

Characterization of a novel mutation causing hepatic lipase deficiency among French Canadians

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Abstract Individuals with hepatic lipase (HL) deficiency are often characterized by elevated levels of triglycerides (TGs) and cholesterol. The aim of the present study was to characterize the molecular defect leading to severe HL deficiency in a Québec-based kindred. In the proband and two of her brothers, the very low to undetectable HL activity resulted from compound heterozygosity for two rare HL gene mutations, a previously unknown missense mutation in exon 5 designated A174T and the previously reported T383M mutation in exon 8 of the HL gene. The mutation at codon 174 resulted in the substitution of alanine for threonine, a polar amino acid, in a highly conserved nonpolar region of the protein involved in the catalytic activity of the enzyme. The severe HL deficiency among the three related compound heterozygotes was associated with a marked TG enrichment of LDL and HDL particles. The two men with severe HL deficiency also presented with abdominal obesity, which appeared to amplify the impact of HL deficiency on plasma TG-rich lipoprotein levels. **Our results demonstrated that HL deficiency in this Québec kindred is associated with an abnormal lipoprotein-lipid profile, which may vary considerably in the presence of secondary factors such as abdominal obesity.**—Ruel, I. L., P. Couture, C. Gagné, Y. Deshaies, J. Simard, R. A. Hegele, and B. Lamarche. **Characterization of a novel mutation causing hepatic lipase deficiency among French Canadians.** *J. Lipid Res.* 2003. 44: 1508–1514.

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Hepatic lipase (HL) is a 476 amino acid glycoprotein lipolytic serine hydrolase that is synthesized and secreted from hepatocytes, and anchored to the liver sinusoidal surface by heparin sulfate proteoglycans (1). Evidence from clinical and animal studies supports a role for HL in the metabolism of several lipoprotein classes (2, 3). Thus, HL has been reported to augment the uptake of HDL

cholesterol by the liver through a reverse cholesterol transport process by participating in the reconversion of large, buoyant HDL₂ to small, dense HDL₃ and by modulating the phospholipid content of these particles (4). HL is also responsible for the hydrolysis of triglycerides (TGs) and phospholipids in large, buoyant LDLs leading to the formation of small, dense, and more atherogenic LDL particles (5). Multiple lines of evidence suggest that HL participates in the conversion of VLDL remnants to LDL (6, 7) and enhances the uptake of remnant lipoproteins by functioning as a ligand between the lipoprotein and cell surface receptors (8). The enzyme can be released into the circulation by intravenous injection of heparin, enabling the measurement of its activity in postheparin plasma (9). However, more specific metabolic functions of HL and its importance as a determinant of plasma lipoprotein levels have yet to be fully elucidated.

The HL gene spans 35 kb of DNA, maps to chromosome 15q21, and is composed of nine exons and eight introns (10, 11). Four missense mutations in encoding exons [R186H (12), L334F (13), S267F (14), and T383M (15)] have been identified and demonstrated to be responsible for HL-deficient phenotypes. The determination of the role of HL in human lipoprotein metabolism has been facilitated by the identification of patients with HL deficiency. This rare genetic disorder, which appears to be inherited as an autosomal recessive trait, has been identified in only five families to date (15–19). Affected individuals with a heterozygous state for HL mutations do not have specific lipoprotein abnormalities, and even patients with complete HL deficiency display a variable phenotype (20). HL-deficient subjects may present with features characteristic of Type III hyperlipoproteinemia,

Abbreviations: CHD, coronary heart disease; HL, hepatic lipase; LPL, lipoprotein lipase; QHLD, Québec-based hepatic lipase deficiency; TG, triglyceride.

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including hypercholesterolemia, hypertriglyceridemia, and β -VLDL, and some have premature cardiovascular disease (20–23). One of the most consistent findings in the lipoprotein phenotype of HL-deficient subjects is an elevation of HDL₂ cholesterol (21, 24, 25) and a marked TG enrichment of LDL and HDL particles (20, 22, 24).

