo, was reported in September 2026 to have missed its primary composite endpoint despite effective Lp(a) lowering, in a population with well-controlled LDL cholesterol [70]. Full publication of these results is awaited, and the interpretation is complex: the required absolute reduction estimated from genetic studies [42,43], the baseline concentrations of the enrolled participants, the duration of treatment relative to lifelong genetic exposure, and the background of intensive LDL control [60] may all be relevant. The ongoing siRNA outcome trials, which achieve deeper reductions, will be crucial in determining whether lowering Lp(a) in adulthood can reverse risk accumulated since childhood. From the perspective of early atherosclerosis, these results reinforce the concept that Lp(a)-related risk is cumulative and that prevention may be most effective when started early.

8. Knowledge Gaps and Future Directions

Several questions remain open. First, the functional consequences of the many KIV-2 SNVs and regulatory variants identified by sequencing are largely uncharacterized, and long-read sequencing of the full *LPA* locus in diverse populations is needed [29,30]. Second, the relative contributions of cholesterol delivery, OxPL-mediated inflammation and antifibrinolysis to early lesion development have not been resolved [16]. Third, prospective data on the optimal age and strategy for Lp(a) screening in children are limited, and evidence that early detection changes outcomes is lacking [45,46]. Fourth, the outcome data for Lp(a)-lowering therapies and their implications for younger individuals with genetically high Lp(a) need careful evaluation. Finally, ancestry-specific reference ranges and risk thresholds are required for equitable implementation [6].

9. CONCLUSIONS

The *LPA* gene is the dominant determinant of plasma Lp(a) concentration, and its polymorphisms, particularly the KIV-2 copy number variation, common single-nucleotide variants and loss-of-function alleles, define a lifelong exposure that is established in early childhood. Converging evidence from molecular biology,

epidemiology and Mendelian randomization identifies Lp(a) as a causal driver of atherosclerosis acting through arterial retention, oxidized phospholipid-mediated inflammation and impaired fibrinolysis. The genetic nature of this risk factor explains its prominent role in premature coronary artery disease, arterial ischemic stroke in children and young adults, and the amplified risk observed in familial hypercholesterolemia. Measurement of Lp(a) at least once in life, and in youth when there is a family history of premature disease or high Lp(a), offers an opportunity to identify individuals at risk long before clinical events. Although the first outcome trial of a targeted Lp(a)-lowering agent did not confirm clinical benefit, the deeper reductions achieved by small interfering RNAs, together with a better understanding of the timing and magnitude of lowering required, may still allow genotype-informed prevention to counteract the early atherogenic effects of *LPA* variation.

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Conflicts of Interest

The author declares no conflicts of interest.

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