Carnitine palmitoyltransferase IA polymorphism P479L is common in Greenland Inuit and is associated with elevated plasma apolipoprotein A-I

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Abstract Carnitine palmitoyltransferase IA, encoded by *CPT1A*, is a key regulator of fatty acid metabolism. Previously, a loss-of-function mutation, namely, c.1436 C→T (p.P479L), was reported in *CPT1A* in the homozygous state in Canadian aboriginal male with presumed CPT1A deficiency. To determine the population frequency of this variant, we determined *CPT1A* p.P479L genotypes in 1111 Greenland Inuit. Associations between genotype and variation in plasma total cholesterol, triglycerides, LDL, HDL, apolipoprotein (apo) B, and apoA-I was also investigated. We found the L479 allele occurs at a high frequency in this sample (0.73), while it was completely absent in 285 nonaboriginal samples. This suggests that the original proband's symptoms were not likely due to the *CPT1A* p.P479L mutation because it is very common in Inuit and because symptoms suggesting CPT1A deficiency have not been reported in any carrier subsequently studied. However, *CPT1A* p.P479L was associated with elevated plasma HDL and apoA-I levels. The association with increased levels of HDL and apoA-I suggest that the polymorphism might protect against atherosclerosis.— Rajakumar, C., M. R. Ban, H. Cao, T. K. Young, P. Bjerregaard, and R. A. Hegele. **Carnitine palmitoyltransferase IA polymorphism P479L is common in Greenland Inuit and is associated with elevated plasma apolipoprotein A-I. *J. Lipid Res.* 2009.** 50: **1223–1228.**

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Carnitine palmitoyltransferase IA (*CPT1A*) is a key gene in fatty acid metabolism (1). CPT1A is the isoform of carnitine palmitoyltransferase I that is expressed primarily in the liver, with other isoforms being expressed in other tissues. The protein consists of a single 773-amino-acid polypeptide chain containing both a catalytic and a regulatory domain (2). CPT1A is localized to the outer mitochondrial membrane and is responsible for transporting long-chain fatty acids from the cytosol to the mitochondrial intermembrane space. This is accomplished through the CPT1A-mediated catalysis of acylcarnitine formation from carnitine and an acyl-CoA. Unlike acyl-CoA, acylcarnitine can be transported across the outer membrane to the intermembrane space, where it is converted back into carnitine and acyl-CoA (1). Fatty acids are transported into the mitochondrion via CPT1A to participate in β-oxidation, the primary catabolic pathway of fatty acid metabolism. Allosteric binding of malonyl-CoA to the regulatory domain of CPT1A can inhibit the formation of acylcarnitine and thus can prevent fatty acid transport into the mitochondrion (1). Malonyl-CoA is an intermediate product of fatty acid biosynthesis, and binding of this molecule to CPT1A signals that fatty acid synthesis is underway and fatty acid catabolism is not presently required. Malonyl-CoA-mediated regulation and the necessity of CPT1A for long-chain fatty acid transport make *CPT1A* an integral gene to the regulation of lipid metabolism (1, 2).

Deficiencies in *CPT1A* are thought to be rare in the general population, with fewer than 30 defined mutations described in the literature (3, 4). Classical symptoms of *CPT1A* deficiency generally begin in childhood and include hypoketotic hypoglycemia with hepatic encephalopathy and impaired liver function. In 2001, six patients with *CPT1A* deficiencies resulting from different mutations were identified and characterized (5). Five of the patients exhibited typical symptoms of *CPT1A* deficiency, but the sixth patient, a Canadian aboriginal male, did not have

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Abbreviations: apo, apolipoprotein; CPT1A, carnitine palmitoyltransferase IA; BMI, body mass index; PPARα, peroxisome proliferator-activated receptor α; LPS, lipopolysaccharide.

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any symptoms until the age of 33, at which point he began to experience painful muscle cramps that worsened with age and eventually required frequent hospitalization (5). This individual was found to be homozygous for a C→T missense mutation at nucleotide position c.1436 of *CPT1A*, which causes the substitution of a conserved proline for a leucine at position 479 (P479L) of the resultant polypeptide. This mutation diminished but did not abolish the catalytic activity of the CPT1A protein and abolished malonyl-CoA-mediated regulation (5). Since this case was reported, the authors identified other P479L carriers among First Nations and Canadian Inuit, which suggests the possibility that the P479L mutation may be relatively common among First Nations and circumpolar populations (6). Curiously, no disease symptoms were described among the other P479L carriers reported, and with only one patient with characterized symptoms suggestive of *CPT1A* deficiency, there is no definitive evidence that the original patient's symptoms were directly attributable to the P479L mutation. However, given that the mutant protein shows diminished activity in vitro and cannot be regulated by malonyl-CoA, the L479 allele retains the potential to affect energy and lipid metabolism.

