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PCSK9 in African Americans and Caucasians in Relation to Lp(a) Level, Apo(a) Size and Heritability

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Context: Inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) reduces lipoprotein(a) [Lp(a)] levels, but the association of PCSK9 with Lp(a) level and its major determinant, apolipoprotein(a) [apo(a)] size, is not fully understood.

Objective: To assess the relationship between PCSK9, Lp(a) level, apo(a) size, age, and ethnicity/race.

Design: Cross-sectional

Setting: General population

Participants: Healthy African Americans and Caucasians (n = 267); age range: 6 to 74 years.

Interventions: None.

Main outcome measure(s): PCSK9 levels, apo(a) isoform and *LPA* allele sizes, and isoform-specific Lp(a) levels.

Results: Plasma PCSK9 levels were significantly higher in African Americans vs Caucasians, in females vs males, and in adults vs children. PCSK9 levels were not associated with total plasma Lp(a) levels either in all participants or in ethnicity-specific analyses. However, PCSK9 levels were significantly positively associated with isoform-specific Lp(a) levels carried by the larger apo(a) size in all participants ($r = 0.139$, $P = 0.0361$). In ethnicity/race analyses, a significant association was seen for African Americans ($r = 0.268$, $P = 0.0199$), but not for Caucasians. In contrast, there were no significant associations of PCSK9 with isoform-specific Lp(a) levels for the smaller apo(a) sizes in all participants nor in ethnic-specific analyses. Furthermore, heritability (h^2) analyses revealed a significant heritability for PCSK9 level in both ethnic groups, with a higher estimate in Caucasians than in African Americans (47% vs 22%, respectively).

Conclusions: Among African Americans, but not Caucasians, PCSK9 levels were associated with isoform-specific Lp(a) levels carried on larger, but not smaller, apo(a) sizes. The findings illustrate a diverging relationship of PCSK9 with isoform-specific Lp(a) levels across ethnicity.

Abbreviations: apo(a), apolipoprotein(a); BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; K, kringle;LDL, low-density lipoprotein; LDL-C, low density lipoprotein cholesterol; Lp(a), lipoprotein(a); PCSK9, proprotein convertase subtilisin/kexin type 9; TC, total cholesterol.

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Inhibition of circulating proprotein convertase subtilisin/kexin type 9 (PCSK9) with monoclonal antibodies is a highly effective therapy to lower low-density lipoprotein cholesterol (LDL-C) concentrations by increasing LDL receptor activity [1-3]. PCSK9 inhibition-induced LDL-C reductions are substantial and evident across heterogeneous patient groups [1-5]. Recent clinical trials with PCSK9 inhibitors have shown reductions in atherosclerotic and recurrent ischemic cardiovascular events [6-8]. Beyond lowering LDL-C levels, several studies have firmly established a reducing effect of PCSK9 inhibition also on Lp(a) levels [9, 10]. As a role for the LDL receptor in Lp(a) clearance has not been clearly demonstrated, the mechanism behind the Lp(a)-lowering effect of PCSK9 inhibitors remains unclear [11].

Lp(a) is characterized by an LDL-like core where the apolipoprotein B-100 (apoB-100) component is linked by a single disulfide bond to apolipoprotein(a) [apo(a)], a protein with a variable number of repeated kringle (K) structures. The role of genetic variability of apo(a) as a predictor of Lp(a) levels is well established [12-14]. An elevated plasma Lp(a) level, primarily determined by a low number of K4 type 2 repeats, is an independent causal risk factor for cardiovascular disease [15, 16]. Studies to date indicate that the association between PCSK9 and Lp(a) is dependent on the apoB moiety in Lp(a) [17]. Interestingly, although statins and PCSK9 inhibitors both upregulate LDL receptors, resulting in lower LDL-C levels, they have opposite effects on Lp(a) [9, 18]. Thus, there is considerable interest to better understand the relationship between PCSK9 and Lp(a). Further, although apo(a) isoform size is a major determinant of Lp(a) levels, little is known about the relationship between apo(a) size variability and PCSK9.

In the current study, we investigated the associations between circulating levels of PCSK9 and Lp(a) in a healthy general population cohort, enrolling both children and adults and African Americans and Caucasians. We conducted in-depth analyses focusing on isoform-specific Lp(a) levels, taking both genotypic and phenotypic characteristics of apo(a) into account. We expected to find a positive association of PCSK9 with isoform-specific Lp(a) levels particularly in African Americans.

