thematic review series

Thematic Review Series: Lipoprotein (a): Coming of Age at Last

Lipoprotein (a): impact by ethnicity and environmental and medical conditions

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Abstract Levels of lipoprotein (a) [Lp(a)], a complex between an LDL-like lipid moiety containing one copy of apoB, and apo(a), a plasminogen-derived carbohydrate-rich hydrophilic protein, are primarily genetically regulated. Although stable intra-individually, Lp(a) levels have a skewed distribution inter-individually and are strongly impacted by a size polymorphism of the *LPA* gene, resulting in a variable number of kringle IV (KIV) units, a key motif of apo(a). The variation in KIV units is a strong predictor of plasma Lp(a) levels resulting in stable plasma levels across the lifespan. Studies have demonstrated pronounced differences across ethnicities with regard to Lp(a) levels and some of this difference, but not all of it, can be explained by genetic variations across ethnic groups. Increasing evidence suggests that age, sex, and hormonal impact may have a modest modulatory influence on Lp(a) levels. Among clinical conditions, Lp(a) levels are reported to be affected by kidney and liver diseases.—Enkhmaa, B., E. Anuurad, and L. Berglund. **Lipoprotein (a): impact by ethnicity and environmental and medical conditions. *J. Lipid Res.* 2016.** 57: **1111–1125.**

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ETHNICITY/RACE AND LIPOPROTEIN (a) LEVELS

Lipoprotein (a) levels in different population groups

One of the most distinctive features regarding lipoprotein (a) [Lp(a)] has been the variability in levels between different population groups. Although substantial knowledge has been obtained regarding genetic variability of apo(a) between different populations, the underlying causes for this difference in levels are still largely unresolved. Early population studies investigating the association of Lp(a) with coronary artery disease (CAD) risk were largely conducted in European populations (1–4). However, striking differences in Lp(a) concentrations and distribution were noted by several groups. As an example, Blacks have a mean Lp(a) concentration twice as high as in Whites (5–8). Beyond Blacks and Whites, a heterogeneous distribution of Lp(a) concentration across Asian populations was noted with substantially elevated Lp(a) concentrations in Indians as compared with Chinese, a finding confirmed in other studies (**Table 1**) (7, 9). The Lp(a) distribution pattern among Chinese was closer to Whites; while among Indians, the pattern was intermediate between those of Blacks and Whites. These findings were extended to seven ethnic groups, representing Caucasians (Tyrolean, Icelandic, Hungarian), Asians (Indian, Chinese, Malay), and Blacks (Sudanese), where the overall pattern was confirmed (10). Another study in four ethnic groups demonstrated a similar ethnic-specific difference with the mean Lp(a) concentration in Ghanaian Blacks being 1.6- to 2-fold higher than those of German, Chinese, or San populations, respectively (Table 1) (11). Also among children, mean Lp(a) levels were 1.7-fold higher in African-Americans versus Caucasians (12). Among the elderly, Lp(a) levels were higher in African-American men compared with Caucasians (13). Notably, a lower Black/White ratio was reported in many studies involving US Blacks versus non-US Blacks, possibly due to gene admixture (13). Among Mexican-Americans, men and women

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Abbreviations: CAD, coronary artery disease; CRP, C-reactive protein; ESRD, end-stage renal disease; HD, hemodialysis; HRT, hormone replacement therapy; IDDM, type 1 diabetes mellitus; IL, interleukin, KIV, kringle IV; LD, linkage disequilibrium; Lp(a), lipoprotein (a); NIDDM, type 2 diabetes mellitus; NIH, National Institutes of Health; OxPL, oxidized phospholipid; PNR, pentanucleotide repeat.

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TABLE 1. Lp(a) concentrations in different ethnic populations

Ethnic Population (Reference)	Lp(a) Level (mg/dl)
Asians	
Chinese (11)	15 (6–93)
Chinese from Singapore (10)	7.2 ± 13.1
Chinese Americans (9)	9 (5–19)[a]
Japanese (62)	19.5 ± 18.5
Asian Indians (9)	15 (8–33)[a]
Indians from Singapore (10)	20.1 ± 15.9
Malaysian from Singapore (10)	12.9 ± 17.9
Caucasians	
Hungarians (10)	8.3 ± 11.0
Tyrolean (10)	14.1 ± 19.4
Icelandic (10)	13.5 ± 17.7
German (11)	9 (1–105)
Non-Hispanic Whites (105)	10 (3–33)[a]
Non-Hispanic Whites (9)	12 (6–30)[a]
Non-Hispanic Whites (8)	8 (3–28)[a]
Hispanics (14)	5.0 ± 0.5[b]
African descent	
Ghanaians (11)	26 (3–240)
San (Bushmen) (11)	15 (4–105)
Sudanese (10)	45.7 ± 25.9
African-Americans (105)	45 (25–75)[a]
African-Americans (8)	31 (15–54)[a]

Data are expressed as mean ± SD or as the median and interquartile range.

[a]To facilitate comparison, Lp(a) levels given in nmol/l in the original article were converted into mg/dl by use of a conversion factor of 2.4 nmol/l = 1 mg/dl.

[b]Data are shown as mean ± SEM.

had significantly lower Lp(a) levels compared with their respective non-Hispanic White counterparts (14). Recent studies in a multi-ethnic population have emphasized the importance of race/ethnicity as a key variable in assigning Lp(a) cutoff values for CAD risk assessment and the need to develop the most clinically useful Lp(a) cutoff values in individual race/ethnicity groups (15).