In the present study, we describe the underlying molecular defects in the HL gene of three patients from the Québec-based Hepatic Lipase Deficiency (QHLD) kindred presenting with very low to undetectable postheparin plasma HL activity. Hegele et al. previously reported the presence of the T383M mutation in the HL gene in one of two alleles among the HL-deficient subjects from the QHLD kindred (15). In vitro expression studies have confirmed that the T383M mutant protein retains partial activity but is poorly secreted (26). We report a previously unknown missense mutation in exon 5 of the HL gene due to a G→A base change resulting in the change of an alanine for a threonine in codon 174 of the mature protein. HL deficiency among three patients from the QHLD kindred resulted from compound heterozygosity for the two missense mutations A174T and T383M in the HL gene. We also describe the effects of severe HL deficiency on lipoprotein phenotype.

METHODS

Subjects

The proband, now a healthy 44-year-old French Canadian female, was referred to our clinic in the early 1980s for investigation of a moderate hyperlipidemia; she was 22 years old at the time. Physical examination was entirely normal. Thyroid, hepatic, and renal functions, as well as fasting blood glucose and urinalyses were normal. Plasma lipid and lipoprotein profile showed unusual abnormalities, including hyperalphalipoproteinemia with an HDL cholesterol value of 2.5 mmol/l, which was observed in spite of a concomitant hypertriglyceridemia of 4.1 mmol/l. Agarose gel electrophoresis of the VLDL fraction isolated by ultracentrifugation revealed a β -VLDL band. Analysis of the apolipoprotein (apo)E phenotype indicated that the patient was a carrier of the apoE3/3 genotype, thus ruling out the diagnosis of dysbetalipoproteinemia associated with the apoE2/2 genotype. It was then hypothesized that this patient could be affected with HL deficiency.

In the early 1990s, measurement of postheparin plasma lipase activities was performed and confirmed the diagnosis of severe HL deficiency. The analyses revealed undetectable HL activity with normal lipoprotein lipase (LPL) activity. First-degree relatives were then investigated: the proband had two sisters and four brothers. Three of the seven first-degree relatives, including the proband, were found to have undetectable HL activity; and sequencing of the HL gene, however, revealed the presence of the T383M missense mutation in one allele only (15). We have recently revisited the family to better understand the molecular defect responsible for HL deficiency in this kindred. The lipid-lipoprotein phenotype was characterized in the first-degree relatives (one of the proband's brothers refused to participate in the study) as well as in six individuals on the proband's paternal side (Fig. 1). The family members were generally healthy with no cases of Type 2 diabetes or previous history of coronary heart disease (CHD). One compound heterozygous male (1-5) was treated for hy-

pothyroidism. Subject 1-8 was taking oral contraceptives, Subject 2-1 received conjugated estrogens alone, and Subjects 2-4 and 2-5 received conjugated estrogens with medroxyprogesterone. Two of the participants also received HMG-CoA reductase inhibitors (2-2 and 2-3), one received a β -blocker (2-2), and finally, Patients 2-1 and 2-2 were taking an angiotensin II receptor inhibitor for essential arterial hypertension. None of the family members were smokers at the time of investigation. All participants gave their written consent to participate in this study, which received the approval from the local ethics committees. Unrelated men were recruited at the Lipid Research Center to serve as control subjects.

Lipid and lipoprotein analyses

Blood was drawn in tubes containing 0.15% EDTA after a 12 h fast, and plasma was isolated by centrifugation (1,500 *g* at 4°C, 15 min). The lipid content of plasma and lipoprotein subfractions isolated by sequential ultracentrifugations was determined by enzymatic methods with a Technicon RA-500 analyzer (Bayer Corporation, Tarrytown, NY) according to standardized procedures that have been described previously (27). Plasma apoB and apoA-I levels were measured by nephelometry (Dade Behring, Newark, DE). The apoE genotype was determined using the procedure described by Hixson and Vernier (28). Nondenaturing 2–16% and 4–30% polyacrylamide gradient gel electrophoreses were used to determine LDL and HDL particle sizes respectively, as previously described (29, 30).