Materials and Methods

Human subjects

The details of human subjects and recruitment criteria for families have been described previously [19]. Briefly, 82 (60 Caucasian and 22 African American) families with 2 parents and 2 biological children were recruited from the general population, residing in the greater Sacramento area using community reach approaches (e.g., meetings with local community members and leaders, informational presentations at community gatherings, distributions of flyers). Families were invited to the University of California (UC) Davis Clinical and Translational Science Center for collection of demographic and medical history information using standardized questionnaires, physical examinations and for blood draws. Race/ethnicity was self-reported for each individual family member, and 182 individuals self-identified as Caucasians and 87 individuals as African Americans. Data from 2 children (1 in each ethnic group) were not included due to unavailability of blood samples, and the present report is based on findings in 181 Caucasians and 86 African Americans. The study was approved by the UC Davis Institutional Review Board and informed consent obtained from all subjects. Minors were asked to give their assents (assent form for 12-17 years old; or letter of information for 8-11 years old), and one of the parents signed the consent forms for their children.

Clinical and biochemical assessment

Blood pressure (BP) was measured with a random-zero mercury sphygmomanometer. Body mass index (BMI) was calculated as body weight (kg) divided by the square of height (m^2). For children and adolescents (6-20 years of age), BMI-for-age growth charts for either boys or girls (Centers for Disease Control and Prevention) were used to obtain a percentile ranking [20]. Concentrations of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides, and apoB-100 were measured using standard procedures. LDL-C concentrations were calculated with the formula of Friedewald et al [21]. Plasma PCSK9 levels were measured with an ELISA (RRID:AB_2847950, Legend-Max Human PCSK9 ELISA kit, Biolegend ISO, San Diego, CA). Lp(a) levels were determined with an apo(a)-size insensitive ELISA (RRID:AB_2847953, Mercodia Inc.) in plasma samples as described [22, 23]. Analyses were run according to the manufacturers' specifications in duplicate samples with 2 different quality controls, which were within the recommended precision for each test.

LPA allele and apo(a) isoform size determinations

LPA allele sizes were determined by genotyping using pulsed-field gel electrophoresis of whole DNA from leucocytes embedded in agarose plugs with a protocol adapted from Lackner et al [24] and Rubin et al [25] as described previously. Apo(a) isoform sizes were determined by Western blotting with sodium dodecyl sulfate-agarose gel electrophoresis of plasma samples, followed by immunoblotting using a modified protocol of Kamboh et al [26]. The results were related to human apo(a) isoform standard with known apo(a) isoforms (Technoclone GmbH, Austria) taking into account the inverse relation between the number of K4 repeats (i.e., apparent molecular mass) and isoform mobility during agarose gel electrophoresis. The protein isoform dominance pattern was assessed by optical analyses of the apo(a) protein expression on the Western blots, followed by a computerized analysis of scans as described previously [10, 25]. To determine isoform-specific Lp(a) levels, total plasma levels were apportioned according to the degree of intensity of the bands on the Western blot as described in detail elsewhere [10, 15, 27].

Statistics

Statistical analyses of data were performed with SAS software, version 9.4 (SAS Institute, Cary, NC). Results were expressed as mean ± standard deviation (or standard error) and/or median with interquartile range (IQR). Values of triglycerides, PCSK9, total and isoform-specific Lp(a) levels, and PCSK9/Lp(a) ratio were logarithmically transformed to achieve normality for statistical inferential analyses. Proportions were compared between groups using χ^2 test or Fisher's exact test as appropriate. Group differences in means for quantitative measures were determined by analysis of variance (ANOVA) by age and race/ethnicity. Associations of PCSK9 levels with other variables, including total and isoform-specific Lp(a) levels, were assessed with Spearman's correlation. Heritability of PCSK9 levels was estimated by the slope of the regression of offspring on mid-parental value using the regression of offspring on mid-parent (ROMP) in nuclear families (61 quartets composing of spouse pairs with 2 biological offspring). Two-tailed *P* values less than 0.05 were considered statistically significant as appropriate.

Results

Characteristics of study population

The characteristics of the study population have been previously reported [19]. Briefly, there were no significant differences in the mean age, proportion of females, BMI, BP,

the levels of TC, LDL-C, HDL-C, apoB-100, and apoA-1 between Caucasians and African Americans when assessed within each age group (children and adults). In contrast, African American adults and children had significantly lower triglycerides levels compared with their respective Caucasian counterparts. As expected, BMI, BP, and levels of TC, LDL-C, triglycerides, and apoB-100 were significantly higher in adults compared with children in both ethnic groups. The HDL-C level was significantly lower in adults compared with children in African Americans ($P = 0.002$) but not in Caucasians.