The apo(a) size polymorphism and Lp(a) levels in Whites and Blacks

Mirroring the copy number variation in the apo(a) gene (16), there is a substantial size heterogeneity of the apo(a) protein ranging from, overall, 12 to more than 50 kringle IV (KIV) repeats, the majority being KIV type 2 (17–20). Most individuals carry two different-size apo(a) alleles, and the degree of heterozygosity at the genetic level is very high (>95%) (17). However, as not all apo(a) alleles are expressed as protein, the degree of heterozygosity at the protein level is somewhat lower (~70%). In general, within an individual, the larger apo(a) isoform is more likely to be "nonexpressed" at the protein level than the smaller isoform. This trend is more apparent in Caucasians with a gradual rise in the nonexpressed allele frequency with an increasing number of KIV repeats. Among African-Americans, a more U-shaped distribution was seen (21) (**Fig. 1**). Furthermore, the smaller apo(a) size in any given individual does not always represent the quantitatively dominating Lp(a) isoform (21, 22). The larger apo(a) isoform is reported to be dominant in about one-quarter of both African-American and Caucasian heterozygotes, whereas dominance of the smaller isoform is more common in Caucasians than in African-Americans (21).

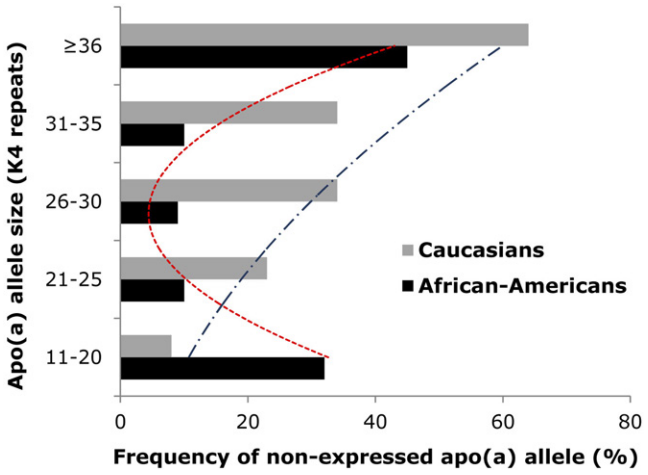

Fig. 1. Frequency distributions of nonexpressed apo(a) alleles across apo(a) size ranges in African-Americans and Caucasians. In general, within an individual, the larger apo(a) isoform is more likely to be nonexpressed at the protein level than the smaller isoform. This trend is more apparent in Caucasians with a gradual rise in the nonexpressed allele frequency with an increasing number of KIV repeats (21). Among African-Americans, a more U-shaped distribution was observed.

An example of frequency distribution of apo(a) alleles and isoform sizes for Caucasians and African-Americans are shown in **Fig. 2**. Among Caucasians, nonexpressed alleles (the gap between the allele and isoform curves) were most frequent in the mid-range, whereas among African-Americans, they were fairly evenly distributed across apo(a) sizes (21).

Associations between *LPA* polymorphisms and Lp(a) levels across populations

As Lp(a) is one of the most heritable quantitative traits in humans (23, 24), efforts to understand the ethnic variability in Lp(a) concentrations have largely focused on genetics. A large proportion of variability in Lp(a) levels can be explained by variations in the *LPA* locus, mainly by the apo(a) gene size polymorphism, although the contribution of this variability to the overall plasma Lp(a) level varies across ethnicities (20–80%) (25). Over time, several genetic variants at the *LPA* locus have been identified predicting Lp(a) levels and explaining some of the variability in Lp(a) concentrations, again with a variable impact across populations. Notably, three SNPs contribute to the African-American/Caucasian difference in Lp(a) concentration (26). Two SNPs (T3888P and G+1/inKIV-8A), both suppressing Lp(a) assembly, were more common in Caucasians, whereas the third SNP (G-21A), increasing apo(a) promoter activity, was more common in African-Americans. In addition, a pentanucleotide repeat (PNR), $[TTTTA]_n$ (8–11 repeats), in the promoter region of *LPA* explained up to 14% of the variation in Lp(a) concentration among Caucasians, independent of KIV repeats (27). Furthermore, the PNR influenced allele-specific apo(a) levels in Caucasians, but not in African-Americans, with a stepwise decrease with increasing PNR number (28).

