Abstract The pharmacologic inhibition of proprotein convertase subtilisin-kexin type 9 (PCSK9) lowers lipoprotein (a) [Lp(a)] concentrations. However, the impact of genetic PCSK9 loss-of-function variants (LOFVs) on Lp(a) is uncertain. We determined the association of PCSK9 LOFVs with Lp(a) measures among black adults. Genotyping for PCSK9 LOFVs was conducted in 10,196 black Reasons for Geographic and Racial Differences in Stroke study participants. Among 241 participants with and 723 randomly selected participants without PCSK9 LOFVs, Lp(a) concentrations, apo(a) kringle IV (KIV) repeats (a proxy for isoform size), and oxidized phospholipid (OxPL) apoB levels were measured using validated methods. Median Lp(a) concentrations among participants with and without PCSK9 LOFVs were 63.2 and 80.4 nmol/l, respectively (P = 0.016). After adjusting for age, sex, estimated glomerular filtration rate, LDL cholesterol, and statin use, participants with versus without a PCSK9 LOFV had a lower median Lp(a) concentration [Δ = −18.8 nmol/l (95% CI: −34.2, −3.3)]. Median apo(a) isoform sizes were 24 and 23 KIV repeats (P = 0.12) among participants with and without PCSK9 LOFVs, respectively [Δ = 1.1 (95% CI: 0.2, 2.0) after adjustment]. Median OxPL-apoB levels among participants with and without PCSK9 LOFVs were 3.4 and 4.1 nmol/l (P = 0.20), respectively [Δ = −1.2 nmol/l (95% CI: −2.4, −0.04) after adjustment].

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Lipoprotein (a) [Lp(a)] is an LDL-like particle synthesized in the liver that consists of a molecule of apo(a) linked via a disulfide bond to a molecule of apoB-100 of LDL (1). Apo(a) consists of repeated loop structures called kringle (2). Specifically, one kringle motif, kringle IV (KIV) type 2 (KIV2), exists in a variable number of copies. The high variability of apo(a) isomer size is due to genetic variants that result in different numbers of KIV2 repeats (3, 4). Small apo(a) isomers are associated with decreased numbers of KIV2 repeats and high Lp(a) levels (5). Oxidized phospholipids (OxPLs) on apoB-100 particles are carried by Lp(a), and high levels of OxPL-apoB are correlated with higher levels of Lp(a) (6).

High Lp(a) protein concentration and small apo(a) isoform size have been associated with an increased risk for atherosclerotic cardiovascular disease (ASCVD) events (7–12). Additionally, elevated concentrations of OxPL-apoB are also associated with a higher risk for ASCVD events (6, 13, 14). The 2018 American College of Cardiology/American Heart Association treatment guideline recognizes high Lp(a) protein concentration as a risk-enhancing factor for ASCVD (15). In randomized controlled trials, the pharmacologic inhibition of proprotein convertase subtilisin-kexin type 9 (PCSK9) lowered Lp(a) concentrations (16, 17). The association between genetic PCSK9 loss-of-function variants (LOFVs) and Lp(a) concentrations and the components apo(a) isoforms and OxPL-apoB is unclear.

In previous studies, PCSK9 LOFVs have been associated with lower LDL cholesterol (LDL-C) and lower rates of myocardial infarction (MI) in black compared with white individuals (18, 19). In a prior study of white adults, PCSK9 LOFVs were associated with 1–2 mg/dl lower median Lp(a) concentrations (20). However, it is not known whether PCSK9 LOFVs are associated with differences in Lp(a) among black adults. Therefore, we examined the association between PCSK9 LOFVs and various Lp(a) phenotypes, including Lp(a) protein concentration, apo(a) isoform KIV repeats, and OxPL-apoB levels among black adults enrolled in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study.

METHODS

Study population

The REGARDS study enrolled 30,239 black and white adults ≥45 years of age from across the contiguous United States between 2003 and 2007 (21). By design, the study oversampled black adults and residents of the Southeastern United States. Genotyping was performed using the blood samples collected from 10,196 black REGARDS participants at baseline (19). Overall, 241 of these participants had a PCSK9 LOFV (defined below). All participants with an LOFV and 723 black participants without an LOFV, randomly selected using a 1:3 ratio, had their Lp(a) phenotypes measured. The institutional review boards of all participating institutions approved this study. All participants provided written informed consent for participation in the REGARDS study, including genetic analyses.

Covariates

Data collection for the REGARDS study included baseline telephone interviews and in-home study visits. The in-home study visits included an electrocardiogram, collection of a blood sample, and a medication inventory following standardized protocols (21).

