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Cholesterol Acyltransferase Gene Mutations Have Accelerated Atherogenesis as Assessed by Carotid 3.0-T Magnetic Resonance Imaging

Carriers of Lecithin

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Objectives The aim of this study was to investigate the role of reduced lecithin: cholesterol acyltransferase (LCAT) function on atherogenesis using 3.0-T carotid magnetic resonance imaging (MRI) and B-mode ultrasound.

Background The role of low high-density lipoprotein cholesterol as a causal factor in atherogenesis has recently been questioned. LCAT plays a key role in high-density lipoprotein cholesterol metabolism.

Methods Carotid 3.0-T MRI and B-mode ultrasound measurements were performed in 40 carriers of LCAT gene mutations and 40 controls, matched for age. Patients with cardiovascular disease were excluded.

Results Carriers had 31% lower LCAT activity levels and 38% decreased high-density lipoprotein cholesterol levels (both $p < 0.001$ vs. controls). Carriers presented with a 10% higher normalized wall index (0.34 ± 0.07 vs. 0.31 ± 0.04, $p = 0.002$), a 22% higher mean wall area (17.3 ± 8.5 mm^2 vs. 14.2 ± 4.1 mm^2, $p = 0.01$), and a 22% higher total wall volume ($1{,}039 \pm 508$ mm^3 vs. 851 ± 247 mm^3, $p = 0.01$ vs. controls) as measured by MRI. The prevalence (20 vs. 5, $p = 0.002$) and the total volume (102 mm^3 vs. 3 mm^3) of atherosclerotic plaque components on MRI relating to lipid-rich tissue or calcification were also higher in carriers than in controls. All differences retained significance after adjustment for age, sex, blood pressure, low-density lipoprotein cholesterol, body mass index, smoking, and family history of cardiovascular disease. Common carotid intima-media thickness measured with ultrasound was increased in carriers by 12.5% (0.72 ± 0.33 mm vs. 0.64 ± 0.15 mm, $p = 0.14$).

Conclusions Carriers of LCAT gene mutations exhibit increased carotid atherosclerosis, indicating an increased risk of cardiovascular disease. The present findings imply that increasing LCAT activity may be an attractive target in cardiovascular prevention strategies. (J Am Coll Cardiol 2011;58:2481–7) © 2011 by the American College of Cardiology Foundation

A low plasma high-density lipoprotein cholesterol (HDL-C) level is among the strongest risk factors for cardiovascular disease (CVD) (1). One of the mechanisms by which high-density lipoprotein (HDL) is considered to convey atheroprotection is the removal of excess cholesterol from lipid-laden foam cells in the artery wall and transport it to the liver for fecal excretion, a process referred to as reverse cholesterol transport (2). A crucial enzyme in HDL metabolism is lecithin:cholesterol acyl transferase (LCAT) (3,4). This plasma enzyme, produced in the liver and small intestine, is predominantly associated with HDL and esterifies free cholesterol using apolipoprotein A-I as a cofactor (3). Homozygotes for deleterious mutations in the LCAT gene are characterized by nearly complete HDL-C deficiency (~90% reduction), whereas heterozygotes have profoundly reduced HDL-C levels (~40% reduction) compared with normal (5–8).

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Abbreviations and Acronyms

BMI = body mass index
CCIMT = common carotid intima-media thickness
CVD = cardiovascular disease
FED = fish eye disease
FLD = familial LCAT deficiency
HDL = high-density lipoprotein
HDL-C = high-density lipoprotein cholesterol
IMT = intima-media thickness
LCAT = lecithin:cholesterol acyltransferase
LDL-C = low-density lipoprotein cholesterol
MRI = magnetic resonance imaging
MWA = mean wall area
NWI = normalized wall index
PC = plaque component

To date, the relationship between LCAT and atherosclerosis has been a matter of debate. Animal studies have not been able to provide a clear answer because both LCAT knockout models and LCAT overexpression models yielded mixed results with respect to atherogenesis, as recently reviewed (9). Human studies have also been conflicting. Hovingh et al. (10) reported that carriers of LCAT gene mutations have increased carotid intima-media thickness (IMT) (as quantified by B-mode ultrasound imaging) compared with family controls. In contrast, Calabresi et al. (11) recently reported that carotid IMT was decreased in carriers while using the same ultrasound methodology. These contradictory outcomes are difficult to interpret and may result from population differences. Furthermore, a limitation of previous studies is that carotid ultrasound lacks statistical power to reliably measure arterial wall thickness in small population studies because ultrasound provides 2-dimensional longitudinal images, whereas atherosclerosis is a 3-dimensional eccentric developing disease. Magnetic resonance imaging (MRI) might overcome these imaging limitations because it enables transverse 3-dimensional imaging of atherosclerosis at high resolution with excellent interscan reproducibility (12).