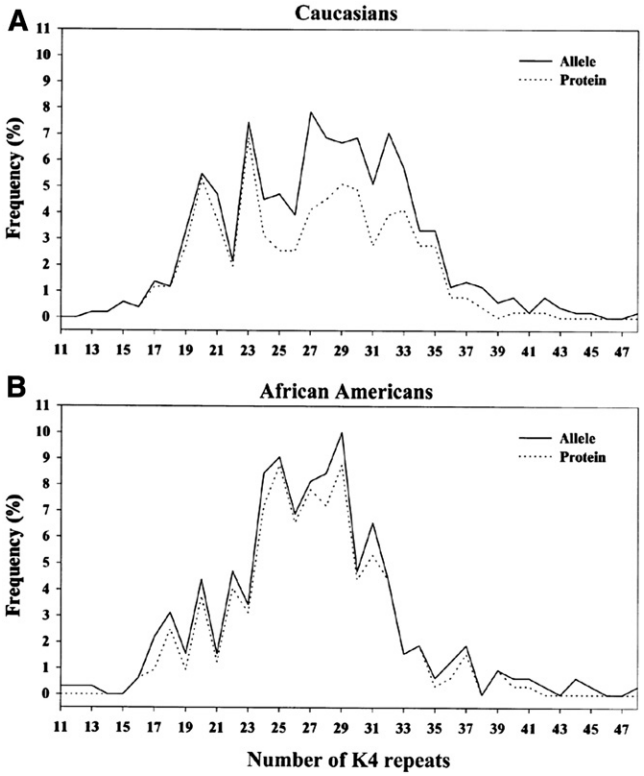

Fig. 2. Frequency distribution of apo(a) alleles and isoforms in Caucasians (A) and African-Americans (B). Alleles are represented by the solid lines and apo(a) protein isoforms by the dashed lines (the dashed lines are not shown where they coincide with the solid lines). The isoform distribution was calculated by dividing the total number of protein bands detected by the total number of alleles, separately for each population. Homozygotes (n = 15) were excluded, as it was not possible to determine whether the single apo(a) protein band corresponded to one or two proteins. The African-American distribution had a narrower and taller peak while the Caucasian distribution was wider. Among Caucasians, nonexpressed alleles (the gap between the allele and isoform curves) were most frequent in the mid-range, whereas among African-Americans, they were fairly evenly distributed across apo(a) sizes. This figure was originally published in (21). © The American Society for Biochemistry and Molecular Biology.

Recently, two SNPs at the *LPA* locus (rs10455872, which maps to intron 25, and rs3798220, located in the protease-like domain) have been associated with high Lp(a) levels and smaller size apo(a) (29–34). Demonstrating the variability in effect across three ethnic groups (non-Hispanic Whites, Mexican-Americans, non-Hispanic Blacks), a total of 15 *LPA* SNPs were associated with Lp(a) concentrations at least in one studied population, six in two populations, but none in three populations (35). Among non-Hispanic Whites, three SNPs together explained 7% of the variation in Lp(a) concentrations; in Mexican-Americans, six SNPs together explained 11%; and among non-Hispanic Blacks, 12 SNPs explained 9% of this variation. These findings point to a variability in the association between SNPs and Lp(a) concentrations across populations, and further, that individual *LPA* variants may contribute to interethnic differences in Lp(a) levels.

A substantial heterogeneity in estimating the proportion of Lp(a) variance explained by SNPs alone or in conjunction with the size polymorphism has been observed (29, 31, 32). Ronald et al. (32) identified a set of nine SNPs accounting for 30% of the variation in Lp(a) concentration, five of which overlapped with a set of seven SNPs identified by others (31). Six of these nine SNPs, of which four had previously been reported (29, 30), predicted Lp(a) concentrations conditional on the number of KIV repeats. Accounting for apo(a) size, SNPs rs3798220 and rs10455872 were associated with Lp(a) concentrations, and together explained 22% of Lp(a) variance. It has been proposed that rs3798220 may affect protein stability (30), whereas rs10455872 may be in linkage disequilibrium (LD) with regulatory variants (36). In an Old Order Amish population, the *LPA* mRNA level was higher in carriers compared with noncarriers of rs10455872, but was not different between carriers and noncarriers of rs3798220 (37). Further, the apo(a) protein level was higher in carriers compared with noncarriers of both rs10455872 and rs3798220 (37). The question arises, to what extent does this pattern vary across ethnicity? Studies in South Asians, Chinese, and Caucasians revealed that SNP rs10455872 was prevalent only in the latter (29). In addition, SNP rs6415084 within the same haplotype block as the KIV repeat polymorphism was associated with both Lp(a) concentrations and the size polymorphism in all three ethnic groups. SNPs and apo(a) size polymorphism together explained a greater proportion of variation in Lp(a) concentration in Caucasians (36%) than in Chinese (27%) or South Asians (21%).

Two additional SNPs at the *LPA* locus (rs6919346 in intron 37 and rs1853021 (+93C/T) in the 5′ untranslated region) were associated with a modestly elevated Lp(a) level, independent of apo(a) size, in Hutterites (a founder population), and for the former SNP, this was replicated in Caucasians (38). In African-Americans, the association between *LPA* +93C/T SNP and Lp(a) concentrations was opposite to that seen in Hutterites (39). A report from the Jackson Heart Study identified multiple common SNPs associated with Lp(a), accounting for up to 7% of Lp(a) level variation, as well as >70% of the African-American/Caucasian interethnic difference (40). In contrast to Caucasians, no single common SNP has been found to explain a large portion of variation in Lp(a) concentrations in African-Americans (29, 31). A limited LD between the apo(a) size polymorphism and common SNPs on the African ancestral background could account for this contrasting result (29). This extensive variability across populations illustrates the complexity of the relationship between Lp(a) concentrations and apo(a) polymorphisms, as well as methodological difficulties in accurately assessing this relationship.

The role of genetic factors beyond the *LPA* gene in regulating Lp(a) levels across ethnicity

Recent genome-wide association studies have reported an impact on Lp(a) by other genes. In Hutterites, eight genes on chromosome 6q26-q27 significantly impacted

Lp(a) concentrations (38). An association of one SNP in the plasminogen (*PLG*) gene, rs14224, with Lp(a) concentrations was replicated in Caucasian males, and the SNP was in LD with the number of KIV repeats (38). In addition, two other SNPs in the *PLG* gene, rs783147 and rs6935921, were associated with Lp(a) levels in Caucasians, explaining 12% and ~4.5% of Lp(a) variation, respectively (41, 42). A locus influencing Lp(a) concentrations on chromosome 2 with several candidate genes, including the *TFPI* gene, was reported from a study of Spanish families (43). Others have shown a positive association of the C-allele at the −174 locus of the human interleukin (*IL*)-*6* gene with elevated Lp(a) concentrations (>60 mg/dl) (44). A meta-analysis by Zabaneh et al. (33) has identified a number of variants in four other loci, in addition to the *LPA* locus, that have a significant impact on Lp(a) levels. However, the findings could only be replicated for one locus (*TNFRSFF11A*). At present, numerous challenges, including use of specialized candidate gene chips with a restricted scope, small sample sizes, lack of replication cohorts, variability across cohorts, and focus on specific subpopulations (population isolates, end stage renal disease, or diabetes mellitus), present limitations that are further complicated by ethnic-specific differences in Lp(a) levels. Future studies addressing such limitations should bring more insights into the nature of Lp(a) heritability.