PCSK9 and Lp(a)/apo(a)-related variables in all participants

In all participants, PCSK9 levels differed significantly by ethnicity/race, age, and sex. Thus, the mean PCSK9 levels were significantly higher in African Americans vs Caucasians (104 ± 29 vs 95 ± 30 ng/mL, respectively; $P = 0.020$), in adults vs children (102 ± 29 vs 92 ± 31 ng/mL; $P = 0.001$) and in females vs males (103 ± 30 vs 94 ± 29 ng/mL, respectively; $P = 0.007$) (Fig. 1). As expected, total plasma Lp(a) levels were significantly higher in African Americans compared with Caucasians [median (IQR): 29 (12-59) vs 9 (2-36) mg/dL or mean ± SD: 38 ± 32 vs 23 ± 29 mg/dL, respectively; $P < 0.0001$]. Similarly, African Americans had significantly higher isoform-specific Lp(a) level associated with the smaller, larger, or dominating apo(a) size compared with Caucasians ($P < 0.0001$ for all). In contrast, the PCSK9/Lp(a) ratio was significantly lower in African Americans vs Caucasians (median [IQR]: 3 [2-10] vs 10 [3-33] or mean ± SD: 12 ± 18 vs 19 ± 21, respectively; $P = 0.0004$).

Both apo(a) isoform and *LPA* allele sizes were determined in all participants. There was no one with 2 *LPA* alleles that did not give rise to apo(a) protein, i.e., we were able to detect at least one apo(a) protein isoform in each individual in this cohort. Approximately 7% of individuals were homozygotes for *LPA* allele sizes, resulting in a heterozygosity index of ~93% for *LPA* genotypes. As we determined both *LPA* allele and apo(a) protein isoform sizes, we were able to pinpoint whether each expressed isoform corresponded to the larger or smaller *LPA* allele size in a given individual. Thus, in all participants, less than 4% of the smaller apo(a) sizes in allele-pairs resulted in an undetectable apo(a) protein, the corresponding rate for the larger apo(a) sizes was ~15%. In summary, PCSK9 levels differed significantly by ethnicity/race, age, and sex with higher levels in African Americans, adults, and females. Expectedly, the majority of individuals had 2 apo(a) alleles, and consequently, 2 detectable apo(a) protein isoforms.

PCSK9 and Lp(a)/apo(a)-related variables by ethnicity and age groups

Within each ethnicity, PCSK9 levels were significantly higher in adults vs children ($P = 0.0213$ for Caucasians; $P = 0.0048$ for African Americans) (Table 1). In addition, the PCSK9/Lp(a) ratio was significantly higher in adults vs children in Caucasians ($P = 0.0223$)

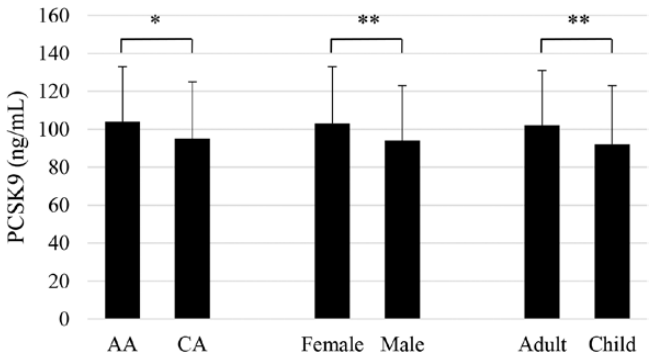

Figure 1. PCSK9 levels by ethnic, gender and age groups. Data are shown with mean and standard deviation. *: $P < 0.05$; **: $P < 0.01$. *Abbreviations*: AA, African Americans; CA, Caucasians.