In the present study, we set out to assess the relationship between LCAT and carotid atherosclerosis using carotid 3.0-T MRI in parallel with carotid B-mode ultrasound imaging, comparing carriers of LCAT mutations and controls. We hypothesized that carriers of LCAT gene mutations had increased atherosclerosis compared with controls.

Methods

Study design. In this study, the extent of carotid atherosclerosis in subjects with LCAT gene mutations and age-matched controls was compared. The study was conducted at the Academic Medical Center in Amsterdam, the Netherlands from October 2008 to October 2009. The study protocol was reviewed and approved by the institutional review board, and all subjects gave written informed consent.

The 3 probands of the families in which we identified LCAT mutations had presented to the ophthalmologists with corneal clouding, after which they were referred to our lipid clinic. Subsequently, we performed genetic testing in their family members to identify subjects with LCAT mutations. Carriers of molecularly diagnosed LCAT mutations (DNA and LCAT activity) were enrolled in this study, irrespective of their age and sex. Probands with CVD and their family members were excluded. For the control group, family members of the included carriers were asked to participate in the study and were first-, second-, or third-degree family members or spouses. They were included if they could be matched for age with a carrier. Because insufficient numbers of unaffected family controls (N = 19) volunteered, we matched the control group with unrelated controls (N = 21) recruited by advertisement. Exclusion criteria for both carriers and controls were a history of CVD, previous carotid surgery, or any contraindication to MRI.

Questionnaire, biometric, and biochemical measurements. The presence of cardiovascular risk factors, use of medication, and family history of CVD were assessed by a questionnaire. Brachial artery blood pressures were measured using an oscillometric blood pressure device (Omron 705IT, Hoofddorp, the Netherlands). The presence of hypertension was defined as a systolic blood pressure >140 mm Hg, a diastolic blood pressure >90 mm Hg or the use of antihypertensive medication. Weight and length were measured to calculate body mass index (BMI).

Ethylenediamine tetraacetic acid plasma obtained through venous blood samples were obtained after overnight fasting and stored using standardized protocols. Plasma total cholesterol, HDL-C and triglyceride levels were analyzed using a commercially available enzymatic method (colorimetric assay with the CHOD-PAP and GPO-PAP kits) (Westburg) on a Cobas Mira autoanalyzer (Roche, Mannheim, Switzerland). Low-density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald equation. LCAT activity was measured using a proteoliposome substrate as previously described (10).

Carotid MRI. Scans were performed with a 3.0-T Philips (Best, the Netherlands) whole-body scanner using a single-element microcoil with a diameter of 5 cm. Cardiac gated axial T1-weighted turbo spin echo image stacks were acquired at end-diastole using a double inversion recovery preparation and active fat suppression. Sequence parameters were slice thickness of 3 mm, imaging matrix size of 240, field of view of 60 × 60 mm, noninterpolated pixel size of 0.25 × 0.25 mm, echo time of 9 ms, recovery time according to the subjects' heart rate (approximately 900 ms), echo train length of 7, echo train duration of 63 ms. To localize the left and right common carotid artery and carotid bifurcation, axial magnetic resonance angiography images were acquired using a time-of-flight sequence. These images together with projection images were used for positioning the scan planes perpendicular to the vessel at a predefined distance distal to the flow divider. Ten slices were scanned of the distal 3.0 cm of the left and right common carotid artery. The slices were located from 9 mm to 39 mm proximal to the carotid flow divider. Each carotid artery was scanned individually. A total of 20 images were

obtained per scan. All images were saved in DICOM format. Standardized equipment and protocols were used for image storage and data management. The imaging protocol and image analysis were described previously (12,13).