ENVIRONMENTAL FACTORS AND Lp(a) LEVELS

Age

Studies in newborns report an increase in Lp(a) levels from birth to the 7th postnatal day with a continued increase up to eight months (45). Among adolescents, Lp(a) concentrations increased in White children aged 11–17 years (12). Among adults, results have been somewhat variable. Lp(a) was associated with age in White women, but not in Black and White men (46, 47). Others report that age was significantly associated with increasing Lp(a) levels in both White men and women (48). An apparent age-related increase in Lp(a) levels was reported in Black, but not in White, female twins (49). Among Japanese, Lp(a) concentration was positively correlated with age for both men and women. Further, an association between Lp(a) and longevity has been suggested among centenarians (50–54). On the other hand, a substantial number of studies report no association between age and Lp(a) concentration (5, 14, 55–59), and the issue of to what extent age per se influences Lp(a) levels remains unresolved.

Sex

Although many studies across population groups have indicated a lack of difference in Lp(a) concentration between males and females (5, 11, 46, 58–61), the effect of sex on Lp(a) levels remains to be established. A small, but significant, elevation in Lp(a) concentration was observed in girls compared with boys for both African-Americans and Caucasians (12). A recent study also reported significantly higher Lp(a) levels in girls than in boys among healthy Arabian adolescents (56). Furthermore, the median Lp(a) concentration was higher in women than men among Whites, but not in Blacks (47). In a Japanese study, Lp(a) concentration was significantly elevated in women compared with men (62). The question has been raised whether such results might be explained by a potential confounding effect of CAD familial predisposition. Addressing this issue, no significant differences in Lp(a) concentrations between brothers and sisters were seen among healthy teenagers with a positive parental history of premature myocardial infarction (63). A study by Frohlich et al. (64) conducted in subjects with European background, found no significant difference in Lp(a) concentrations between men and women without CAD, but 2-fold increased Lp(a) concentrations in women compared with men, both with CAD. These associations remained significant after adjustments for covariates, including age. A recent study by the same group conducted in subjects with familial hypercholesterolemia reported a similar median Lp(a) concentration between men and women, although in a subgroup of subjects with CVD, Lp(a) levels were significantly higher in women (65). Among women with familial hypercholesterolemia, Nenseter et al. (66) found higher Lp(a) levels in CVD-susceptible versus CVD-resistant subjects. Thus, while a number of studies indicate higher Lp(a) levels among women, in particular under CVD-positive conditions, there are many potential confounders, such as ethnicity/race, apo(a) size distribution, menopause status, and differences in assay methodology.

Diet, normal food intake, and fasting/nonfasting state

Although there is a strong genetic impact on Lp(a) concentrations, a number of studies have reported differences in Lp(a) levels due to variations in the intake of dietary *trans*-fatty acids and saturated fat. Beyond this observation, many studies focusing on dietary interventions have failed to detect any significant effects on Lp(a) levels (67–69). Mensink et al. (70) reported an Lp(a)-increasing effect from diets rich in *trans*-monounsaturated fatty acids, and a similar result was obtained by Nestel et al. (71) with a diet enriched in elaidic acid. Reduction of saturated fat was associated with an increase in Lp(a) levels, whereas addition of saturated fat was associated with a decrease in Lp(a) levels (72, 73). In nonhuman primates, the substitution of dietary saturated fat with either mono- or polyunsaturated fatty acids resulted in a significant reduction in Lp(a) concentrations (74). In a double-blind cross-over study of moderately hypercholesterolemic postmenopausal women, compared with a partially-hydrogenated soybean oil-enriched diet, a corn oil-enriched diet lowered Lp(a) by 5% (75). Consumption of a low-fat high-carbohydrate diet for 4 weeks significantly increased Lp(a) concentration compared with a high-fat low-carbohydrate diet, and changes in Lp(a) were strongly correlated with changes in the oxidized phospholipid (OxPL)/apoB ratio (76). Among overweight/obese postmenopausal women, a 6 month hypocaloric dietary intervention significantly

decreased Lp(a) concentrations by 4% (77). In the Omni Heart Trial, a randomized, three-period crossover feeding study, participants were given DASH-type healthy diets rich in carbohydrates, protein, or unsaturated fat for 6 weeks each (78). Compared with baseline, all interventional diets increased mean Lp(a) levels by 2–5 mg/dl. A diet rich in unsaturated fat increased Lp(a) levels less than a protein-rich diet, with a difference of 1.0 mg/dl in Whites and 3.7 mg/dl in Blacks. A diet rich in unsaturated fat increased Lp(a) levels less than a carbohydrate-rich diet, with a difference of −0.6 mg/dl in Whites and −1.5 mg/dl in Blacks, while a protein-rich diet increased Lp(a) levels more than a carbohydrate-rich diet, with a difference of 0.4 mg/dl in Whites and 2.2 mg/dl in Blacks. Generally, diets high in unsaturated fat increased Lp(a) levels less than diets rich in carbohydrate or protein, with greater changes in Blacks than Whites. These results suggest that substitutions of saturated fat with dietary mono- and polyunsaturated fatty acids may be preferable over protein or carbohydrates with regard to Lp(a). Overall, the magnitude of the observed changes in Lp(a) concentrations due to dietary interventions has been relatively modest. Presently, clinical guidelines do not specify whether Lp(a) concentrations should be measured in the fasting or nonfasting state. In the Copenhagen General Population Study and the Copenhagen City Heart Study participants, Lp(a) concentrations were minimally affected in response to normal food intake (17 mg/dl at fasting versus 19 mg/dl at 3–4 h since the last meal) (79).

