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Variation in *ANGPTL4* and risk of coronary heart disease: the Atherosclerosis Risk in Communities Study

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Abstract

An E40K loss-of-function variant in the *ANGPTL4* gene is associated with substantially reduced plasma triglyceride levels in white persons, but its association with cardiovascular disease occurrence has not been reported. The prospective, population-based Atherosclerosis Risk in Communities Study measured the E40K *ANGPTL4* variant in approximately 10000 white participants and determined its association with coronary heart disease (CHD) incidence (n = 1318 events) between 1987-1989 and 2004. Compared with noncarriers, carriers of 1 or 2 copies of the 40K variant (3.8% frequency) had a 19-mg/dL lower age- and sex-adjusted mean triglyceride level, 5-mg/dL lower low-density lipoprotein cholesterol, and 4-mg/dL higher high-density lipoprotein cholesterol. The age-, sex-, and field center–adjusted hazard ratio of CHD was 0.63 (95% confidence interval, 0.45-0.89). Adjustment for nonlipid confounding factors did not change this hazard ratio appreciably. Carriers also appeared to have reduced risk of incident stroke, prevalent peripheral artery disease, and carotid atherosclerosis; but these associations were based on few events among 40K carriers and were not statistically significant. In conclusion, in this prospective study, the 40K variant of *ANGPTL4* appeared to confer reduced genetic risk for CHD.

1. Introduction

It is well established that higher blood levels of low-density lipoprotein cholesterol (LDL-C) and lower levels of high-density lipoprotein cholesterol (HDL-C) increase the risk of atherosclerotic cardiovascular disease (CVD). Whether higher blood triglyceride levels increase the risk of atherosclerotic events has been less clear. However, a recent meta-analysis involving 10158 incident coronary heart disease (CHD) cases from 29 studies and corrected for within-person measurement error reported that triglycerides have a moderate independent association with CHD incidence [1]. Comparing the top vs the bottom third of usual log-triglyceride values, the adjusted odds ratio (OR) of CHD was 1.72 (95% confidence interval [CI], 1.56-1.90).

A recent report from 3 cohort studies indicated that an E40K loss-of-function variant in *ANGPTL4*, a gene involved in partitioning of fatty acids between sites of storage and sites of oxidation, is associated with substantially reduced plasma levels of triglyceride and increased HDL-C in white persons [2]. The E40K polymorphism, which is not currently listed in the Single Nucleotide Polymorphism Database, entails a 118G to A base substitution at codon 40 changing the amino acid from glutamic acid to lysine. In the Atherosclerosis Risk in Communities (ARIC) Study, the 40K variant (1 or 2 copies) was present in 4% of white persons but was very rare in African Americans. Besides lower triglyceride and higher HDL-C, 40K carriers had modestly decreased LDL-C and insulin levels [2]. Whether the *ANGPTL4* E40K variant is associated with cardiovascular events has not yet been explored.

We used data from the ARIC Study to determine whether there is an association between the *ANGPTL4* E40K variant and incidence of CHD. As secondary analyses, some of which had low statistical power, we

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also looked at associations with prevalence of carotid atherosclerosis or peripheral artery disease (PAD) and incidence of ischemic stroke.

2. Materials and methods

2.1. Population

The ARIC Study is a cohort study of CVD in 4 US communities [3]. Between 1987 and 1989, 7082 men and 8710 women aged 45 to 64 years were recruited from Forsyth County, North Carolina; Jackson, MS (African Americans only); suburban Minneapolis, MN; and Washington County, Maryland. The ARIC Study protocol was approved by the institutional review board of each participating university. After written informed consent was obtained, including that for genetic studies, participants underwent a baseline clinical examination (visit 1). Follow-up examinations of the cohort occurred 3 times, at intervals of roughly 3 years. The response rates for visits 2 (1990-1992), 3 (1993-1995), and 4 (1996-1998) were 93%, 86%, and 80%, respectively. Participants completed annual telephone interviews between visits and after visit 4.

2.2. Risk factor measurements

Risk factors examined in these analyses were ascertained at visit 1, as described in detail in the ARIC Study manuals of operation [4]. Participants were asked to fast for at least 12 hours before the clinical examination. Blood was drawn from an antecubital vein of seated participants into vacuum tubes containing ethylenediaminetetraacetic acid (for measurement of lipids and DNA extraction) or a serum separator gel (glucose). Serum and plasma aliquots were stored at −70°C and were shipped to central laboratories for analyses. Total cholesterol and triglycerides were measured by enzymatic methods, and HDL-C was measured after dextran-magnesium precipitation. Low-density lipoprotein cholesterol was calculated [5]. Serum glucose was assayed by a hexokinase/glucose-6-phosphate dehydrogenase method. *Prevalent diabetes mellitus* was defined as a fasting glucose of at least 126 mg/dL [6] or a self-reported history of or treatment of diabetes. Seated systolic and diastolic blood pressures (SBP and DBP) were measured 3 times using a random-zero sphygmomanometer, and the average of the last 2 measurements was used for analysis. A standard 12-lead electrocardiogram was recorded.