Table 1. PCSK9 and Lp(a)/Apo(a)-Related Variables by Ethnicity and Age Groups

Characteristics	Caucasians			African Americans			*P* Value for Interethnic Differences	
	Children (N = 65)	Adults (N = 116)	*P* value for differences between age groups	Children (N = 36)	Adults (N = 50)	*P* value for differences between age groups	Children	Adults
PCSK9, ng/mL:			**0.0213**			**0.0048**	NS	**0.0078**
Mean ± SD	90 ± 34	98 ± 27		94 ± 26	111 ± 30			
Median (IQR)	86 (65-109)	93 (78-113)		90 (78-108)	110 (89-125)			
Lp(a), mg/dL:			NS			NS	0.0575	**0.0003**
Mean ± SD	27 ± 28	21 ± 29		38 ± 29	38 ± 34			
Median (IQR)	13 (3-47)	7 (2-32)		32 (14-63)	27 (10-56)			
PCSK9/Lp(a) ratio:			**0.0223**			NS	NS	**0.0016**
Mean ± SD	17 ± 22	20 ± 20		11 ± 19	12 ± 17			
Median (IQR)	5.8 (1.7-24.3)	11.2 (3.4-35.9)		2.9 (1.6-7.8)	3.7 (1.9-10.8)			
ISL - larger, mg/dL:			NS			NS	NS	**0.0002**
Mean ± SD	9 ± 2	9 ± 14		13 ± 13	16 ± 14			
Median (IQR)	5 (2-13)	3 (1-11)		8 (5-18)	12 (2-25)			
ISL - smaller, mg/dL:			NS			NS	**0.0333**	**0.0008**
Mean ± SD	19 ± 22	14 ± 19		27 ± 22	26 ± 24			
Median (IQR)	7 (2-31)	5 (2-24)		22 (7-41)	20 (7-42)			
ISL – dominating, mg/dL:			NS			NS	NS	**0.0004**
Mean ± SD	20 ± 22	15 ± 20		27 ± 22	25 ± 23			
Median (IQR)	9 (2-31)	6 (2-26)		23 (7-40)	19 (7-39)			
Apo(a) size - larger (K):			NS			NS	NS	NS
Mean ± SD	30 ± 4	31 ± 4		30 ± 3	31 ± 3			
Median (IQR)	31 (29-33)	30 (28-34)		30 (27-33)	30 (29-33)			
Apo(a) size - smaller (K):			NS			NS	NS	**0.0183**
Mean ± SD	25 ± 4	26 ± 4		25 ± 3	24 ± 4			
Median (IQR)	25 (2130)	25 (23-30)		25 (21-28)	25 (21-27)			

Logarithmically transformed values were used for statistical inferential analyses. *Abbreviations:* Apo(a), apolipoprotein(a); IQR, interquartile range; ISL, isoform-specific Lp(a) level; IQR, interquartile range; K, kringles; Lp(a), lipoprotein(a); PCSK9, proprotein convertase subtilisin/kexin type 9.

but not in African Americans ($P > 0.05$) (Table 1). Among adults, interethnic differences reached a statistical significance for PCSK9 ($P = 0.0078$), Lp(a) ($P = 0.0003$) and for all isoform-specific apo(a) levels ($P < 0.0009$), with African American adults having higher levels than Caucasian adults. The PCSK9/Lp(a) ratio, however, was significantly lower in African American adults than in Caucasian adults ($P = 0.0016$). Among children, total and isoform-specific Lp(a) levels were higher in African American children than in Caucasian children, reaching a statistically significant interethnic difference for isoform-specific Lp(a) level associated with the smaller apo(a) sizes ($P = 0.0333$) (Table 1). Furthermore, apo(a) dominance patterns were similar between African Americans and Caucasians, with ~11% of participants having a larger apo(a) dominating pattern and the remaining participants having ~42% and ~47%, respectively, the co-dominating and smaller dominating patterns. Overall, these results confirmed the findings in all participants, with higher PCSK9 levels in adults vs children, regardless of ethnicity, as well as higher Lp(a) levels in African Americans vs Caucasians, regardless of age.

Associations between PCSK9 and Lp(a)/apo(a)-related variables

While PCSK9 levels were not significantly correlated with either total plasma Lp(a) level or isoform-specific Lp(a) level for the smaller or the dominating apo(a) size regardless of ethnicity ($P > 0.05$ for both), PCSK9 levels had a significant positive correlation with isoform-specific Lp(a) level associated with the larger apo(a) size in all participants ($r = 0.139$, $P = 0.0361$) and in African Americans ($r = 0.268$, $P = 0.0199$) (Table 2). As seen in Fig. 2A, compared with Caucasians, African Americans had a higher average isoform-specific apo(a) level for larger apo(a) sizes except for the few subjects at the extreme lower end of the larger isoform size spectrum. Furthermore, PCSK9 levels were significantly negatively associated with the larger apo(a) isoform sizes in all participants ($r = -0.139$, $P = 0.0366$) (Table 2). As seen in Fig. 2B, the distributions of apo(a) sizes for the larger apo(a) isoforms were similar between the two ethnic groups ($P < 0.05$). There was however a slight difference in the distribution of apo(a) sizes for the smaller isoform between African Americans and Caucasians (average size, 25 ± 4 vs 26 ± 4 K repeats, respectively; $P = 0.0149$).