Exercise and BMI

Many population-based and cross-sectional studies have been unable to detect an association between Lp(a) and physical activity level (49, 80–86). However, in a large multicenter study of Finnish children and young adults, an inverse correlation was seen between Lp(a) concentration and physical activity with a dose-response relationship (87). In line with these findings, physical fitness was inversely associated with Lp(a) concentration in young children and adolescents with diabetes mellitus (88). In addition, Lp(a) levels were higher in experienced distance runners and in body builders who exercised regularly, suggesting a possible effect of prolonged high-intensity exercise training on Lp(a) levels (89, 90). Overall, the magnitude of exercise-induced changes in Lp(a) levels was modest, and any impact related to specific apo(a) size isoforms has not been addressed. Despite improvements in fitness and other plasma lipoprotein concentrations, intervention studies extending from a few weeks to 4 years have not reported any changes in median Lp(a) concentration in response to moderate exercise training (83, 91–94). In a large number of Japanese subjects, Lp(a) concentrations were significantly lower in subjects with a BMI of >26 kg/m^2 than in subjects with a BMI of ⩽26 kg/m^2 in both sexes, and BMI in females was a significant independent variable (62). On the other hand, many studies have not found any impact of BMI on Lp(a) concentrations across gender groups (5, 46, 47, 49, 59).

Inflammation

The inflammatory response is mediated by systemic acute phase reactants, such as C-reactive protein (CRP), fibrinogen, and serum amyloid A (95–97), as well as vascular inflammatory biomarkers, such as pentraxin 3 (PTX-3) and lipoprotein-associated phospholipase A_2 (98, 99). The apo(a) gene contains response elements to inflammatory factors such as IL-6, and Lp(a) stimulates release of proinflammatory cytokines from vascular endothelial and smooth muscle cells, as well as from monocytes and macrophages (100, 101). A recent study reported increased Lp(a) levels in individuals with elevated IL-6 levels, and that an IL-6 blockade by tocilizumab reduced Lp(a) levels (102). Furthermore, expression of IL-6 response genes in human liver biopsies was correlated with *LPA* gene expression in vivo, and treatment with tocilizumab inhibited IL-6-induced *LPA* mRNA and protein expression in human hepatocytes (102). Importantly, OxPLs, which possess strong proinflammatory potentials, are preferentially carried on Lp(a) particles (103). Of note, the correlation between OxPL and Lp(a) concentration was stronger in individuals with smaller apo(a) isoforms than in individuals with larger apo(a) isoforms (104). These findings suggest a synergy between inflammation and Lp(a), and the magnitude of this relationship may differ across different ethnic/racial populations.

The impact of an inflammatory burden, as detected by elevated concentrations of biomarkers for systemic and vascular inflammation on Lp(a) levels associated with a defined apo(a) size, has been explored in several studies (105–107). These levels have been characterized as isoform- or allele-specific apo(a) levels (**Fig. 3**). Increased CRP and fibrinogen concentrations were significantly associated with higher allele-specific Lp(a) levels for smaller apo(a) size in African-Americans, while a higher plasma lipoprotein-associated phospholipase A_2 activity was associated with an elevated allele-specific Lp(a) level for smaller apo(a) size in both African-Americans and Caucasians (105, 106). Further, a significant association between elevated serum amyloid A, an HDL-associated systemic inflammatory biomarker, and a higher allele-specific Lp(a) level for smaller apo(a) size was found in African-Americans (107). Taken together, these findings suggest a potential for an additive effect between molecular properties of Lp(a), in particular small size apo(a), and inflammation in promoting Lp(a)-associated CVD risk. Furthermore, fibrinogen was positively correlated with Lp(a) levels in Japanese and Whites and independently predicted levels (48, 62). Consistent with this finding, fibrinogen was also significantly associated with Lp(a) levels in older Italian subjects (60). An inflammatory score summarizing the intensity of the proinflammatory state based on four different biomarkers (CRP, fibrinogen, IL-6, and IL-1 receptor antagonist) was significantly correlated with Lp(a) concentration in this study. Among Spanish White subjects with metabolic syndrome, the CRP concentration was 2-fold greater in subjects with high Lp(a) concentrations (⩾30 mg/dl) (108). In the latter group, many other inflammatory