Quantitative image analysis was performed using semi-automated measurement software (VesselMass, Leiden University Medical Center, Leiden, the Netherlands) (14). One reader, blinded to group and any other data of the participants, analyzed all the images. The mean wall area (MWA), lumen area, outer wall area, and total wall volume were measured. The normalized wall index (NWI) was calculated as: NWI = MWA/outer wall area. Also, the prevalence of plaque components (PCs) and total PC volume (mm^3) were assessed. PC was defined as a T1-weighted image on which an area of decreased signal intensity within the artery wall was identified. Previous studies showed that areas in the artery wall with decreased signal intensity on T1-weighted images represent either lipid-rich tissue or calcification (15). The prevalence of PC was reported as the total number of images per group that showed PC. Also the volume of PCs was quantified and reported as the sum of all PC volumes of all subjects per group.

Carotid ultrasound imaging. Carotid B-mode ultrasound scans of the left and right common, bulb, and internal carotid arterial far walls were assessed with a single-angle imaging protocol, with the transducer axis parallel to a virtual ear-to-ear line, according to our standardized protocol as previously described (16). One experienced and certified sonographer performed all scans, and 1 reader analyzed all the images, blinded to group and any other data of the participants. Images were analyzed quantitatively offline by 1 certified image analyzer using validated software (eTrack, Academic Medical Center, Amsterdam, the Netherlands). The primary ultrasound parameter was defined as the mean common carotid intima-media thickness (CCIMT) (defined as the average far wall IMT of the left and right distal 1 cm of the common carotid artery). A secondary ultrasound endpoint entailed the mean carotid IMT, defined as the average far wall IMT of the left and right common, bulb, and internal carotid arterial wall segments.

Outcome parameters. The NWI was the primary outcome parameter of the study. A priori, based on previous study data and assuming a 2-sided α of 0.05 and β of 0.2 (power of 80%), we calculated that a sample of at least 38 subjects per group was required to detect a 0.02 difference in the NWI between groups. Secondary MRI outcome parameters were MWA (square millimeters), and total wall volume (cubic millimeters). Secondary ultrasound outcome parameters were CCIMT (millimeters) and IMT (millimeters). Exploratory endpoints were PC prevalence (number) and total PC volume (cubic millimeters) assessed by MRI.

Statistical analysis. Continuous variables are expressed as mean ± SD, unless otherwise specified. Differences in demographic, biometric, and biochemical parameters between carriers of LCAT gene mutations and controls were assessed using an unpaired Student *t* test or chi-square test, where appropriate. Differences in carotid imaging parameters between carriers of LCAT gene mutations and controls were assessed using an unpaired Student *t* tests, unless otherwise specified. In addition, a multivariate model was used with generalized estimating equations in the SAS procedure GENMOD (SAS Institute Inc., Cary, North Carolina) to account for age, sex, hypertension (systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or the use of antihypertensive medication), LDL-C, BMI, smoking, family history of CVD, and correlations within families due to clustering of genetic and/or environmental factors. To compare the agreement between MRI and ultrasound scans within patients, we assessed the infraclass correlation coefficients (r) and mean paired difference between MWT (MRI) and CCIMT (ultrasound). Statistical analyses were done using SPSS version 16.0 (SPSS Inc., Chicago, Illinois) and SAS version 9.0 (SAS Institute Inc., Cary, North Carolina).

Results

Population characteristics. We studied 40 carriers of LCAT gene mutations (from 14 families of Dutch descent) and 40 age-matched controls, 19 of whom were family members and 21 were unrelated individuals. Mutations in the LCAT gene can either cause loss of enzymatic activity on only HDL (α activity) or loss of activity on both HDL and LDL (α and β activity, respectively) (8). Clinically, this translates into 2 different autonomic recessive disorders: fish eye disease (FED) (only loss of α activity) and familial LCAT deficiency (FLD) (loss of both α and β activity) (5–7). Whereas both FED and FLD patients present with low HDL-C, only FLD patients also exhibit lower LDL-C levels (5–7). Of the carriers, 38 had 1 mutant LCAT allele, whereas 2 were homozygotic for a defect that underlay clinically manifest FED (corneal pacification). Thirty-three of the 40 carriers had a mutation that is known to cause FED when present on both alleles. Four individuals were heterozygotes for a mutation that is known to cause FLD when present on both alleles. Finally, 3 subjects carried LCAT gene point mutations, but it is unknown whether they cause FED or FLD when present on both alleles (no homozygous patients described). Table 1 summarizes the demographic, lifestyle, and clinical characteristics of carriers and controls. Age, sex, smoking, alcohol use, blood pressure, diabetes, fasting glucose level, fasting insulin level, Homeostatic Model Assessment index, hypertension, and the Framingham risk score were similar. BMI tended to be higher in the carriers, but this was not statistically significant. In addition, more lipid-lowering medication, especially statins, and Ascal (calcium carbsalate) were prescribed in the carriers.