Lipolytic enzyme activity determinations

LPL and HL activities were measured in subjects after a 12 h fast, 10 min after an intravenous injection of heparin (60 IU/kg body weight). LPL and HL activities were determined in postheparin plasma after preincubation with SDS, as previously described by Watson et al. (31). The two lipolytic enzyme activities were expressed as micromoles of free fatty acids released per milliliter of plasma per hour. The coefficient of variation for the analysis was 4.8%.

Amplification of the exons of the HL gene by PCR

DNA was extracted from leukocytes as described earlier (32). PCR primers, homologous to intron sequences flanking the exons of the HL gene and containing 18–23 nucleotides, were designed based on published HL gene structure (10). Sequences of amplification primers are available on request. The PCR was carried out using an automated 9600 GeneAmp (PE Applied Biosystems, Foster City, CA) in a total volume of 50 μ l after 35 cycles (30 s at 95°C, 30 s at 55°C, and 90 s at 72°C).

DNA sequencing

The nucleotide sequence of both strands of the PCR products was determined by the dideoxy nucleotide chain termination method (33) using a T7 sequencing kit from Amersham Pharmacia Biotech, Inc. (Piscataway, NJ). After the identification of the novel A174T missense mutation in exon 5 of the HL gene in the proband, its allele frequency was determined in 50 unrelated normal subjects by a complete sequencing of exon 5 of the HL gene. All family members of the QHLD kindred were then genotyped for the A174T mutation with digestion of the PCR-amplified exon 5 with *Sac*I. The T383M mutation in the HL gene was detected by standard PCR followed by digestion with the enzyme *Nla*III, as previously described (15).

Statistics

Plasma, HDL, and LDL-TG levels were log₁₀-transformed in order to reduce the skewness of their distribution, although un-

transformed values are shown in tables. Age, BMI, waist girth, and all lipid parameters in the different HL mutation groups, and in control subjects were compared using a general linear model with the Duncan posthoc test to locate subgroup differences. The statistical analyses were performed with the SAS software package (SAS Institute).

RESULTS

In order to establish the molecular defect underlying HL deficiency in the proband, we sequenced all nine coding exon and introns exon boundaries of the HL gene from PCR-amplified DNA. Sequencing of the PCR products revealed a variable site in exon 5 of the HL gene: the proband presented a normal G base on one allele as well as an abnormal base on the other allele, an A, at the first position of codon 174 in the sequencing gel. This novel single nucleotide mutation resulting in the substitution of alanine for threonine at amino acid 174 was identified in the proband and her two younger brothers (Fig. 1). The T383M missense mutation in exon 8 was found in the proband, her mother, and three brothers. The results obtained in the first-degree relatives suggest that the father had the A174T mutation. He had a myocardial infarction at age 49 but died at the age of 55 from an oropharyngeal cancer. The allele frequency of the A174T variant was determined by direct sequencing of exon 5 in 50 unrelated normal subjects. Each HL gene variant site was di-allelic (Table 1). None of the control subjects were carriers of the A174T mutation in the HL gene. Gene variants of previously reported codons 193 and 202 in exon 5 were present in the controls with a frequency of 35% and 49%, respectively.

The proband and all first-degree relatives of the proband were E3 homozygotes. The three subjects carrying the A174T and T383M mutations were found to have extremely low to undetectable HL activity, with normal LPL activity. For the purpose of the present study, we arbitrarily refer to these compound heterozygotes as patients with complete HL deficiency. As shown in Fig. 1, the two compound heterozygous males for the A174T and T383M mutations (1-5 and 1-6) were hypertriglyceridemic and exhibited abdominal obesity. Compared with her two brothers with complete HL deficiency, the complete HL-deficient proband female (1-1) presented elevated HDL cholesterol levels, mostly due to a greater proportion of HDL₂ cholesterol compared with HDL₃ cholesterol levels. The two completely HL-deficient men were also characterized by small LDL particles (252.7 and 250.2 Å for Subjects 1-5 and 1-6, respectively), which was not found in the proband, who had very large LDL particles (265.8 Å, not shown).