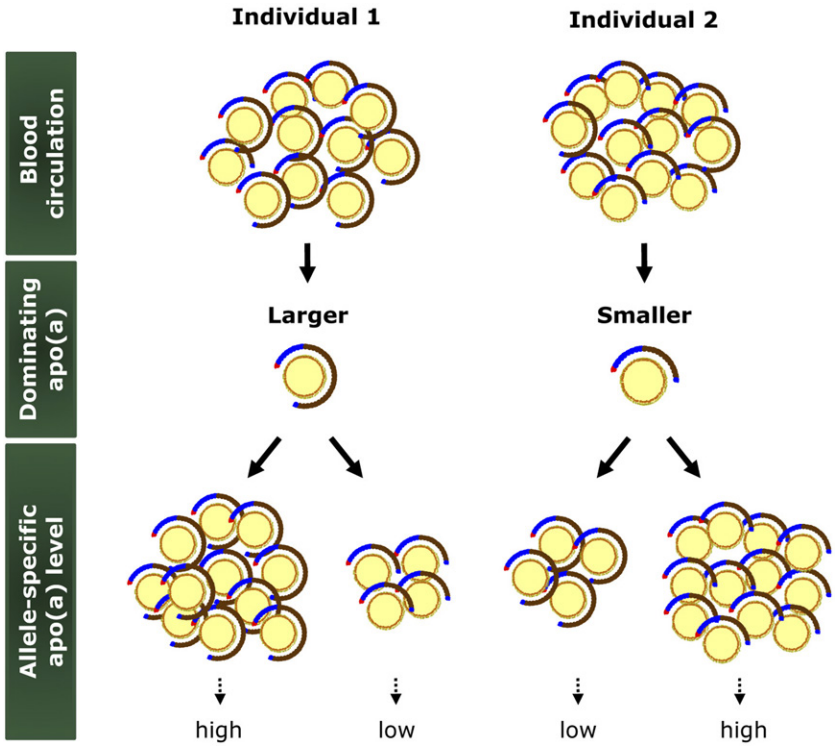

Fig. 3. Lp(a) and allele-specific apo(a) levels. Due to a high heterozygosity index at the genetic level, the total plasma Lp(a) level represents two particle populations, one carrying smaller size apo(a) and the other carrying larger size apo(a), in the majority of individuals. Depending on the dominance pattern of apo(a), some individuals have higher allele-specific apo(a) levels with larger apo(a) sizes (Individual 1) and others have higher allele-specific apo(a) levels with smaller apo(a) sizes (Individual 2).

cytokines were elevated as well. In a recent study in the Copenhagen General Population Study and the Copenhagen City Heart Study participants, median Lp(a) concentrations were higher (21 mg/dl) in subjects with CRP levels >10 mg/l than among subjects with CRP levels <1 mg/l (18 mg/dl) (79). Collectively, findings to date suggest that the presence of a proinflammatory state may contribute to higher Lp(a) levels. At present, however, data on the extent to which systemic or vascular inflammation might affect Lp(a) concentrations across various ethnic/racial or geographical groups is scarce, and further studies are warranted to explore these associations. Overall, beyond underscoring an impact of inflammation on Lp(a) concentrations, these findings reinforce the concept that inflammation-associated events may contribute to the ethnic-specific or age-related differences in Lp(a) concentrations.

Menopause

Selby et al. (49) reported no association of menopausal status with Lp(a) concentration for either Whites or Blacks, but found a significantly lower Lp(a) concentration in postmenopausal women receiving hormone replacement therapy (HRT). A meta-analysis of studies conducted between 1966 and 2004 quantifying the effects of HRT in postmenopausal women reported an average of 25% reduction in Lp(a) levels (109). In a Japanese study, Lp(a) levels were significantly higher in postmenopausal than in premenopausal or perimenopausal women. After six months of HRT, Lp(a) levels decreased by 19% and remained stable for four years (110). Also, in the Framingham Offspring Study, the mean plasma Lp(a) concentration in postmenopausal subjects was higher than in premenopausal subjects, although no significant difference was found after adjustment for age (46). In the Women's Health Study, Lp(a) concentrations were lower among women taking HRT versus those not taking HRT (111). In a recent double-blind placebo-controlled trial among postmenopausal women, treatment with letrozole, an oral nonsteroidal aromatase inhibitor, resulted in more than a doubling of mean Lp(a) levels (112). Treatment with tibolone, a synthetic steroid drug, at a dose of 2.5 mg/day for a year in postmenopausal women significantly decreased Lp(a) concentration by 28% (113).

Pregnancy

An early case report by Berg, Roald, and Sande (114) reporting on a woman with a high Lp(a) level that had given birth to three children with very low birth weights, suggested that Lp(a) may interfere with the placental circulation and cause fetal growth retardation. Subsequently, a high Lp(a) concentration was seen in a family with severe preeclampsia (115), focusing attention on the relation between Lp(a) and pregnancy. A longitudinal study reported an increase in Lp(a) levels during the first trimester, reaching its maximum in the middle of the second trimester, approximately 3-fold higher than levels at eight weeks, before returning to baseline levels at birth (116). Similar

findings have been reported by others (117–123). However, other studies have not reported changes in Lp(a) levels during normal pregnancy (124–127). In pregnancies complicated with preeclampsia or hypertension, a significantly elevated Lp(a) concentration has been observed in some studies (128–136), but not consistently (120, 121, 137–143). Of note, the majority of these studies did not assess apo(a) isoform sizes. One longitudinal study reported no change in Lp(a) concentration during pregnancy in women carrying small apo(a) isoforms versus an increase in women carrying large apo(a) isoforms (119). In two studies, apo(a) isoform distribution was similar in women with preeclampsia and normal controls (137, 144).