In addition, PCSK9 levels were significantly positively correlated with LDL-C ($r = 0.332$, $P < 0.0001$) and apoB ($r = 0.308$, $P < 0.0001$) in all participants as well as in both Caucasians ($r = 0.370$, $P < 0.0001$ for LDL-C; $r = 0.306$, $P < 0.0001$ for apoB) and African Americans ($r = 0.275$, $P < 0.05$ for LDL-C; $r = 0.341$, $P < 0.01$ for apoB).

Overall, correlation analyses revealed a relatively weak but significant positive association between PCSK9 level and isoform specific Lp(a) level for the larger apo(a) size in African Americans only.

PCSK9 phenotypic resemblance between parents and offspring values

Capitalizing on the family study setting, we next studied the degree of resemblance in PCSK9 phenotypes between parents and offspring by ethnicity. In both ethnic groups, we

Table 2. Correlations of PCSK9 With Lp(a)/Apo(a)-Related Variables

Variables	Overall	African Americans	Caucasians
Total plasma Lp(a) level	0.081	0.195	−0.012
Isoform-specific Lp(a) level for:			
Larger isoform	**0.139***	**0.268***	0.054
Smaller isoform	0.029	0.150	−0.063
Apo(a) sizes for:			
Larger isoform	**−0.139***	−0.118	−0.148
Smaller isoform	0.013	−0.146	0.101

Correlation procedure was performed using logarithmically transformed values. *: $P < 0.05$

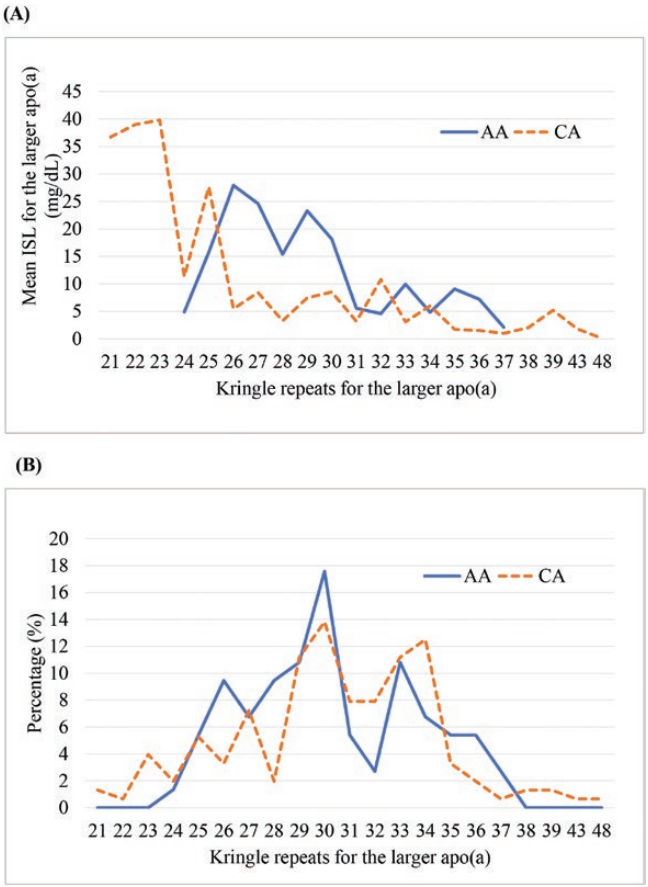

Figure 2. Distributions of **(A)** isoform-specific Lp(a) level (ISL) associated with the larger apo(a) sizes, and **(B)** Kringle repeats of the larger apo(a) isoforms in African Americans and Caucasians.

found significant resemblance between parental and offspring values. In Caucasians, ~47% of the variation in the PCSK9 levels of the offspring was explained by their parents' values ($R^2 = 0.466$, $P < 0.0001$) (Fig. 3A), while the corresponding degree of resemblance in African Americans was lower but still significant at ~22% ($R^2 = 0.218$, $P = 0.029$) (Fig. 3B). Overall, these findings indicate that PCSK9 levels are partly genetically determined and the heritability of PCSK9 phenotypes is greater in Caucasians than in African Americans.