Table 1 also gives the results of lipid, (apo)lipoprotein, and LCAT activity measurements. Carriers had 8% lower

Table 1 Characteristics of Carriers of LCAT Gene Mutations and Controls

	Carriers of LCAT Gene Mutations (n = 40)	Controls (n = 40)	p Value
Characteristics			
Age, yrs	42.4 ± 13.0	42.3 ± 14.1	0.97
Male	27 (68)	23 (58)	0.36
Body mass index, kg/m^2	25.7 ± 4.0	24.5 ± 3.5	0.17
Smokers	6 (15)	6 (15)	1.0
Alcohol use, U/week	5.8 ± 5.5	7.8 ± 7.9	0.22
Medication use			
Statin	11 (28)	1 (3)	0.05
Ezetimibe	3 (8)	0 (0)	0.08
Niacin	3 (8)	0 (0)	0.08
Fibrate	1 (3)	0 (0)	0.31
Aspirin	3 (0)	0 (0)	0.08
Blood pressure, mm Hg			
Systolic	131 ± 13	128 ± 13	0.29
Diastolic	78 ± 9	76 ± 9	0
Hypertension	10 (25)	6 (15)	0.26
Glucose metabolism			
Fasting glucose, mmol/l	5.2 ± 0.8	5.3 ± 0.9	0.49
Fasting insulin, mU/l	5.1 ± 8.9	5.2 ± 7.3	0.94
HOMA index	1.2 ± 2.1	1.5 ± 2.4	0.67
Diabetes	0 (0)	1 (3)	0.31
Lipid metabolism			0.04
Total cholesterol, mg/dl	175.4 ± 44.1	190.8 ± 41.6	
LDL-C, mg/dl	126.5 ± 33.4	123.6 ± 31.4	0.69
HDL-C, mg/dl	34.1 ± 13.9	54.4 ± 16.2	<0.001
Triglycerides, mg/dl	104.4 (80.8–146.2)	82.3 (55.3–126.1)	0.06
Apolipoprotein B, mg/dl	103.1 ± 25.6	100.7 ± 23.8	0.68
Apolipoprotein A-I, mg/dl	119.9 ± 31.9	150.6 ± 25.7	<0.001
LCAT activity, nmol · ml^{-1} · h^{-1}	9.24 ± 2.95	12.85 ± 2.92	<0.001

Values are mean ± SD or n (%). Male sex, smokers, medication use, hypertension, diabetes: p value for chi-square test; for other parameters: p for Student *t* test. Hypertension was defined as systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or the use of antihypertensive medication. For triglycerides, we report the median and interquartile range; p value for *t* test after log-transformation.

HDL-C = high-density lipoprotein cholesterol; HOMA index = Homeostatic Model Assessment index; LCAT = lecithin:cholesterol acyltransferase; LDL-C = low-density lipoprotein cholesterol.

total cholesterol ($p < 0.04$), which could be attributed to a 38% reduction of HDL-C levels ($p < 0.001$) with similar LDL-C levels in both groups. Plasma triglyceride levels were 27% higher in carriers compared with controls ($p < 0.06$). Apolipoprotein B levels were identical, whereas carriers had 20% lower apolipoprotein A-I levels ($p < 0.001$). LCAT activity levels were 31% lower in carriers compared with controls ($p < 0.001$).

Carotid MRI and ultrasound. Mean ± SD of MRI and ultrasound parameters are shown in Table 2. The NWI, the primary endpoint of this study, was significantly increased in carriers compared with controls ($p = 0.02$), as shown in Figure 1. Statistical corrections for differences in age, sex, hypertension, LDL-C, BMI, smoking, family history of CVD, and clustering of genetic and/or environmental factors in families rendered stronger statistical significance ($p = 0.002$). The NWI in unaffected family controls was similar to that of unrelated controls (0.30 ± 0.04 vs. 0.31 ± 0.05, $p = 0.57$). We also assessed differences in plaque composition. The prevalence of PC related to lipid-rich tissue or calcification (PC prevalence) was 25% higher (20 vs. 6) and the total PC volume was 34 times larger in carriers than in controls. Ultrasound CCIMT, and IMT were increased in carriers, but these differences did not reach statistical significance. There was excellent agreement between MWT (MRI) and CCIMT (ultrasound), with an intraclass correlation coefficient of 0.91 (95% confidence interval: 0.86 to 0.94, $p < 0.001$), and a mean paired difference of 0.01 ± 0.11 mm.