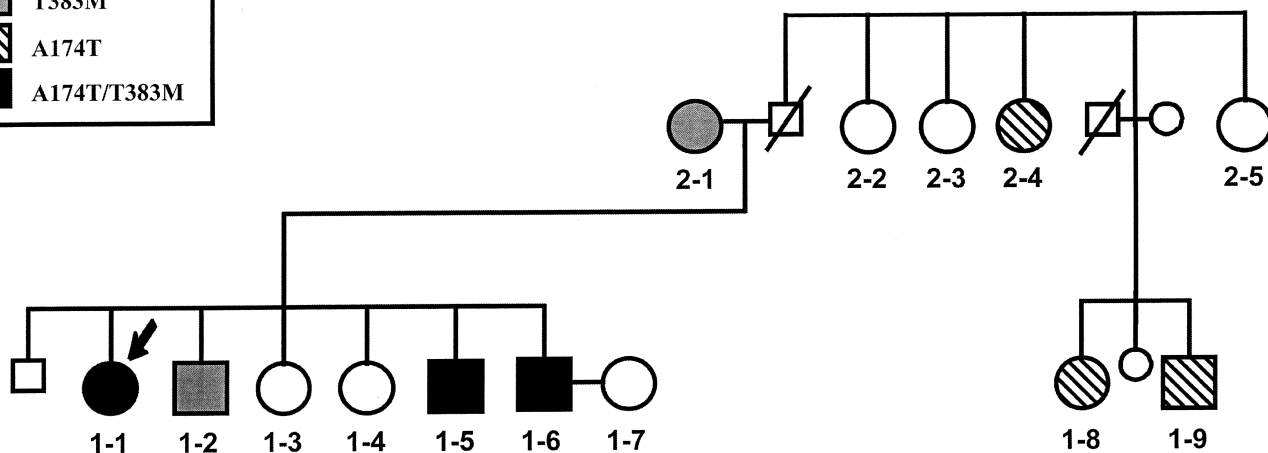
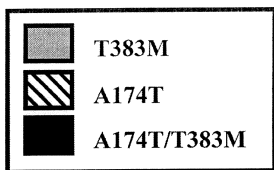
The mean concentrations of cholesterol and TG in plasma and lipoprotein fractions of the complete and partial HL-deficient, unaffected family members, and unrelated control subjects are shown in Table 2. Carriers of the A174T/T383M combination presented an altered lipoprotein-lipid profile compared with control subjects, while partial HL-deficient patients, i.e., patients presenting with

only one of the two mutations in the HL gene, tended to have an intermediate lipoprotein-lipid profile. The three complete HL-deficient patients were characterized by a marked hypertriglyceridemia (5.5 ± 4.0 mmol/l) versus partial HL-deficient patients and control subjects (A174T: 1.45 ± 0.37 mmol/l; T383M: 1.79 ± 0.61 mmol/l; and controls: 1.48 ± 0.58 mmol/l; $P = 0.007$). They also presented a marked 3- to 4-fold TG enrichment of LDL and HDL particles. In addition, gradient gel electrophoresis confirmed that the three patients with severe HL deficiency had large HDL particles (106.7 ± 2.3 vs. 83.0 ± 0.8 Å in noncarriers; $P < 0.0001$) representing the HDL₂ subclass. These subjects also presented phospholipid-enriched HDL particles compared with the control subjects (1.54 ± 0.30 vs. 1.15 ± 0.18 , $P = 0.02$). Partial HL-deficient patients presented low HL activity compared with noncarriers (A174T: 4.8 ± 1.0 and T383M: 3.7 ± 1.5 μmol/ml/h vs. 14.0 ± 7.2 μmol/ml/h for noncarriers; $P = 0.0006$). In all subjects, the postheparin plasma LPL activities were within normal range. Finally, partial HL-deficient patients carrying the A174T mutation presented a lipoprotein-lipid profile similar to that of those carrying the T383M mutation in the HL gene.