Anthropometrics were taken with the subject wearing a scrub suit and no shoes. Body mass index (BMI) was calculated (weight in kilograms/height in meters squared). Questionnaires assessed education; smoking status; antihypertensive and lipid-lowering medications within the past 2 weeks; number of cigarettes smoked per day and duration of smoking (pack-years computed); and usual consumption of wine, beer, and hard liquor (grams per day computed). Level of sports physical activity was assessed by the questionnaire of Baecke et al [7].

2.3. Genotyping

The E40K single nucleotide polymorphism is located at position 1033320 in Contig NT_077812.2 (National Center for Biotechnology Information genome build 36.2), and context sequence is as follows:

GTCGCCGCGCTTTGCGTCCTGGGAC[G/A]AGATGAATGTCCTGGCGCACGGACT.

Using stored DNA from ARIC participants, fluorogenic 5′-nucleotidase assays for the *ANGPTL4* alleles encoding E40K or the wild-type protein were performed using the TaqMan assay system (Applied Biosystems, Foster City, CA), as previously described [2]. The assays were carried out on a 7900HT Fast Real-Time PCR instrument with probes and reagents purchased from Applied Biosystems.

2.4. Ascertainment of prevalent CVD

For exclusion in incidence analyses, *prevalent CHD at baseline* was defined as a self-reported history of physician-diagnosed myocardial infarction (MI), coronary artery bypass surgery, or coronary angioplasty, or evidence of a previous MI by electrocardiogram. *Prevalent stroke* was defined, for exclusion, as a self-reported history of physician-diagnosed stroke.

Prevalent PAD was defined as intermittent claudication by the questionnaire of Rose et al [8] or an ankle/brachial BP index less than 0.9. The ankle/brachial BP index was computed by dividing the average of ankle SBP measurements by the average of brachial SBP measurements [7]. Using the Dinamap 1846 SX automated oscillometric device (Criticon, Tampa, FL), trained technicians measured 2 ankle BPs, taken 5 to 8 minutes apart, at the posterior tibial artery in a randomly selected leg while the participant was prone. This automated BP measurement device has high validity compared with the standard Doppler ultrasound measurement and high reliability [9]. Two brachial artery SBPs were measured, usually in the right arm, with the participant supine [10]. The questionnaire of Rose et al identifies intermittent claudication as exertional leg pain relieved within 10 minutes by resting.

High-resolution B-mode ultrasound (Biosound 2000 II SA; Biosound, Indianapolis, IN) was used to measure intima-media thickness (IMT) bilaterally in the extracranial carotid arteries, in the areas of the common carotid artery (1 cm proximal to the dilatation of the carotid bulb), the carotid bifurcation (1 cm proximal to the flow divider), and the internal carotid artery (1 cm distal to the flow divider). Standardized protocols for scanning and reading were used based on a technique validated by Pignoli et al [11]. To enhance the reproducibility of carotid artery measurements, standardized interrogation angles were used. Centralized training, certification, and quality control programs were implemented for both the sonographers and the readers to ensure reliability and validity of these measurements [12]. The mean IMT values at the 6 carotid sites were combined to produce an overall mean IMT. In case of missing data at any

of the 6 carotid sites, maximum likelihood techniques were used to estimate the mean carotid IMT. Correlations between scans at different visits 7 to 10 days apart, performed by different sonographers and read by different readers, were 0.77, 0.73, and 0.70 for the carotid bifurcation, internal carotid, and common carotid, respectively. For this report, IMT was analyzed both as continuous (mean IMT) and categorical (<1 mm or ≥1 mm) variables.

2.5. Ascertainment of incident events

Events occurring between the baseline clinic examination and December 31, 2004, were identified by means of annual telephone interviews, triennial examinations, and community-wide surveillance procedures [3]. Hospital records and death certificates were surveyed for diagnoses of interest. For potential hospitalized CHD events, trained abstractors recorded presenting symptoms and cardiac enzyme levels; up to 3 electrocardiograms were photocopied and coded using the Minnesota Code. Myocardial infarction was classified using standardized criteria [3]. Out-of-hospital deaths were investigated by review of death certificates, contact with families (when possible) and physicians, and use of coroner records. *Incident CHD* was defined as definite CHD death [3], definite or probable hospitalized MI [3], unrecognized MI by electrocardiographic criteria at ARIC visits 2 to 4, or a coronary revascularization procedure.