We sought to determine *1*) whether this polymorphism was private to First Nations and Inuit populations; *2*) the allele frequency; and *3*) whether there were any significant associations between *CPT1A* genotype and variations in plasma lipid, lipoprotein, and apolipoprotein levels. We thus screened a sample of 1111 Greenland Inuit as well as 50 Canadian Inuit and 285 control samples from nonaboriginal populations.

MATERIALS AND METHODS

Study subjects

Blood samples and data were collected from March 1999 to September 2001 from male and female Inuit over the age of 35 living in three selected areas of Western Greenland: Nuuk (population 14,000), Qasigiannguit (population 1,400), and four individual villages (population 240–275 each) in the Uummannaq district (7). Although there is substantial admixture of Danish genes in the population of Greenland Inuit, this population is related to the Inuit people of Canada, where the *CPT1A* P479L mutation has been observed, as well as the Inuit and Yupik of Alaska and Siberia (5, 8). Age, sex, and body mass index (BMI) were among phenotypic traits recorded from subjects.

Genotype at c.1436 for the C→T polymorphism in *CPT1A* was determined in 1,111 study subjects (497 males and 614 females). In addition, 285 control genotypes were determined from populations of South Asian, European Caucasian, and Chinese Canadians (95 genotypes for each ethnicity) to ensure that the L479 variant is rare in the general population. These samples are described in detail elsewhere (9). To confirm reports that this mutation is common in Canadian Inuit, 50 Canadian Inuit from a previously described sample were genotyped as well (10).

Plasma lipoprotein analyses

Blood for lipoprotein analyses was centrifuged at 2,000 rpm for 30 min, and plasma was stored at −70°C. Biochemical analysis for lipids and lipoproteins was performed as previously described to determine fasting plasma concentrations of total cholesterol, triglycerides, LDL-cholesterol, HDL-cholesterol, apolipoprotein (apo) B, and apoA-I (7).

Genotype analyses

Leukocyte DNA was extracted from blood for genotyping as described (7). SNaPShot (Applied Biosystems, Mississauga, ON) single-nucleotide extension minisequencing was used to determine genotypes. To apply this technique, DNA was first amplified by PCR using a 30 μl reaction mixture containing 60 ng of genomic DNA, 3.0 μl of PCR buffer (200 mM Tris-HCl, pH 8.4, and 500 mM KCl), 0.9 μl of 50 mM $MgCl_2$, 4.8 μl of deoxynucleoside triphosphate (0.2 mM), 0.5 μl each of the following primers: GGGACAGGTGCAAAGTGAAT (5′) and GTGCTGGGATTACAGGTGTG (3′) (0.4 mM), and 1.0 units of *Taq* Platinum polymerase (Invitrogen, Mississauga, ON). Reaction conditions were 5 min at 94°C, followed by 30 cycles of 94°C denaturing for 30 s, 62°C annealing for 30 s, and 72°C extension for 30 s, followed by a final extension at 72°C for 10 min. Four microliters of the amplification product was then purified with 2 μl of rAPid alkaline phosphatase treatment (Roche, Mississauga, ON), 0.1 μl of exonuclease I (New England Biolabs, Pickering, ON), and 6.0 μl of deionized water and incubated for 1 h at 37°C followed by 15 min at 72°C. SNaPShot genotyping was then performed on the amplified and purified DNA at the London Regional Genomics Centre Sequencing Core using the SNaPShot primer 5′-ACTCCTGGGCAGATGCGC-3′.

Statistical analyses

A χ^2 test was used to assess deviation in genotype frequency from Hardy-Weinberg equilibrium. ANOVA was performed to determine the sources of variation for study subjects' fasting plasma levels of total cholesterol, triglycerides, LDL-cholesterol, HDL-cholesterol, apoB, and apoA-I using the *CPT1A* P479L genotype as the independent class variable. Age, sex, and BMI were entered as covariates. F tests were performed using type III sum of squares, which is appropriate for imbalanced study designs. For phenotypes showing significant association with genotype, least squares analysis was performed to determine effect of each genotype on phenotypic values. All statistical analysis was performed using SAS version 9.0 with $P < 0.05$ as a nominal level of significance.

RESULTS

Baseline phenotypic characteristics of Greenland Inuit

For the 1,111 Greenland Inuit study subjects whose *CPT1A* P479L genotype and plasma lipoprotein concentrations were determined, baseline levels of total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, apoA-I, and apoB are shown in **Table 1**. Mean age, BMI, and the percentage of study subjects who were female are also shown.