MEDICAL CONDITIONS AND Lp(a) LEVELS

Kidney disease

Due to the strong genetic control of the *LPA* gene, Lp(a) levels remain unaffected by most clinical conditions. Kidney disease represents an exception as one of the few clinical conditions shown to impact Lp(a) levels, with increased levels reported in patients with nephrotic syndrome, as well as in end-stage renal disease (ESRD) or during dialysis treatment (145–156). In patients with nephrotic syndrome, a decrease in Lp(a) levels has been seen after remission of the syndrome or after antiproteinuric treatment (151–153, 155, 157). In a larger study, Kronenberg et al. (158) reported a more pronounced increase in Lp(a) among carriers of larger apo(a) sizes. Similarly in patients with mild and moderate nephrotic syndrome, an increase in Lp(a) concentration was seen among carriers of large, but not small, apo(a) isoforms (159). Underlying reasons for the increase remain unresolved, but it has been proposed that a decreased plasma albumin level and reduced oncotic pressure may contribute (160). These results underscore the value of assessing Lp(a) concentrations contributed by particles carrying specific apo(a) sizes, i.e., allele-specific apo(a) levels (21, 105).

A large number of studies have investigated Lp(a) in ESRD patients (145, 161–171), and elevated Lp(a) levels are seen both in patients undergoing hemodialysis (HD) or continuous ambulatory peritoneal dialysis (145, 161–169). Further, a mild glomerular filtration rate impairment was associated with a higher Lp(a) level in a recent study of diabetic patients (172). In other studies, however, Lp(a) concentrations did not differ from those of controls (173–177). In a large multicenter study, Kronenberg et al. (145) reported higher Lp(a) levels in patients undergoing continuous ambulatory peritoneal dialysis compared with HD. Also in this case, patients with large apo(a) isoforms showed an elevation in Lp(a) levels. A similar apo(a) phenotype-specific elevation of Lp(a) was also found in some other studies in HD patients (178–181), but not uniformly (166, 182), raising the possibility that the differences observed could be due to sample size, use of different methodologies, or the definition of what constitutes small versus large apo(a) size. As for the nephrotic syndrome, the underlying pathogenic mechanism for the elevation of Lp(a) in ESRD is unknown. Increased hepatic synthesis has been suggested (183), but an impact on catabolism cannot be ruled out. Further studies are necessary to clarify whether the elevation of Lp(a) concentration and/or apo(a) isoform size contribute to elevated CVD risk in ESRD patients.

The influence of renal transplantation on Lp(a) concentrations has also been investigated and prospective studies generally demonstrate a decrease of Lp(a) levels following kidney transplantation (169, 184–193), although the follow-up period has been limited. In contrast, mixed results regarding Lp(a) have been reported from cross-sectional studies (163, 169, 174, 185, 194–204). Notably, the decrease of Lp(a) in renal transplant patients was independent of the modality of immunosuppressive therapy (169, 184–191), arguing against a contribution by an inflammatory component.

Liver disease

The liver plays a key role in lipid metabolism (205, 206). As plasma Lp(a) originates from the liver and the concentration of Lp(a) is mainly related to the hepatic apo(a) synthetic rate (17, 207, 208), pathophysiological processes affecting liver function have the potential to influence Lp(a) levels. In general, hepatocellular damage has been associated with reduced Lp(a) levels, where the decrease in levels has been in parallel with disease progression (209–212). Thus, patients with liver cirrhosis and hepatitis have lower Lp(a) concentrations compared with healthy controls (209–215). Geiss et al. (216) reported a 41% reduction in Lp(a) concentration in patients with acute hepatitis A, B, and C, and the decrease was independent of apo(a) isoform size. Notably, a significant increase in Lp(a) concentrations was seen in those patients with chronic active hepatitis C that responded completely to a 6 month interferon treatment regimen, raising the possibility of an inflammation-mediated effect or improved liver function (210). It has been suggested that a change in Lp(a) levels, together with ferritin and α-fetoprotein levels, could constitute a sensitive and early index of liver damage or an index of liver function (209, 210, 214, 217).

The effect of alcohol consumption on Lp(a) concentration has been investigated in a number of studies. In two studies, male alcohol drinkers exhibited reduced values of Lp(a) (218, 219). On the other hand, no significant differences in Lp(a) concentration between different types of alcohol consumption were found among healthy French men (220), in postmenopausal women (221), and in Spanish men and women (222). Two recent randomized controlled trials reported conflicting results on the effect of red wine on plasma Lp(a) concentrations. Thus, in one study Lp(a) decreased after regular daily ingestion of red wine (30 g alcohol/day) (223), while no effect of red wine was seen in another study (224).

Diabetes mellitus

To date, the role of Lp(a) in diabetes mellitus remains unclear. There are many contradictory reports in

the literature regarding the role of Lp(a) in diabetes mellitus, while some studies found no impact of diabetes mellitus on Lp(a) concentrations, others reported an elevation or a decrease of Lp(a) concentrations. Early studies reported elevated Lp(a) concentrations in patients with type 1 diabetes mellitus (IDDM) (225–230), as well as in patients with type 2 diabetes mellitus (NIDDM) (231, 232). Furthermore, some recent studies in Asian populations report an association between an elevated Lp(a) concentration and incident NIDDM (233–235). Rainwater et al. (236) reported significantly lower Lp(a) concentrations in NIDDM patients compared with matched nondiabetic controls in the San Antonio Heart Study. An inverse relationship between Lp(a) concentrations and NIDDM has been reported, as well as a negative correlation between Lp(a) and triglyceride levels in diabetic patients, including IDDM and NIDDM (236–239). In a recent report from the ERIC-Norfolk study, a strong inverse correlation between the Lp(a) level and new-onset NIDDM was observed (240). However, a genetic variant associated with an elevated Lp(a) level (i.e., rs10455872) was not associated with the risk of NIDDM, suggesting that elevated Lp(a) levels were not causally related to a lower risk of diabetes. On the other hand, a number of large case-control studies report similar Lp(a) concentrations in patients with IDDM (241–243) or NIDDM (242, 244, 245) compared with controls.