For potential hospitalized stroke events, a nurse abstracted signs, symptoms, and relevant diagnostic findings, including brain computed tomography and magnetic resonance reports. The ARIC Study used the National Survey of Stroke criteria [13]. From the abstracted data, the stroke diagnosis was assigned independently by both computer algorithm and a physician reviewer. A second physician reviewer adjudicated disagreements between the two. Incident ischemic stroke for this analysis included definite or probable ischemic (thrombotic or embolic) stroke.

Table 1
Age- and sex-adjusted baseline risk factor levels (mean ± SE or percentage) in relation to the E40K variant in *ANGPTL4*; ARIC white participants, 1987-1989

Risk factor	*ANGPTL4* 40K carrier		*P* for difference
	No (GG)	Yes (AG or AA)	
n (%)	10,106 (96.2)	401 (3.8)	–
Triglycerides (mg/dL)	131 ± 0.8	112 ± 4.2	<.0001
Geometric mean triglycerides	113	99	<.0001
LDL-C (mg/dL)	138 ± 0.3	133 ± 1.9	.007
HDL-C (mg/dL)	51.5 ± 0.1	55.2 ± 0.8	<.0001
Glucose (mg/dL)	107 ± 0.3	104 ± 1.7	.09
BMI (kg/m^2)	27.7 ± 0.1	26.8 ± 0.3	.0005
SBP (mm Hg)	121 ± 0.2	119 ± 0.9	.006
DBP (mm Hg)	73.7 ± 0.1	72.0 ± 0.5	.002
Pack-years of smoking	317 ± 3.6	367 ± 20.2	.015
Sport index (range 1-5)	2.43 ± 0.01	2.56 ± 0.04	.0009
Alcohol intake (g/wk)	42.1 ± 0.8	44.3 ± 4.4	.61
High school graduate (%)	76.6	84.0	.0003
Diabetes (%)	10.8	6.7	.007
Current smoker (%)	25.7	26.0	.88
Hypertension med use (%)	25.2	18.9	.003
Lipid-lowering med use (%)	3.0	1.6	.11

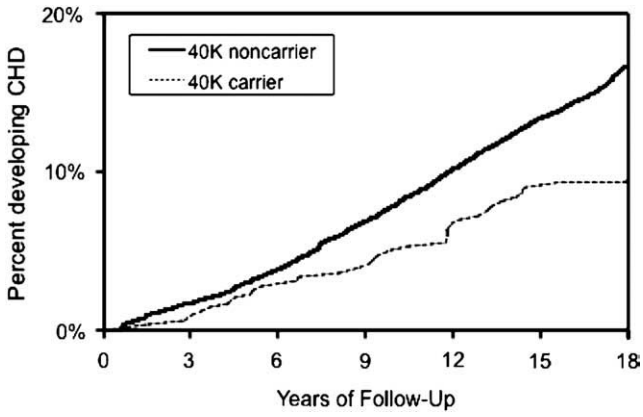


Fig. 1. Cumulative incidence of CHD by E40K *ANGPTL4* variant; ARIC white participants.

2.6. Data analysis and statistical methods

Because *ANGPTL4* 40K carriers were very rare in African Americans, we restricted the analysis to white persons. From the original ARIC cohort (n = 11478 white persons), we successively excluded participants who denied permission for DNA testing (n = 113), who had missing DNA or *ANGPTL4* genotypes (n = 615), or who had not fasted for 8 hours (n = 243). This left 10507 (5561 women and 4946 men). Of these, 9622 had no prevalent CHD or stroke and therefore were included in incidence analyses. The prevalent PAD analysis involved 10126, and prevalent carotid atherosclerosis analysis involved 9952.

Our hypothesis was that carriers of *ANGPTL4* E40K would have reduced risk of all 4 CVD outcomes, but the primary focus was on incident CHD. Statistical analysis was performed using SAS software (version 9.1; SAS Institute, Cary, NC). Allele and genotype frequencies were compared with values predicted by Hardy-Weinberg equilibrium using the χ^2 goodness-of-fit test. To explore possible confounding factors, age- and sex-adjusted means or prevalences of various risk factors were computed by *ANGPTL4* genotype and compared by *t* test. Hazard ratios (HRs) for the associations of the *ANGPTL4* variant with incident disease were calculated using Cox proportional hazards regression. Person-years at risk were calculated from the time of baseline clinical examination until the date of CVD diagnosis, death, loss to follow-up, or December 31, 2004, whichever occurred first. The proportional hazards assumption of the Cox model was found not to be violated by testing an interaction between *ANGPTL4* variants and time. The ORs of prevalent disease in relation to *ANGPTL4* variant were calculated using logistic regression.