CPT1A P479L genotype and allele frequencies

CPT1A P479L genotype frequencies for Greenland Inuit, Canadian Inuit, and control populations are shown in **Table 2**. In the Greenland sample, there were 601 L479/L479 homozygotes, 421 heterozygotes, and 89 P479/P479 homozygotes. L479 was the major allele in Greenlanders, with a frequency of 0.73. This allele was altogether absent from the South Asian, European Caucasian, and Chinese control populations. The L479 allele was also present in

TABLE 1. Baseline phenotypic characteristics (mean ± SD) of Greenland Inuit

Measurement	Value
Number	1,111
Percent female (%)	55.3
Age (years)	43.6 ± 14.2
BMI (kg/m^2)	26.3 ± 5.0
Total cholesterol (mmol/L)	5.95 ± 1.16
Triglycerides (mmol/L)	1.16 ± 0.67
HDL-cholesterol (mmol/L)	1.56 ± 0.44
LDL-cholesterol (mmol/L)	3.86 ± 1.08
apoA-I (g/L)	1.75 ± 0.30
apoB (g/L)	0.93 ± 0.24

Canadian Inuit, with a frequency of 0.93. Genotype frequencies determined from Greenland and Canadian Inuit did not show significant deviation from expectations based on Hardy-Weinberg equilibrium (both $P > 0.05$).

Determinants of plasma lipoprotein levels

Results of ANOVA are summarized in **Table 3**. Significant relationships were found between *CPT1A* P479L genotype and plasma concentrations of both HDL-cholesterol ($P < 0.05$) and apoA-I ($P < 0.0001$). Additionally, BMI was found to significantly associate with all lipoprotein levels measured ($P < 0.0001$), while age significantly associated with all lipoproteins but apoB ($P < 0.0001$), and sex associated significantly with plasma concentrations of triglycerides ($P < 0.05$), HDL-cholesterol ($P < 0.05$), and apoA-I ($P < 0.0001$).

Association between CPT1A P479L genotype and plasma lipoproteins

CPT1A P479L genotypes and the corresponding levels of HDL, apoA-I, and triglycerides are shown in **Table 4**. Lipoprotein levels vary significantly with age, sex, and BMI. There was a significant relationship ($P < 0.05$) between the presence of the L479 allele and elevated levels of HDL and apoA-I, with L479/L479 homozygotes having higher levels of HDL and apoA-I than heterozygotes and heterozygotes having higher concentrations than P479/P479 homozygotes, suggesting that the L479 allele shows incomplete dominance. A similar nonsignificant trend with increasing triglycerides was observed.

DISCUSSION

The principal novel finding of this study is that the *CPT1A* L479 variant occurs frequently in the Greenland Inuit population and is associated with significantly higher plasma levels of HDL-cholesterol and apoA-I in carriers than in those lacking the allele (Tables 2–4). Furthermore, homozygotes are common among healthy controls, suggesting that if this allele is pathogenic, it would require additional genetic or environmental factors to be present. Single nucleotide polymorphisms in candidate genes for lipid metabolism are associated with variations in plasma lipoprotein levels in populations with low genetic and environmental variability (11, 12). In this sample of Greenland Inuit, plasma levels of the lipids, lipoproteins, and apolipoproteins measured have already been shown to be associated with common variants of genes that show replicable associations with plasma lipid, lipoprotein, and apolipoprotein levels in other populations (12–14).

We have also confirmed a high L479 allele frequency in Canadian Inuit and have shown that it is absent from nonaboriginal populations, although larger sample sizes are required to be more secure about its complete absence (Table 2). The P479L polymorphism was also initially described in a Canadian aboriginal male, and other occurrences have been reported in Canadian First Nations communities (5, 6). This suggests that the P479L polymorphism in *CPT1A* is private to Inuit and Canadian First Nations people. Only one other variant of *CPT1A*, c.2129 G→A, has ever been suggested to be specific to a particular population, a Hutterite with a high prevalence of *CPT1A* deficiency and a substantial degree of consanguinity (15).