Information on sociodemographic factors (age, sex), comorbidities, and menopausal hormone (i.e., hormone replacement therapy [HRT]) use in women were obtained during the telephone interview. History of coronary heart disease (CHD) was defined as a self-report of a prior MI or coronary revascularization procedure or evidence of MI on the study electrocardiogram. History of stroke was defined by self-report. Participants were asked to fast overnight prior to their in-home study visit. Fasting blood samples were used to measure total cholesterol, HDL cholesterol, and triglycerides. LDL-C was calculated using the Friedewald equation (22) and corrected for Lp(a) cholesterol as described previously (23). The Chronic Kidney Disease Epidemiology Collaboration equation was used to calculate estimated glomerular filtration rate (eGFR) (24). Reduced eGFR was defined as <60 ml/min/1.73 m². Statin use was determined through the medication inventory.

PCSK9 genotyping

Genotyping of the variant Y142X (rs67608943) and C679X (rs28362286) SNPs was conducted at the University of Vermont using a Taqman assay on DNA that was extracted from packed white blood cells. Participants with at least one minor allele at Y142X or C679X were categorized as being PCSK9 LOFV carriers. One participant genotyped had both variants. Therefore, results for carriers of both variants were not presented.

Lp(a) protein concentration, apo(a) isoform, and OxPL measurements

Lp(a) protein concentration and apo(a) isoforms were measured at the Northwest Lipid Metabolism and Diabetes Research Laboratories (Seattle, WA). Lp(a) protein concentration was measured using a direct binding double monoclonal antibody-based ELISA reference method (25). For the current study, Lp(a) protein concentration is reported as a continuous variable in nmol/l. Apo(a) isoform size was determined using a high-resolution SDS-agarose gel electrophoresis followed by immunoblotting as previously reported (2). Individuals may express one or two apo(a) isoforms, and data for the relative proportion of each isoform in heterozygous individuals are provided in the current study. The migration in the gel of the visualized apo(a) isoform size is directly proportional to the number of KIV repeats. Apo(a) isoform size was defined as the number of KIV repeats in the predominant isoform or the average of both isoforms when they were equally expressed. These data are reported as a continuous variable. OxPL-apoB levels were measured at the University of California San Diego with an established ELISA and reported as a continuous variable (6).

Statistical analysis

Participant characteristics were summarized as mean and SD or proportion, overall, and among those with and without a PCSK9 LOFV. Tests of statistical significance for differences between groups were conducted using t-tests for continuous measures and Chi-square tests for categorical measures. We plotted histograms showing the distributions of Lp(a) protein concentration, apo(a) KIV repeats, and OxPL-apoB levels among participants with and without PCSK9 LOFVs. The distributions of Lp(a) protein concentration and OxPL-apoB were right-skewed, and accordingly median (25th, 75th percentiles) levels of Lp(a) phenotypes were calculated for participants with and without PCSK9 LOFVs.

We calculated differences in median Lp(a) protein concentration among participants with versus without PCSK9 LOFVs using
TABLE 1. Characteristics of black REGARDS study participants included in the current analysis

|                      | Overall (n = 964) | PCSK9 LOFVs |
|----------------------|------------------|-------------|
|                      | No (n = 723)     | Yes (n = 241) | P     |
| Age (years)          | 63.8 ± 8.8       | 63.8 ± 8.6    | 63.7 ± 9.2 | 0.81 |
| Females (%)          | 60.8             | 60.6         | 61.4      | 0.82 |
| History of CHD (%)   | 13.5             | 14.2         | 11.4      | 0.28 |
| History of stroke (%)| 7.4              | 8.2          | 5.0       | 0.10 |
| eGFR <60 ml/min/1.73 m² (%) | 11.3         | 10.5         | 13.8      | 0.16 |
| HDL (mg/dl)          | 54 ± 16          | 54 ± 16      | 54 ± 16   | 0.57 |
| Triglycerides (mg/dl)| 111 ± 56         | 111 ± 55     | 111 ± 58  | 0.21 |
| LDL-C (mg/dl)        | 109 ± 39         | 118 ± 37     | 85 ± 32   | 0.001 |
| Statin use (%)       | 26.1             | 30.4         | 13.3      | 0.001 |

Values are means ± SDs unless otherwise indicated.

quantile regression with progressive adjustment. Model 1 included adjustment for age and sex. Model 2 included adjustment for age, sex, eGFR, and corrected LDL-C. Model 3 included adjustment for age, sex, eGFR, corrected LDL-C, and statin use. Using the variables in model 4, we additionally tested for effect modification by statin use by including an interaction term between statin use and having a PCSK9 LOFV. Prior evidence suggests that HRT may modify Lp(a) concentration (26); therefore, we tested for effect modification among women by including a main effect for HRT and an interaction term between HRT and having a PCSK9 LOFV. Men were not included in the test for effect modification by HRT because no male REGARDS study participants with Lp(a) levels measured for this analysis reported taking HRT.