Discussion

In this study among healthy African Americans and Caucasians with normal lipid levels and largely free of lipid-lowering therapy (≥93%), we found a significant positive association of PCSK9 levels with isoform-specific Lp(a) levels carried on the larger apo(a) isoform in all participants and particularly in African Americans. We also found a significant negative association of PCSK9 levels with larger apo(a) isoform sizes independent of levels in all participants. Notably, there was no significant association of PCSK9 with isoform-specific Lp(a) level in Caucasians. In addition, total plasma Lp(a) level was not associated with PCSK9 level in either ethnic group. PCSK9 levels differed significantly by ethnicity, sex, and age, with higher levels in African Americans vs Caucasians, in females vs males, and in adults vs children. Furthermore, the PCSK9/Lp(a) ratio differed between the two ethnic groups, with African Americans having a lower ratio than Caucasians. We also noted a significant resemblance between parental and offspring PCSK9 values in both ethnic

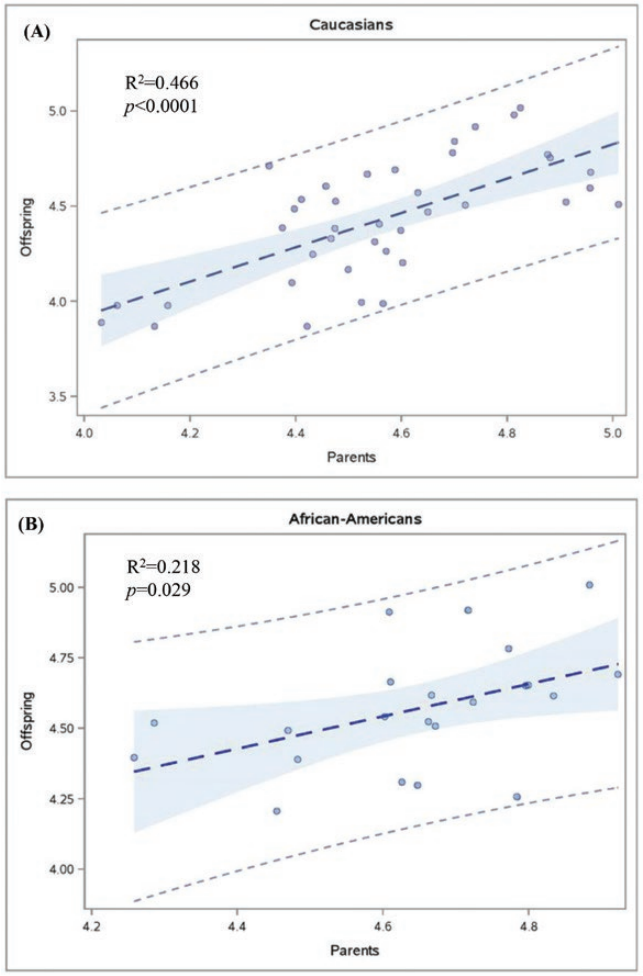

Figure 3. Degree of phenotypic resemblance in PCSK9 levels between parents and offspring. Regression fit plots were created using the average values of 2 parents or 2 offspring in a given family for: **(A)** Caucasians (n = 39 quartets) and **(B)** African Americans (n = 22 quartets). Solid line represents the fit, shaded parts represent 95% confidence limits, and the separated lines represent 95% prediction limit. Age and sex adjusted R^2 and P values are shown.

groups, with a greater proportion of offspring values explained by the parental values in Caucasians vs African Americans.

Similar to levels in our bi-ethnic children, mean PCSK9 levels in healthy French Canadian children (≤16 years) were 85 ± 25 μg/L and higher in females than in males [28]. As in our study, PCSK9 levels were positively associated with LDL-C in children [29] and in adults [17] free of lipid-lowering therapy. In the latter study [17], PCSK9 levels were significantly positively associated with total plasma Lp(a) levels, but not with the average number of K4 repeats, among adults with high Lp(a) levels. In a cohort of hypercholesterolemic patients, PCSK9 levels did not differ between the high-molecular weight (HMW) and low-molecular weight (LMW) apo(a) phenotype groups, but were higher in statin-treated compared with non–statin-treated patients [30]. Furthermore, PCSK9 levels were significantly positively correlated with plasma Lp(a) levels in the LMW group, but not in the HMW group, independently of statin therapy [30].