Table 2
Associations of E40K variant in *ANGPTL4* with incident CHD; ARIC white participants, 1987-2004

	40K carrier		
	No	Yes	
CHD			
Event (n)	1285	33	
Person-years	135 620	5633	
Age-, sex-, and field center–adjusted HR (95% CI)	1.0	0.63	(0.45-0.89)
Adjusted HR[a] (95% CI)	1.0	0.61	(0.43, 0.87)
Lipid-adjusted HR[b] (95% CI)	1.0	0.76	(0.54-1.08)

[a] Adjusted for baseline age, sex, field center, education (<high school, ≥high school), diabetes (yes, no), cigarette smoking (pack-years), BMI (continuous), SBP (continuous), and hypertensive medication (yes, no).
[b] Adjusted for baseline age, sex, field center, plasma triglycerides, LDL-C and HDL-C, and lipid-lowering medication.

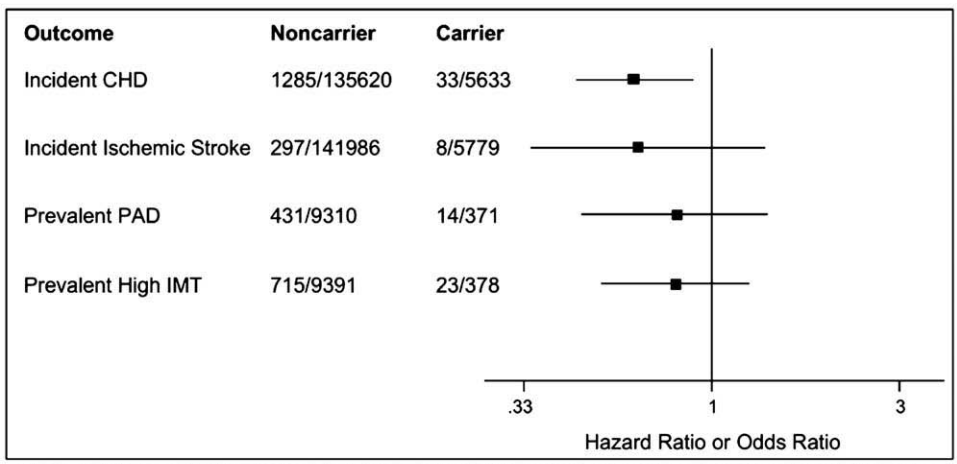
The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the article as written.

3. Results

The mean age at baseline of the 10507 ARIC white participants included was 54 years. As shown in Table 1, 3.8% carried the 40K variant (1 or 2 copies). Genotype frequencies conformed to Hardy-Weinberg equilibrium expectation. Compared with noncarriers, carriers had 19-mg/dL lower age- and sex-adjusted mean triglyceride levels, 5-mg/dL lower mean LDL-C levels, and 4-mg/dL higher HDL-C levels. They also had lower mean BMI, BPs, antihypertensive medication use, and diabetes prevalence, as well as more pack-years of smoking, sports participation, and high school completion. Some of these differences between carriers and noncarriers were modest, but statistically significant given the precision afforded by the large number of noncarriers.

Between 1986-1988 and the end of 2004, incidence of CHD, our primary end point, occurred in 1318 participants (589 clinical nonfatal or fatal MI, 83 other fatal CHD events, 61 silent MI, and 585 coronary revascularizations). Coronary heart disease risk was significantly lower in 40K carriers than noncarriers (Fig. 1 and Table 2). The age-, sex,- and field center–adjusted HR was 0.63 (95% CI, 0.45-0.89), $P = .009$. With adjustment for nonlipid confounding factors, this HR was virtually unchanged. Adjustment for triglycerides, HDL-C and LDL-C levels, and use of lipid-lowering medication, in a model to explore mechanisms, attenuated the HR to 0.76 (95% CI, 0.54-1.08), $P = .13$. Among the 4 lipid variables, HDL-C contributed most to the HR attenuation. This attenuation is consistent with these lipid variables, particularly HDL-C, being intermediaries, in part, of the association between E40K and incident CHD.