In a prospective Women's Health Study of healthy women with a 13 year follow up, Mora et al. (246) found an inverse association of Lp(a) concentration with risk of NIDDM with a 20–50% lower relative risk in quintiles 2–5 compared with quintile 1. A similar inverse association was reported from a general population of Danish men and women (246). The pathophysiological mechanism that may underlie the role of Lp(a) in diabetes remains unclear. Rainwater and Haffner (247) reported that Lp(a) concentrations were inversely correlated with insulin and 2 h glucose levels in both diabetics and nondiabetics. A recent in vitro study demonstrated that insulin suppresses apo(a) production in primary cynomolgus monkey hepatocytes, which may account for the lower Lp(a) levels found in NIDDM (248).

Regarding the relationship between apo(a) isoforms and diabetes, one study has reported comparable distributions of apo(a) sizes for patients with NIDDM and controls (249). In contrast, several studies reported a higher prevalence of low molecular weight isoforms in NIDDM (250–252). Findings to date underscore that larger studies using more defined populations are required to better understand the relationship of Lp(a) concentrations and apo(a) phenotypes with diabetes mellitus.

CONCLUSIONS

Much progress has recently been made in understanding the genetic regulation of Lp(a) and the role of genetic variability predicting Lp(a) levels in different ethnic groups. Many studies have confirmed ethnic differences in Lp(a) levels where subjects of African descent have about twice as high levels as Caucasians, Hispanics, and many

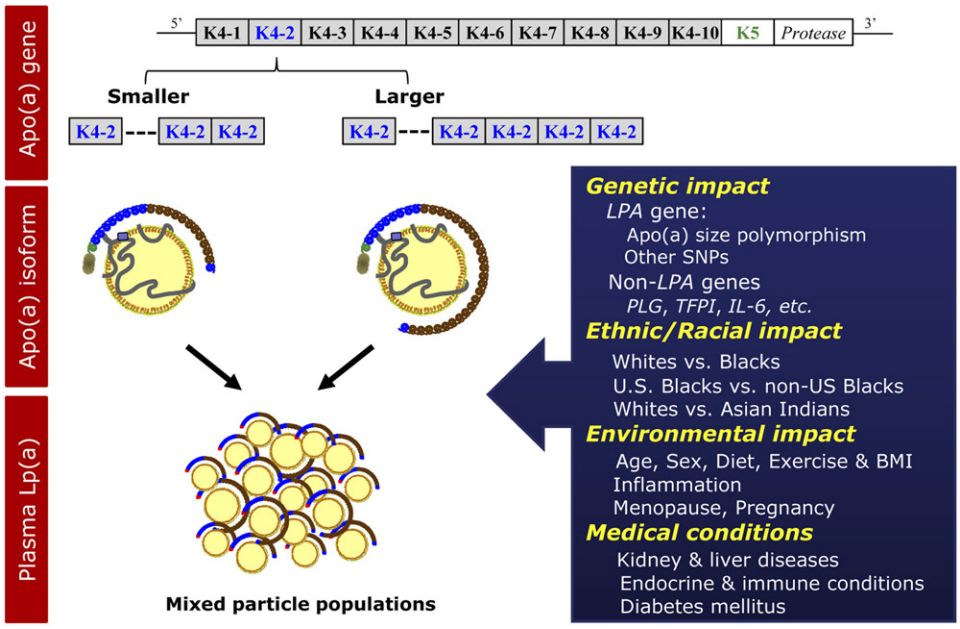

Fig. 4. Regulation of plasma Lp(a) levels. Lp(a) levels are primarily regulated by the apo(a) gene size polymorphism, i.e., copy number of KIV repeats. In addition, recent evidence suggests a role for other SNPs in the *LPA*, as well as non-*LPA* genes in the regulation of plasma Lp(a) levels. As noted in the Fig. 3, in the majority of individuals, two different populations of Lp(a) particles carrying different-sized apo(a) contribute to the overall plasma Lp(a) level. Lp(a) levels differ substantially between various ethnic/racial groups with higher levels in Blacks than in Whites. Evidence also supports a modulatory effect of age, sex, and hormones, although with a modest size on plasma Lp(a) levels. Among clinical conditions, Lp(a) levels are reported to be affected by kidney and liver diseases. K, kringle.

Asian populations, while intermediate levels are reported for South Asians. This interesting, but so far unresolved, variability might provide a possibility to assess any potential evolutionary advantage associated with Lp(a); however, as suggested in previous studies, the observed interethnic difference could also be due to the apo(a) allele distribution in the subset of the population that presumably left Africa and subsequently gave rise to other population groups. Initially, few, if any, environmental conditions were found to impact Lp(a) levels, considered as stable over the lifespan in any given individual. Although more recent studies support an impact by inflammation and some chronic disease conditions (**Fig. 4**), this fascinating lipoprotein still presents many challenges to be unlocked. During the last few years, advances have been made in the development of specific therapeutic options to lower Lp(a) levels. This has opened opportunities to carefully assess the role of Lp(a) in promoting CVD across ethnic/racial populations with differences in Lp(a) levels, as well as in a range of clinical conditions. In particular, the ability to lower Lp(a) levels by up to 78% with a new antisense drug designed to reduce hepatic apo(a) synthesis (253) offers possibilities to assess a role of Lp(a) in a variety of disorders, such as liver and kidney disease.

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