Because the mutation was first characterized in a Canadian aboriginal subject, and because the mutant allele is common in this population, it may simply be coincidental that this individual possessed the mutation and exhibited apparently atypical symptoms of *CPT1A* deficiency, such as late-onset painful muscle cramps that worsened with age (5). *CPT1A* is not expressed in muscles, and symptoms have not been described in any other individuals with the P479L polymorphism. There has also been no mechanistic link postulated between the mutation's effect on the protein and the initial proband's symptoms. Therefore, it cannot be definitively stated that the proband's symptoms were due to his *CPT1A* genotype, and it is quite possible that symptoms were unrelated to *CPT1A* and may have resulted from another cause. The P479L mutation may not, in fact, confer a CPT1A deficiency syndrome at all, given the very large number of homozygotes in the healthy screened Greenland sample. In the majority of deficiencies, the mutant CPT1A is expressed at similar levels as in control cells but exhibits undetectably low levels of activity (3–5). In cultured fibroblasts from the

TABLE 2. Genotype frequencies for *CPT1A* P479L polymorphism

Population	n	P479/P479	P479/L479	L479/L479
Greenland Inuit	1,111	0.080	0.379	0.541
Males	497	0.103	0.370	0.527
Females	614	0.062	0.386	0.552
Canadian Inuit	50	0.020	0.100	0.880
Chinese Canadian (control)	95	1.000	0.000	0.000
European Caucasian Canadian (control)	95	1.000	0.000	0.000
South Asian Canadian (control)	95	1.000	0.000	0.000

P479 and L479 refer to amino acids present at position 479 of resultant polypeptide from each allele of *CPT1A*.

TABLE 3. Summary of ANOVA showing determinants of lipoproteins in Greenland Inuit

		Total Cholesterol		Triglycerides		HDL		LDL		apoA-I		Apo B	
Source of Variation	*df*	F	*P*	F	*P*	F	*P*	F	*P*	F	*P*	F	P-value
Age	1	83.80	<0.0001	29.25	<0.0001	79.42	<0.0001	58.51	<0.0001	27.90	<0.0001	2.58	n.s.
Sex	1	0.47	n.s.	4.13	0.0432	15.08	0.0001	0.08	n.s.	50.56	<0.0001	0.16	n.s.
BMI	1	32.15	<0.0001	192.40	<0.0001	134.08	<0.0001	49.77	<0.0001	71.42	<0.0001	70.70	<0.0001
CPT1A P479L genotype	2	0.05	n.s.	2.48	n.s.	3.24	0.0396	1.13	n.s.	13.84	<0.0001	2.09	n.s.

CPT1A P479L, carnitine palmitoyltransferase IA genotype. *P* value indicates probability of a greater between-group F value using ANOVA; n.s. indicates relationship is not significant ($P > 0.05$).

original P479L patient, CPT1A was still expressed at normal levels, but activity was only diminished to 22% of the observed activity in control cells (5). This residual activity may explain why P479L carriers do not experience the characteristic symptoms of *CPT1A* deficiency.

In addition to its diminished activity, the variant CPT1A P479L protein is also insensitive to malonyl-CoA, the principal inhibitor of CPT1A, which acts to downregulate β-oxidation during lipid synthesis (1, 5). Several residues in CPT1A have been shown to be involved in malonyl-CoA binding (16, 17). Of particular interest are Ala-478 and His-483. These residues are in close proximity to Pro-479, and because the P479L mutant is the only natural mutant to diminish malonyl-CoA sensitivity while retaining catalytic function, the region from Ala-478 to His-483 has been proposed as a malonyl-CoA coupling domain (16). The model structure of CPT1A based on the carnitine acetyltransferase crystal places this domain close to carnitine and acyl-CoA binding sites as well as the proposed malonyl-CoA binding site (16, 18, 19).

The basis of the elevated levels of HDL cholesterol and apoA-I seen in P479L carriers is not clear. Hepatic intracellular fatty acid levels affect activation of peroxisome proliferator-activated receptor α (PPARα) (20, 21). PPARα is a transcription factor that can activate a number of genes related to fatty acid transport and metabolism, and in humans, PPARα activation can lead to increased production of HDL-cholesterol and apoA-I (21). Perhaps a mechanism other than catalysis could underlie the elevated HDL-cholesterol and apoA-I levels observed in individuals possessing the L479 allele, although a significant amount of further experimentation would be required to evaluate this hypothesis.

The higher levels of HDL-cholesterol and apoA-I associated with the L479 allele (Table 4) might have implications for lipoprotein metabolism. HDL, and associated apoA-I, protect against atherosclerosis by mediating cholesterol efflux from macrophages (reverse cholesterol transport), inhibition of LDL oxidation, and protection of the endothelium (22). HDL-mediated reverse cholesterol transport is the primary means by which cholesterol is removed from nonhepatic cells and returned to the liver (23). Elevated plasma HDL results in greater reverse cholesterol transport and is therefore thought to cause arterial plaque regression (24). HDL can also help prevent the pathogenesis of atherosclerosis by inhibiting LDL oxidation. Oxidized LDL can transform macrophages to foam cells, recruit monocytes to atherosclerotic lesions, and damage the endothelium, leading to the progression of plaque formation (23). HDL also protects the endothelium through several mechanisms at the initiation of atherosclerosis (22, 25).