DISCUSSION

To date, very few patients with HL deficiency have been described (14, 15, 18, 20, 24, 34). In the present study, we describe a QHLD kindred in which the HL-deficient proband and two of her brothers are compound heterozygotes for two missense mutations, one in exon 5 of the HL gene and the other in exon 8. The T383M mutation in exon 8 has been previously reported in this family (15). However, the T383M mutation has been described as being “required but not sufficient” for expression of complete HL deficiency (15). Durstenfeld et al. demonstrated that the T383M mutation in the HL gene results in the secretion of a reduced amount of enzyme protein with about 40% of the wild-type enzyme activity (26). Therefore, the very low (or absence of) HL activity in three individuals from the QHLD kindred could not have been completely explained by the presence of the T383M mutation alone. The complete sequencing of all of the exons of the HL gene in the proband then revealed a second missense mutation, the A174T, in exon 5 of the HL gene. Severe HL deficiency was apparent in the proband as well as in her two brothers carrying both mutant alleles (A174T/T383M compound heterozygotes). The very low to undetectable HL activity was associated with an abnormal lipoprotein phenotype principally characterized by a marked TG enrichment of HDL and LDL particles. Two family members of the QHLD kindred were heterozygous for the T383M mutation and three for the A174T mutation and were characterized by a lipid-lipoprotein phenotype similar to that of unaffected subjects.

Complete HL deficiency among the compound heterozygotes suggests that the A174T mutation has a significant impact on HL activity. The mutation results in the



Pedigree number	1-1	1-2	1-3	1-4	1-5	1-6	1-7	2-1	2-2	2-3	2-4	1-8	1-9	2-5
Age (yrs)	42	42	40	39	37	35	37	73	74	70	66	41	37	59
BMI (kg/m ²)	25.7	25.7	27.9	29.3	30.5	32.3	23.0	27.3	28.7	20.8	28.4	26.7	26.1	25.9
Waist girth (cm)	78	96	92	89	107	103	75	89	101	85	102	79	89	92
TG (mmol/L)	2.02	1.36	1.39	1.26	4.53	9.82	0.71	2.23	2.11	1.44	1.40	1.85	1.11	1.44
Chol (mmol/L)	6.33	5.56	6.29	4.60	7.73	7.67	4.23	5.68	4.86	5.68	6.34	6.08	7.12	6.90
LDL-C (mmol/L)	3.62	3.76	4.29	2.84	3.68	1.88	2.67	3.14	2.97	3.46	4.16	3.79	5.45	5.17
HDL-C (mmol/L)	2.28	1.18	1.55	1.27	1.41	0.96	1.44	1.72	0.97	1.78	1.86	1.51	1.35	1.17
ApoE Genotype	3/3	3/3	3/3	3/3	3/3	3/3	3/3	3/3	3/3	3/3	3/3	4/3	4/3	3/3

Fig. 1. Pedigree of the Québec-based Hepatic Lipase Deficiency kindred. Squares represent males and the circles females. The arrow indicates the proband. Small symbols represent subjects not studied. Slashes identify deceased subjects. apoE, apolipoprotein E; BMI, body mass index; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; TG, triglyceride.

substitution of a nonpolar amino acid, alanine, for a polar one, threonine, at amino acid 174 in the mature HL protein. The three different lipases (LPL, HL, and pancreatic lipase) share a high degree of homology in their protein sequences, particularly near the three amino acids that compose the catalytic triad responsible for enzyme activity (35). Aspartic acid at position 172 of the mature protein is one of the three amino acids of the catalytic triad and is surrounded by mainly nonpolar amino acids. The A174T mutation introduces a nonhydrophobic amino acid in a highly conserved hydrophobic region of the active site of the HL protein, suggesting a significantly altered enzymatic activity. However, our three heterozygous carriers of the A174T mutation exhibited similar HL catalytic activities compared with the two affected individuals with the heterozygous state for the T383M mutation, both representing about 30% that of noncarriers. On the basis of our results and because of the small number of heterozygous subjects bearing either mutation, we cannot discern if the deficiency imparted by the novel A174T mutation is clinically more severe than the deficiency imparted by the T383M mutation.