Fig. 2 depicts the associations of E40K variation with CHD and the other, secondary CVD end points (incident stroke, prevalent PAD, and carotid atherosclerosis). The secondary end points had few events among carriers, leading to wide CIs; but the hazard or ORs were all less than 1.0, indicating a consistent direction of associations. The ischemic stroke HR of 0.65 (95% CI, 0.33-1.32) was imprecise but similar to that for CHD (HR = 0.63; 95% CI, 0.45-0.89). The ORs of prevalent PAD (0.81; 95% CI, 0.46-1.37) and carotid atherosclerosis (0.81; 95% CI, 0.52-1.25) also suggest lower risk in carriers than noncarriers but with statistical imprecision. All of these estimates were virtually unchanged when adjusted for nonlipid confounding factors.



Graph depicts hazard ratio or odds ratio (95% confidence interval) of each cardiovascular disease for 40K carriers compared with noncarriers. For incident events, the numbers of events/person years are shown for noncarriers and carriers. For prevalent disease, the numbers of cases/noncases are shown. High carotid intima-media thickness (IMT) represents IMT ≥1 mm.

Fig. 2. Age-, sex-, and field center–adjusted associations of E40K *ANGPTL4* variant with incident CHD and ischemic stroke, and prevalent PAD and carotid atherosclerosis; ARIC white participants.

4. Discussion

This population-based study of middle-aged white persons found that carriers of the 40K variant in *ANGPTL4* had approximately 63% of the rate of CHD compared with noncarriers. The 40K variant was also associated with less incident ischemic stroke and prevalent PAD and carotid atherosclerosis, but these associations were imprecisely estimated and not statistically significant. Pooling of our results with those from other cohorts using meta-analyses will help confirm or refute these findings. A portion of the inverse association between the 40K variant and CHD seems to be attributable to its effect on plasma lipids because adjustment for lipids (particularly HDL-C) moderately attenuated the HR. It, of course, remains possible that nonlipid pathways may also contribute to the association.

The role of *ANGPTL4* in lipid metabolism is still being clarified. Administration of ANGPTL4 protein to mice increases plasma triglyceride concentrations [14], whereas inhibition of ANGPTL4 with a neutralizing antibody lowers triglyceride concentrations [15]. Studies of an ANGPTL4 transgenic mouse model indicate that overexpression of *ANGPTL4* causes fasting hypertriglyceridemia due to inhibition of lipoprotein lipase–dependent very low-density lipoprotein (VLDL) and chylomicron lipolysis [16,17]. Overexpression also up-regulates cholesterol synthesis in the liver, increases insulin sensitivity in the liver, but decreases insulin sensitivity in the periphery [16]. Conversely, an ANGPTL4 knockout mouse has reduced plasma triglyceride concentrations because of increased VLDL clearance and decreased VLDL production and has modestly lower cholesterol levels [15,17]. ANGPTL4 also controls lipoprotein lipase in adipose tissue [18]. Thus, the lipid differences in *ANGPTL4* 40K carriers and noncarriers (Table 1) seem to be, at least in part, due to the 40k variant.

Because the 40K variant affects triglycerides more than other lipids, its association with CHD may further support a role for triglycerides in causing atherosclerosis and CHD [1]. However, the 40K allele also seemed to be associated with some other components of the metabolic syndrome (Table 1); and these may have contributed to the CHD association. In particular, HDL-C seemed to have the largest impact when lipid variables were explored as intermediaries. In addition, we found BMI to be lower in 40K carriers than noncarriers, a finding not observed in the previous ARIC analysis that excluded individuals with diabetes or taking lipid-lowering medication [2]. An association with BMI is consistent with evidence that lipoprotein lipase, which ANGPTL4 inhibits, is associated with obesity [19,20]. Further large studies in humans are needed to corroborate if, and how, the 40K variant decreases risk of CHD.

A drawback of our study was the relatively few CVD events among 40K carriers. The CHD association was strong and statistically significant, but the findings for secondary CVD end points may be due to chance. Another drawback may be the somewhat unexpected associations of *ANGPTL4* E40K with a number of nonlipid risk factors (Table 1). These associations suggest the possibility of confounding; yet adjustment for these variables had little impact on our results.

Relatively few common genes (eg, *APOE*, *PCSK9*) have so far been shown to consistently predict incident CVD [21]. Although our findings warrant replication, they suggest that this low-frequency 40K variant may be involved in genetic risk for CHD specifically, if not for atherosclerotic CVD in general. Yet, the 40K variant is rare enough that it likely explains only a small proportion of CVD events in the population; and routine screening for it would have no current clinical value. On the other hand, this variant could be useful in the context of a future genetic risk score for CVD based on multiple variants.

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