However, it is difficult to determine whether the increased plasma HDL-cholesterol and apoA-I associated with the *CPT1A* P479L polymorphism contributes to lower cardiovascular disease end points among Greenlanders. It has long been believed that incidence of cardiovascular disease is relatively low among Inuit living a traditional, nonwesternized lifestyle (26). This has often been attributed to the high consumption of polyunsaturated fatty acids from fish and marine mammals by the Inuit, but it may be that there are genetic causes as well (27). Genetic factors that may influence lipid metabolism in the Inuit warrant investigation, as the incidences of obesity and lipid profiles suggesting cardiovascular risk are known to be on the increase in Greenland and are most likely increasing in other circumpolar regions as well (28). A shift toward a more "westernized" diet and lifestyle in arctic communities may be to blame, though there has been no definitive study to demonstrate this. Increasing exposure to environmental risk factors make it ever more important to under-

TABLE 4. Significant associations between *CPT1A* P479L genotype and plasma lipoproteins in Greenland Inuit

Genotype	n	HDL[a] (LSM ± SEM) (mmol/L)	apoA-I[b] (LSM ± SEM) (g/L)	Triglycerides[c] (LSM ± SEM) (mmol/L)
P479/P479	89	1.47 ± 0.04	1.62 ± 0.03	1.04 ± 0.07
P479/L479	421	1.55 ± 0.02	1.72 ± 0.01	1.15 ± 0.03
L479/L479	601	1.58 ± 0.02	1.78 ± 0.01	1.19 ± 0.03

P479 and L479 refer to amino acids present at position 479 of resultant polypeptide from each allele of *CPT1A*; LSM, least squares (fully adjusted) means. Significant associations are defined as those with $P > 0.05$.

[a] HDL shows significantly increasing levels ($P < 0.05$) from P479/P479 to P479/L479 to L479/L479.

[b] apoA-I shows significantly increasing levels ($P < 0.05$) from P479/P479 to P479/L479 to L479/L479.

[c] Triglycerides do not show a significant association with CPT1A genotype but show a trend toward increasing levels from P479/P479 to P479/L479 to L479/L479.

stand the genetic factors contributing to cardiovascular disease in circumpolar people. Although environmental cardiovascular disease risk factors may be increasing, the observation that cardiovascular disease incidence is low among Greenlanders may be anecdotal, and there are, in fact, a number of conflicting reports on whether or not incidence of the disease in the current era is higher or lower in the Inuit than in nonaboriginals (29). Without knowing the development of cardiovascular disease end points in this sample of Greenlanders, the elevated HDL-cholesterol and apoA-I associated with the *CPT1A* polymorphism cannot be definitively linked to reduced risk of cardiovascular disease. However, because HDL and apoA-I play such crucial roles in many processes that protect against atherosclerosis, it remains possible that *CPT1A* P479L might impart some protection, although this would require further study (22, 23).

In addition, apoA-I has also been shown to have anti-infection properties. apoA-I appears to sequester endotoxic lipopolysaccharide (LPS) released by gram-negative bacteria (30). Endotoxicity of LPS results from its binding to endogenous LPS binding protein, which then binds CD_{14} receptors of macrophages and monocytes to initiate a pathological signaling cascade (31). Not only has apoA-I been shown to readily bind to LPS, but it has been shown to reduce mortality of cells treated with LPS and functions in vivo to reduce mortality of mice treated with LPS (30). *Helicobacter pylori* infections occur with relatively high frequency and low severity in arctic populations, and some aspects of *H. pylori* pathogenesis are mediated through LPS (32, 33). It is thus possible that elevated apoA-I levels may modulate *H. pylori* infection among Inuit, although this would require further study.

In summary, we have demonstrated a high frequency of the L479 allele in Greenland Inuit and have shown that the L479 allele is significantly associated with higher plasma levels of HDL-cholesterol and apoA-I (Tables 3, 4). It would be important to determine whether this variant exists in other native populations, such as in Native Americans. Regardless of the mechanism underlying the association, the increased HDL and apoA-I levels associated with this frequent, but private, polymorphism may protect against cardiovascular disease and infection in Inuit and First Nations individuals. Also, the high incidence of the allele and the lack of widespread reported symptoms similar to those observed in the original P479L patient suggest that this mutation may not necessarily confer a *CPT1A* deficiency syndrome and that the original patient's symptoms and *CPT1A* mutation was probably coincidental.

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