The above analyses were repeated separately for apo(a) KIV repeats and OxPL-apoB levels. Given the potential influence of apo(a) isoform size on Lp(a) concentration and OxPL-apoB levels (13), in a sensitivity analysis we examined the association of PCSK9 LOFVs with Lp(a) concentration and OxPL-apoB levels, separately, within tertiles of the apo(a) isoform size distribution. Missing covariate data (supplemental Table 1) were imputed using fully conditional specification with 10 data sets (27). P < 0.05 was considered statistically significant. All analyses were conducted using SAS version 9.4 (Cary, NC).

RESULTS

Participants were aged 63.8 ± 8.8 years: 60.8% were women, 13.5% had a history of CHD, 7.4% had a history of stroke, and 11.3% had reduced eGFR (Table 1). Among women, 10.6% were taking HRT. There was no evidence of differences between participants with and without PCSK9 LOFVs with respect to mean age or the proportions that were women, had a history of CHD or stroke, reduced eGFR, or were taking HRT. Participants with versus without PCSK9 LOFVs had a lower mean LDL-C (85 vs. 118 mg/dl; P < 0.001) and were less likely to be taking a statin (13.3% vs. 30.4%; P < 0.001).

Median (25th, 75th percentiles) Lp(a) concentrations for participants with and without PCSK9 LOFVs were 63.2 nmol/l (30.4, 119.6) and 80.4 nmol/l (39.7, 138.4), respectively (Fig. 1, Table 2). After multivariable adjustment, the median Lp(a) protein level was lower for participants with versus without PCSK9 LOFVs (Δ = −18.8 nmol/l; 95% CI: −34.2, −3.3). There was no evidence of effect modification between PCSK9 LOFVs and statin use or HRT on Lp(a) protein concentration (Pinteraction = 0.41 and 0.74, respectively).

Among all participants, 157 (16.3%) had a single apo(a) isoform and 807 (83.7%) had two apo(a) isoforms. The median (25th, 75th percentiles) number of apo(a) KIV repeats for participants with and without PCSK9 LOFVs were 24 (21, 27) and 23 (20, 26), respectively (Fig. 2, Table 3). After multivariable adjustment, participants with versus without PCSK9 LOFVs had a larger number of KIV repeats (Δ = 1.1; 95% CI: 0.2, 2.0). There was no evidence of effect modification between PCSK9 LOFVs and statin use or HRT on apo(a) isoform KIV repeats (Pinteraction = 0.44 and 0.82, respectively).

Median (25th, 75th percentiles) OxPL-apoB levels for participants with and without PCSK9 LOFVs were 3.4 nM (1.2, 8.2) and 4.1 nM (1.7, 8.5), respectively (P = 0.20) (Fig. 3, Table 4). After multivariable adjustment, median OxPL-apoB levels were lower for participants with versus without PCSK9 LOFVs (Δ = −1.2 nM; 95% CI: −2.4, −0.04). There was no evidence of effect modification between PCSK9 LOFVs and statin use or HRT on OxPL-apoB levels (Pinteraction = 0.36 and 0.88, respectively).

PCSK9 LOFVs were associated with lower median Lp(a) concentration and OxPL-apoB levels among participants in the middle and upper tertiles of the apo(a) isoform size distribution and higher median Lp(a) and OxPL-apoB in the lowest tertile of the apo(a) isoform size distribution.

Fig. 1. Distribution of Lp(a) protein concentration among participants with and without PCSK9 LOFVs. Seven participants included in the analyses had a measured Lp(a) ≥500 nmol/l (four without LOFVs and three with LOFVs) and are not presented in the figure.
PCSK9 loss-of-function variants and Lp(a) phenotypes

(supplemental Fig. 1). After multivariable adjustment there were no statistically significant differences in median Lp(a) concentration or OxPL-apoB levels comparing those with versus without PCSK9 LOFVs in any tertile of apo(a) isoform size (supplemental Tables 2 and 3, respectively).