The role of HL as a lipolytic enzyme in lipoprotein metabolism has been established for some time (6, 36). By

modulating the phospholipid and TG content of IDL, LDL, and HDL particles, HL contributes significantly to determining their lipid composition, density, size, and thereby their metabolic fate. It has been shown that increased levels of HL activity lead to phospholipid and TG-depleted LDL particles that are smaller and denser (5). The enzyme is also responsible for the removal of phospholipids and TG in HDL₂ particles, regenerating smaller HDL particles, HDL₃ particles (4). On the other hand, the absence of HL activity leads to a block in both pathways, causing an accumulation of TG within lipoproteins that results in large, buoyant LDL particles and mature HDL₂ particles in plasma (24, 34). The present study confirms and expands the latter observation by demonstrating that very low to absent HL enzymatic activity, as seen in the proband, is associated with remarkably larger and TG-rich HDL particles compared with unaffected family members.

Data from HL-deficient individuals provided evidence that secondary factors such as age, gender, and obesity can modify the phenotypic expression of HL mutations (13, 20). Our results support the hypothesis that maleness and/or abdominal obesity may have exacerbated the impact of the A174T/T383M mutation combination on

TABLE 1. Hepatic lipase gene variants in exon 5 and their frequencies in 50 control subjects

Variant	Exon	Base	Codon	DNA Change	Amino Acid Change	Genotype Frequency	Minor Allele Frequency
A174T	5	593	174	G→A ^a	Ala→Thr	GG 100% GA 0% AA 0%	0%
N193S	5	651	193	A→G	Asn→Ser	AA 36% AG 58% GG 6%	35%
T202T	5	679	202	C→G	Thr→Thr	CC 24% CG 54% GG 22%	49%

^a Nucleotide specifying minor allele for each site indicated in italic type.

plasma TG and cholesterol levels and on LDL particle size and HDL cholesterol levels in the two men compared with the female proband. Indeed, the two men with complete HL deficiency were not characterized as having large LDL particles or elevated HDL cholesterol levels when compared with the proband. Whether this lack of “protection” attributed to very low levels of HL activity was due to the presence of abdominal obesity in the male patients or simply to the gender difference remains to be determined. We also observed that simple heterozygous carriers of the T383M or the A174T mutation from the QHLD kindred were characterized by a lipid-lipoprotein profile similar to that of control subjects. As reported previously, heterozygous carriers of a functional mutation may present an al-

tered lipoprotein-lipid phenotype only if interactions between the environment and/or other genes occur (12). In the present study, all participants heterozygous for the A174T or the T383M mutation were generally healthy, particularly the younger subjects. The absence of secondary factors such as abdominal obesity in those subjects may have contributed to blunt the impact of the mutation on the lipoprotein-lipid profile. The nonlipolytic role of HL as a ligand and its contribution to variations in the lipoprotein profile among patients with HL deficiency will need to be addressed in future studies.

Despite the suggested prominent role of HL in lipoprotein metabolism, the association of HL with the risk of atherosclerosis and the clinical implications of altered lipoprotein composition (i.e., TG enrichment) in the pathophysiology of premature CHD among complete HL-deficient subjects of the Québec kindred are unknown. Atherosclerosis has been reported to be present in several human HL-deficient patients (20, 22, 24, 34, 37). Moreover, there is a history of premature CHD in the Québec family studied herein. The father of the proband had a myocardial infarction at age 49 and one of the proband's paternal uncles died of an myocardial infarction at age 55. Both of them were carriers of the A174T mutation. On the other hand, the T383M mutation, on the mother's side, does not seem to be associated with premature CHD. The role of HL deficiency in the pathogenesis of CHD is controversial, and the absence of symptoms and signs of atherosclerosis in the compound heterozygotes in the present family does not provide additional evidence on

TABLE 2. Comparison of plasma lipid and lipoprotein values between complete and partial hepatic lipase-deficient subjects, unaffected family members, and unrelated control subjects