The approach we used in the current study differs from those in previous studies in several ways. First, we assessed both *LPA* allele (pulsed-field gel electrophoresis) and apo(a) isoform (Western blotting) sizes for each allele/isoform within a given individual, while others used the average size of 2 apo(a)s or a 2-group broad categorization (HMW

and LMW). Second, we quantified the amount of Lp(a) level contributed by each *LPA* allele/apo(a) isoform to the circulating level, i.e., allele- (isoform-) specific level, while others assessed only total plasma Lp(a) level. Third, in cases where one of the *LPA* alleles was silent, i.e., did not give a rise to any detectable protein, we were able to pinpoint which one of the two alleles (larger vs smaller) was expressed and accordingly determined allele/isoform-specific levels. Using this approach, we observed a significant positive association of PCSK9 with isoform-specific Lp(a) level carried by the larger-sized apo(a) in a given isoform-pair in our healthy African Americans. The contrasting directional association of PCSK9 with isoform-specific Lp(a) level for the larger-sized apo(a) (positive) vs the number of K4 repeats of the larger sized apo(a) (negative) is notable and these findings corroborate one another. As seen in Fig. 2, within the size range of the larger of the 2 apo(a) isoforms in a given individual, those with fewer K4 repeats were associated with a higher isoform-specific Lp(a) level—thus explaining the presence of a seemingly contrasting association.

While PCSK9 levels were somewhat higher in African Americans vs Caucasians, particularly among adults, the PCSK9/Lp(a) ratio differed considerably; although any effect of PCSK9 inhibitors has not been shown to differ across ethnicity [31]. An increase in apo(a) fractional catabolic rate (~25%) and a modest decrease in apo(a) production rate (~9%) has been reported during treatment with PCSK9 inhibitors [32]. Our finding of an association between PCSK9 and larger apo(a) sizes in African Americans is of interest in this context, as the main difference in Lp(a) levels across African American and Caucasian ethnicity is due to higher allele/isoform-specific Lp(a) levels for mid/larger apo(a) sizes in the former group. Further studies to address the reducing effect of PCSK9 inhibitors on Lp(a) levels have the potential to advance our understanding of Lp(a) metabolism.

To our knowledge, this study is one of the first reports on PCSK9 heritability and on the extent to which variations in PCSK9 levels in offspring can be explained by parental values. A previous study in a cohort of 188 sibling pairs (Europeans), consisting of patients with familial combined hyperlipidemia and their normolipidemic relatives, estimated the extent to which plasma PCSK9 levels could be accounted for by genetic factors [33]. In the latter study, the intraclass correlation for PCSK9 level was reported to be 0.42 ($P < 0.0001$), corresponding to a maximum heritability of 0.84. We also found a highly significant ($P < 0.0001$) high phenotypic resemblance between parental and offspring PCSK9 values in our Caucasian participants. Although the corresponding estimate in our African American participants was lower than the Caucasian estimate, it was nonetheless significant. Taken together, these findings support the notion that circulating PCSK9 level is a heritable trait and that genetic factors contribute to PCSK9 levels. Future studies assessing PCSK9 levels across different stages of life and across various populations may shed light into the heritability of PCSK9 level—a major target for reducing cardiovascular disease events in later life through lowering of LDL-C.

This study has some limitations and strengths. The cross-sectional study design limits our ability to evaluate any causative and longitudinal effects of factors that might influence levels of PCSK9 and/or Lp(a). In addition, there is a need to replicate these findings in larger studies. However, the present family-based study setting reduces the potential impact of variable genetic as well as environmental factors. Another strength is the inclusion of two ethnic groups. As noted above, we assessed isoform-specific Lp(a) levels.

In conclusions, circulating levels of PCSK9 were significantly and positively associated with Lp(a) level carried by the larger apo(a) size among healthy African Americans but not among Caucasians. To what extent this finding might contribute to the higher Lp(a) levels observed in the former group and/or clinical implication remains to be established. Taken together, the findings illustrate a diverging relationship of PCSK9 with isoform-specific Lp(a) levels and contribute to a better understanding of the relationship between PCSK9 and Lp(a)—a highly heritable trait—under normal physiological conditions.

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Disclosure Summary: The authors have nothing to disclose.

Data Availability: The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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