**DISCUSSION**

In the current study, black adults with PCSK9 LOFVs, which genetically confer lower LDL-C, had lower median Lp(a) protein concentration and OxPL-apoB levels independent of age, sex, eGFR, Lp(a)-corrected LDL-C, and statin use. Apo(a) isoform sizes were marginally larger among those with versus without PCSK9 LOFVs after multivariable adjustment. These associations were consistent among participants taking and not taking statins and among women taking and not taking HRT.

PCSK9 plays an important role in regulating circulating LDL-C levels, and sequence variations in the PCSK9 gene that cause loss-of-function mutations are associated with lower levels of LDL-C and lower CVD risk (18, 19). The mechanism by which these variants lower LDL-C is uncertain; however, it has been suggested that the loss of PCSK9 function may result in elevated hepatic LDL receptor activity (28). The genetic association between PCSK9 LOFVs and Lp(a) concentration has been examined in an analysis of three Danish cohorts, in which adults with versus without PCSK9 LOFVs had ~2.5 nmol/l lower Lp(a) levels (20). Pharmacologic PCSK9 inhibition lowered Lp(a) concentrations by 25% to 30% in randomized trials (29–31). The Effects of Lipoprotein Metabolism from PCSK9 Inhibition Utilizing a Monoclonal Antibody study examined putative mechanisms for the reduction in Lp(a) concentration with PCSK9 inhibitors. This study reported that monotherapy with a PCSK9 inhibitor lowered Lp(a) concentrations by decreasing the hepatic production of Lp(a) particles, whereas the combination of a PCSK9 inhibitor with a statin lowers Lp(a) by upregulating LDL receptor-mediated Lp(a) clearance (32). The lower Lp(a) concentrations among carriers of PCSK9 LOFVs is consistent with the pharmacologic effect reported with PCSK9 inhibitors (33).

Higher Lp(a) levels are associated with an increased risk for ASCVD events (9). The 2018 American College of Cardiology/American Heart Association cholesterol treatment guideline identifies high Lp(a) levels as a risk-enhancing marker for ASCVD but does not include recommendations to lower Lp(a) (15). The European Atherosclerosis Society consensus panel recognizes Lp(a) as a ASCVD risk factor and recommends treating Lp(a) to levels less than 125 nmol/l for adults with immediate or high ASCVD risk (10). PCSK9 has been shown to lower Lp(a) concentration in multiple randomized placebo-controlled trials. In the randomized placebo-controlled LDL-C Assessment with Prpropriate Convertase Subtilisin Kexin Type 9 Monoclonal Antibody Inhibition Combined with Statin Therapy-Thrombolysis in Myocardial Infarction

![Fig. 2. Distribution of apo(a) KIV isoforms among participants with and without PCSK9 LOFVs.](image-url)
57 trial, randomization to evolocumab was associated with a 32% larger reduction in Lp(a) concentration compared with placebo (34). In the FOURIER trial, participants randomized to receive evolocumab (either 140 mg every 2 weeks or 420 mg every month) had a 26.9% median reduction in Lp(a) concentration at 48 weeks (33). In the FOURIER trial, evolocumab resulted in greater absolute reductions in Lp(a) concentration and CVD events for participants with higher baseline Lp(a) levels. In a recent analysis from the multicenter phase 3b Anitschkow trial \[ n = 129 \text{ with } \text{Lp(a)} \geq 125 \text{ nmol/l} \], randomization to evolocumab resulted in a 13.9% mean reduction in Lp(a) concentration at 16 weeks compared with placebo (35). In two phase 3 trials, randomization to alirocumab versus placebo resulted in a 17.7% and 25.6% greater reduction in Lp(a) among adults with and without familial hypercholesterolemia over 24 weeks compared with placebo (16, 36). It is unknown whether these changes in Lp(a) concentration in participants randomized to treatment with PCSK9 inhibitors contributed to their lower ASCVD event rates (33).

Lp(a) concentrations are higher for black adults, and a larger proportion of black compared with white adults have medium-sized apo(a) isoforms (37, 38). The Dallas Heart Study reported higher levels of OxPL-apoB among black compared with white adults (13). In the current study of black adults, we provide evidence that PCSK9 LOFVs are associated with lower Lp(a) levels. Additionally, there was a larger absolute difference in Lp(a) concentration between those with and without LOFVs compared with previous observational cohorts composed of white participants (20). The current finding contradicts a previous study on 1,802 adults of African descent, in which carriers and noncarriers of PCSK9 LOFVs did not have statistically significantly different Lp(a) levels (39). However, the prior study included only 33 participants with a PCSK9 LOFV.