Discussion

The present study shows that carriers of LCAT gene mutations exhibit increased carotid artery wall thickening as assessed by 3.0-T MRI compared with age-matched controls. This finding has clinical relevance because carotid artery wall thickening is associated with an increased risk of cardiovascular events (17,18). Although previous carotid ultrasound studies were unable to achieve consensus on the impact of LCAT gene mutations on carotid atherosclerosis (10,11), the current MRI data lend support to the concept that decreased LCAT function, as a result of LCAT gene mutations, is associated with accelerated atherogenesis.

Table 2 Carotid 3.-T Magnetic Resonance Imaging and B-mode Ultrasound Parameters for Carriers of LCAT Gene Mutations and Controls

	Carriers of LCAT Gene Mutations (n = 40)	Controls (n = 40)	p Value*	Adjusted p Value†
3.0-T MRI				
NWI	0.34 (0.07)	0.31 (0.04)	0.02	0.002
MWA, mm^2	17.3 (8.5)	14.2 (4.1)	0.02	0.01
TWV, mm^3	1,039 (508)	851 (247)	0.02	0.01
LA, mm^2	32.5 (6.7)	31.3 (5.1)	0.32	0.72
Plaque composition analysis				
PC presence	20 (2.5)	5 (0.6)	0.002‡	
Total PC volume, mm^3	102	3		
B-mode ultrasound				
CCIMT, mm	0.72 (0.33)	0.64 (0.15)	0.19	0.14
IMT, mm	0.75 (0.36)	0.69 (0.23)	0.39	0.53

Values are n (%) or n. *p Value for the unadjusted model. †p Value for multivariate model adjusting for age, sex, body mass index, hypertension, low-density lipoprotein cholesterol, smoking status, and family history of cardiovascular disease and accounting for clustering of genetic and/or environmental factors in families. ‡p Value for chi-square test.

CCIMT = mean common carotid intima media thickness; IMT = average mean intima media thickness of the common, bulb, and internal carotid arteries; LA = lumen area; LCAT = lecithin:cholesterol acyltransferase; MWA = mean wall area; NWI = normalized wall index; PC = plaque component; TWV = total wall volume.

The aim of our study was to test the hypothesis that decreased LCAT function is associated with accelerated atherogenesis. To this end, we investigated 2 parameters of atherosclerosis with MRI: arterial wall thickening and the presence of PC. First, the data show that the carriers of LCAT gene mutations have thickened carotid artery walls compared with controls with significant increases in NWI, MWA, and total wall volume. These differences remained statistically significant after adjustments for age, sex, hypertension, LDL-C, BMI, smoking, family history of CVD, and clustering of genetic and/or environmental factors in families. Second, carriers presented with a 32% increased prevalence of PC and 16.5 times larger total PC volume compared with controls. These are features of carotid artery plaques that have been associated with increased cardiovascular event rates (17,18). Combined, these findings point to accelerated atherogenesis in individuals with reduced LCAT function.

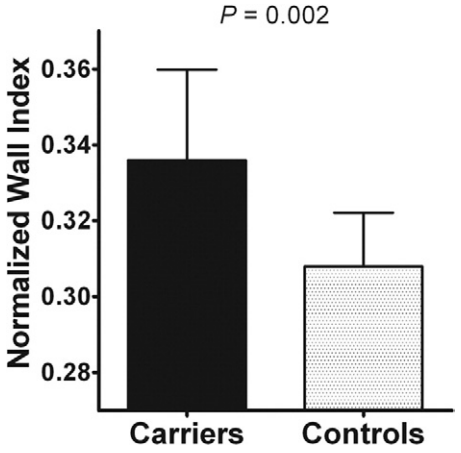

Figure 1 Comparison of Carotid Atherosclerosis in Carriers of Lecithin:Cholesterol Acyltransferase Gene Mutations and Controls

The mean and 95% confidence intervals for a normalized wall index measured by 3.0-T magnetic resonance imaging are shown for each group. The p value is adjusted for age, sex, body mass index, hypertension, low-density lipoprotein cholesterol, smoking status, family history of cardiovascular disease, and clustering of genetic and/or environmental factors in families.