	HL Mutation			Noncarriers (n = 11)	P ^a
	A174T/T383M (n = 3)	A174T (n = 3)	T383M (n = 2)		
Age (yrs)	38 ± 4	48 ± 16	57 ± 22	46 ± 14	0.49
BMI (kg/m ²)	29.5 ± 3.4	27.1 ± 1.2	26.5 ± 1.1	27.3 ± 4.3	0.84
Waist girth (cm)	96.0 ± 15.7	90.0 ± 11.5	92.5 ± 4.9	93.5 ± 11.7	0.77
Cholesterol (mmol/l)					
Plasma	7.2 ± 0.8	6.5 ± 0.5	5.6 ± 0.1 ^b	5.3 ± 0.9 ^b	0.02
LDL	3.1 ± 1.0	4.5 ± 0.9	3.4 ± 0.4	3.5 ± 0.8	0.32
HDL	1.55 ± 0.67	1.57 ± 0.26	1.45 ± 0.38	1.31 ± 0.29	0.50
Triglycerides (mmol/l)					
Plasma	5.5 ± 4.0	1.45 ± 0.37 ^b	1.79 ± 0.61 ^b	1.48 ± 0.58 ^b	0.01
LDL	1.26 ± 0.39	0.41 ± 0.05 ^b	0.35 ± 0.01 ^b	0.24 ± 0.08 ^{b,c,d}	<0.001
HDL	0.78 ± 0.20	0.32 ± 0.09 ^b	0.37 ± 0.13 ^b	0.23 ± 0.04 ^{b,c,d}	<0.001
Phospholipids (mmol/l)					
Plasma	4.16 ± 0.39	3.38 ± 0.13 ^b	3.10 ± 0.38 ^b	2.81 ± 0.32 ^b	<0.001
LDL	1.44 ± 0.32	1.71 ± 0.13	1.35 ± 0.08	1.25 ± 0.26	0.09
HDL	1.54 ± 0.30	1.38 ± 0.14	1.33 ± 0.17	1.15 ± 0.18 ^b	0.02
Apolipoprotein B (g/l)	1.48 ± 0.30	1.32 ± 0.10	1.06 ± 0.02 ^b	1.04 ± 0.23 ^b	0.03
Apolipoprotein A-I (g/l)	1.80 ± 0.58	1.67 ± 0.22	1.64 ± 0.48	1.45 ± 0.21	0.18
LDL size (Å)	256.2 ± 8.4	253.2 ± 3.7	255.6 ± 3.4	253.6 ± 7.5	0.65
HDL size (Å)	106.7 ± 2.3	83.6 ± 0.2 ^b	83.2 ± 0.4 ^b	83.0 ± 0.8 ^b	<0.001
HL activity (μmol/ml/h)	0.37 ± 0.44	4.8 ± 1.0	3.7 ± 1.5	14.0 ± 7.2 ^{b,c,d}	<0.001
LPL activity (μmol/ml/h)	3.1 ± 0.7	3.9 ± 1.6	2.4 ± 0.2	4.5 ± 2.1	0.25

HL, hepatic lipase; LPL, lipoprotein lipase. Values are expressed as mean ± SD. Lipase activities are expressed as μmol of free fatty acids released per ml of plasma per h.

^a P values for all variables (except for age) were obtained after an adjustment for age and gender.

^b Significantly different compared with complete HL-deficient subjects.

^c Significantly different compared with partial HL-deficient subjects (A174T).

^d Significantly different compared with partial HL-deficient subjects (T383M).

this issue. It must be stressed that the three patients with complete HL deficiency are presently aged 44, 38, and 36, perfectly healthy, and with no signs yet of premature CHD.

Conclusion

We report a previously unknown missense mutation in exon 5 of the HL gene; a G→A base change resulting in the change of an alanine for a threonine in codon 174 in a highly conserved area of the mature protein. Among the three patients from the QHLD kindred, the two missense mutations A174T and T383M cosegregated with complete HL deficiency. The very low to undetectable HL activity in these individuals was associated with abnormally TG-rich LDL and HDL particles. On the other hand, partial HL deficiency was associated with a normal lipoprotein-lipid profile. Our results also indicated that the typical dyslipidemic phenotype associated with severe HL deficiency can vary considerably in the presence of secondary factors such as abdominal obesity.¹⁹

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