There was no evidence that statin use modified the association between PCSK9 LOFVs and Lp(a) concentrations. This result complements a meta-analysis of 29,069 participants in 7 randomized placebo-controlled statin outcome trials that reported statin therapy did not change Lp(a) concentrations (40). This meta-analysis further reported that baseline Lp(a) levels were approximately linearly correlated with the risk for ASCVD events regardless of statin use and independent of traditional ASCVD risk factors. The Postmenopausal Estrogen/Progestin Intervention trial and Heart and Estrogen/Progestin Replacement Study previously reported that HRT use was associated with reductions in Lp(a) concentrations (41, 42). In the current study, the association between PCSK9 LOFVs and Lp(a) was not modified use of HRT.

Small apo(a) isoform sizes have been associated with high Lp(a) concentration as well as increased CHD risk in previous observational studies (7, 8). However, there are limited data on the association between PCSK9 LOFVs and apo(a) isoforms. Previous work by Tavori and colleagues

| PCSK9 LOFVs | No | Yes | \( P \) |
|----------------|----|-----|-----|
| Median apo(a) KIV repeats (25th, 75th percentile) | 23 (20, 26) | 24 (21, 27) | 0.12 |
| Differences (95% CIs) in median values (KIV repeats) | | | |
| Model 1 \(^a\) | 0 (reference) | 1.0 (0.2, 1.8) | 0.01 |
| Model 2 \(^b\) | 0 (reference) | 0.80 (−0.5, 2.1) | 0.21 |
| Model 3 \(^c\) | 0 (reference) | 1.2 (0.4, 1.9) | 0.092 |
| Model 4 \(^d\) | 0 (reference) | 1.1 (0.2, 2.0) | 0.02 |

\(^a\) Adjusted for age and sex.
\(^b\) Adjusted for age, sex, and eGFR.
\(^c\) Adjusted for age, sex, eGFR, and corrected LDL-C.
\(^d\) Adjusted for age, sex, eGFR, corrected LDL-C, and statin use.

**Fig. 3.** Distribution of OxPL content on apoB-100 among participants with and without PCSK9 LOFVs.
reported that while plasma PCSK9 levels correlated with Lp(a) mass concentration, they were not correlated with the number of apo(a) KIV repeats (43). In the current study of black adults, genetic PCSK9 LOFVs were associated with small differences in median apo(a) isoform size.

OxPL-apoB enhances the atherogenicity of Lp(a) and increases the risk of ASCVD events (6). Despite this there are limited data on the association between PCSK9 LOFVs and OxPL-apoB levels. An analysis of 3,821 participants of the European Prospective Investigation of Cancer-Norfolk study found no differences in OxPL-apoB levels for carriers and noncarriers of PCSK9 LOFVs (1,574 vs. 1,694 relative light units; \( P = 0.83 \)) (44). However, this study included only white participants and assessed the R46L LOFV. The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering trial previously reported that OxPL-apoB levels were higher among participants taking a statin regardless of CVD risk, although the association with PCSK9 variants was not examined (13). We provide evidence that the PCSK9 LOFVs Y142X and C679X in blacks are associated with lower OxPL-apoB. Previously, it has been shown that carriers of Y142X and C679X variants have lower LDL-C levels and CHD risk than carriers of the R46L variant (18).

Strengths of the current study include the use of data from a geographically diverse US population of black adults. Most previous research has been conducted in predominately white populations, and black and white individuals have different PCSK9 LOFVs. Few data have reported the association between PCSK9 LOFVs and Lp(a) protein concentration in black adults. In addition, we measured Lp(a) protein concentration using an assay independent of apo(a) isoform heterogeneity and measured apo(a) isoform KIV repeats using an assay with high sensitivity and resolution. We also acknowledge some limitations. Participants were genotyped for select PCSK9 LOFVs chosen a priori (19); however, other SNPs linked to high levels of LDL-C may also be associated with Lp(a) phenotypes. Circulating PCSK9 levels have not been measured in the REGARDS study and, therefore, could not be included in the current analysis. LDL-C as quantified in the current study corrects for the cholesterol content of Lp(a) (23). However, at higher Lp(a) levels, a higher proportion of cholesterol is contained in Lp(a) molecules, and it is difficult to disentangle these two measures. Therefore, the true effect of PCSK9 inhibition on LDL-C is uncertain in patients with elevated Lp(a). Additionally, given the relatively modest sample size available, the current study may have been underpowered to detect effect modification by statin use or HRT.

In conclusion, in this study of black adults, PCSK9 LOFVs were associated with lower concentrations of Lp(a) and OxPL-apoB. These results complement data from clinical trials showing pharmacologic PCSK9 inhibition lowers Lp(a) concentrations.

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