We also assessed atherogenesis by means of carotid ultrasound IMT measurements. Whereas IMT parameters tended toward an increase in carriers, the differences did not reach statistical significance. The latter most likely pertains to the lack of power, as attested to by the significant MRI findings. In fact, we previously showed that the measurement variability of carotid 3.0-T MRI is less compared with that of ultrasound IMT (12).

Various studies have attempted to unravel the relationship between LCAT function and CVD in humans. Recent genome-wide association studies revealed that LCAT correlates with HDL-C levels, but not to CVD risk (19,20). The prevalence of single nucleotide polymorphisms in the population, however, is low, and it is unknown whether these single nucleotide polymorphisms actually affect LCAT function. Moreover, total variation in HDL-C explained by LCAT single nucleotide polymorphisms was very small. Therefore, genome-wide association studies may not be the most sensitive technique to detect a relationship between LCAT and CVD. In cross-sectional studies in patients with either angiographically documented coronary artery disease or acute myocardial infarction, both decreased and increased LCAT activity have been observed (21–23). A recent prospective nested case-control study examined LCAT concentration in 2,785 healthy subjects with a follow-up of 6 years (24). In this study, LCAT levels did not differ between cases and controls. However, because the variation of LCAT concentration in this population was small, a potential contribution of LCAT to CVD risk may

have been overcome by other risk factors, such as diabetes mellitus, smoking, blood pressure, BMI, and LDL-C.

Two previous imaging studies have addressed the relationship between LCAT and atherosclerosis in carriers of LCAT gene mutations using carotid IMT. Hovingh et al. (10) showed that carotid IMT was significantly increased in the carriers, whereas Calabresi et al. (11) showed the opposite, with carotid IMT being significantly decreased in carriers. This apparent discrepancy may be explained by differences in the populations. The carriers in the current study and in the Hovingh et al. (10) study predominantly had a different type of LCAT mutation than those in the study of Calabresi et al. (11). In both the Hovingh et al. (10) study and the present study, the vast majority of carriers of LCAT gene mutations exhibited a loss of α activity (LCAT activity on HDL), whereas Calabresi et al. (11) predominantly investigated individuals with loss of function mutations of α and β activity (LCAT activity on HDL and LDL). Accordingly, LDL-C levels in the current study were 23% higher compared with those in the Calabresi et al. (11) study (127 mg/dl vs. 103 mg/dl, respectively). In fact, the average LDL-C of the patients studied by Calabresi et al. (11) was in line with the National Cholesterol Education Program ATPIII guidelines. In fact, the absence of the primary trigger of atherosclerosis, that is, increased LDL-C, in the Calabresi et al. (11) study may be an important explanation why they did not observe increased atherogenesis in their familial LCAT-deficient patients.

To date, it has been unclear how to monitor and treat carriers of LCAT gene mutations. Whereas, ideally, a prospective, randomized, controlled trial is required to settle this issue, this type of evidence is unlikely to become available given the rareness of the disease. Considering the present data combined with the fact that decreased levels of HDL-C are strongly associated with CVD risk, we propose close monitoring and treatment of CVD risk factors in both heterozygous and homozygous patients with LCAT gene mutations. The current study results support a distinct role of LCAT in atherogenesis. Whether this effect relates to the effects on HDL-C or to, for example, the anti-inflammatory properties (25,26) attributed to LCAT cannot be determined by the current study.

Study limitations. A limitation inherent to this type of small cohort study is referral bias of the examined individuals. Carriers and family controls were recruited using the same method, whereas unrelated controls were recruited by advertisement. Nonetheless, related and unrelated controls were similar in terms of the NWI, so it is unlikely that differences in recruitment methods introduced bias. Furthermore, we attempted to minimize this effect by excluding patients with pre-existing CVD and included only carriers identified in families in which the probands were asymptomatic for CVD. These probands presented either with marked corneal clouding or low HDL-C levels identified through (random) screening for CVD risk factors.

Conclusions

The present study shows that carriers of LCAT gene mutations have increased carotid atherosclerosis compared with controls. Our data have 2 clinical implications. First, because carriers of LCAT gene mutations have experienced lifelong exposure to marked dyslipidemia and the current data suggest that they are at increased risk of the development of atherosclerosis, close monitoring and treatment of CVD risk factors is advocated. Second, based on these data, it is tempting to speculate that increasing LCAT activity is an interesting target to reduce cardiovascular risk (27,28).

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