A single Ser 259Arg mutation in the gene for lipoprotein lipase causes chylomicronemia in Moroccans of Berber ancestry

Foubert, L.; Bruin, T.; de Gennes, J.L.; Ehrenborg, E.; Furioli, J.; Kastelein, J.J.P.; Benlian, P.; Hayden, M.R.

Publication date
1997

Published in
Human Mutation

HUMAN MUTATION 10:179–185 (1997)

RESEARCH ARTICLE

A Single Ser259Arg Mutation in the Gene for Lipoprotein Lipase Causes Chylomicronemia in Moroccans of Berber Ancestry

Luc Foubert,[1,2] Taco Bruin,[3] Jean Luc De Gennes,[2] Ewa Ehrenborg,[1] Jean Furioli,[4] John Kastelein,[3] Pascale Benlian,[1,5*] and Michael Hayden[1]

[1]*Medical Genetics, University of British Columbia, Vancouver, British Columbia V6T 1Z4, Canada*
[2]*Endocrinology, Hôpital Pitié Salpétrière, 75013 Paris, France*
[3]*Lipid Research Group, Academic Medical Centre, P.O. Box 22700, 1100 DE Amsterdam, the Netherlands*
[4]*Paediatrics, Hôpital François Quesnay, Mantes-la-Jolie, France*
[5]*Molecular Biology, Hôpital Saint Antoine, 75012 Paris, France*

Communicated by Ronald G. Worton

Lipoprotein lipase (LPL) is the rate-limiting enzyme for the hydrolysis of triglyceride-rich lipoproteins. Numerous *LPL* gene mutations have been described as a cause of familial chylomicronemia in various populations. In general, allelic heterogeneity is observed in LPL deficiency in different populations. However, a founder effect has been reported in certain populations, such as French Canadians. Although familial chylomicronemia is observed in Morocco, the molecular basis for the disease remains unknown. Here, we report two unrelated Moroccan families of Berber ancestry, ascertained independently in Holland and France. In both probands, familial chylomicronemia manifested in infancy and was complicated with acute pancreatitis at age 2 years. Both probands were homozygous for a Ser259Arg mutation, which results in the absence of LPL catalytic activity both in vivo and in vitro. In heterozygous relatives, a partial decrease in plasma LPL activity was observed, sometimes associated with combined hyperlipidemia. This mutation previously unreported in other populations segregated on an identical haplotype, rarely observed in Caucasians, in both families. Therefore, LPL deficiency is a cause of familial chylomicronemia in Morocco and may result from a founder effect in patients of Berber ancestry. Hum Mutat 10:179–185, 1997.

KEY WORDS: **lipoprotein lipase; mutation; Morocco; chylomicronemia; genetics**

INTRODUCTION

Lipoprotein lipase (LPL), functions as a dimer bound to heparan sulfate proteoglycans at the surface of capillary endothelium to hydrolyse triglycerides, using apolipoprotein CII (ApoC-II) as a cofactor (Olivecrona and Bengtsson-Olivecrona, 1993). When lipolysis is defective, this results in an accumulation of large triglyceride-rich lipoproteins, namely chylomicrons, in plasma. Familial chylomicronemia is a recessive disorder usually manifesting in childhood (Brunzell, 1995). On a normal diet, patients often present with abdominal pain, hepatosplenomegaly, lipemia retinalis, eruptive xanthomata, and massive hypertriglyceridemia, sometimes complicated with acute pancreatitis.

Familial chylomicronemia has been reported in Asians, Blacks, and Caucasians with a prevalence of $1/10^6$. Molecular heterogeneity of causative mutations is the general rule in the genes for LPL or ApoC-II (Hayden et al., 1991; Fojo, 1992; Brunzell, 1995). Moreover, recurrent mutations that result in the same nucleotide or codon substitution, have been reported in patients of different ancestries (Monsalve et al., 1990). However, in populations with a high frequency of inbreeding, a few mutations may account for most cases with LPL deficiency. For example, in French Canadians, three founder mutations (Gly188Glu,

Received 12 August 1996; accepted 17 November 1996.

*Correspondence to: Pascale Benlian, Department of Molecular Biology, Hôpital Saint Antoine, 184 Rue du Faubourg Saint Antoine, 75012 Paris, France; E-mail: pascale.benlian@sat.ap-hop-paris.fr; Fax: 33.1.49.282206.

Contract grant sponsor: INSERM; Contract grant number: 91CN45; Contract grant sponsor: Medical Research Council of Canada; Contract grant sponsor: ARCOL; Contract grant sponsor: French Ministry of Foreign Affairs (Bourse Lavoisier); Contract grant sponsor: International Atherosclerosis Society; Contract grant sponsor: Swedish Society of Medicine.

Pro207Leu, Asp250Asn) cause more than 90% of cases with LPL deficiency (Ma et al., 1991; Wood et al., 1993). To our knowledge, there have been no reports of LPL deficiency in Morocco.

Here, we report two unrelated Moroccan families of Berber ancestry, with probands diagnosed independently with early-onset familial chylomicronemia, in Holland and France. In both probands, a homozygous Ser259Arg mutation resulted in an absence of LPL catalytic activity, both in vivo and in vitro. An identical haplotype, rarely observed in Caucasians, segregated with the mutation in these families. Therefore, LPL deficiency is a cause of familial chylomicronemia in Morocco and may result from a founder effect in patients of Berber ancestry.

SUBJECTS AND METHODS

Subjects

Proband 1, the youngest of a sibship of four, was born in October 1985. His parents were first cousins and of Berber ancestry. Both originated from Taroudannt (South Morocco) and had emigrated to France in 1980. At age 6 months, the proband was discovered with asymptomatic chylomicronemia (triglycerides (TG) = 2,000 mg/dl) when a blood sample was taken as part of a routine assessment prior to ear surgery. Further investigations revealed a decreased post-heparin lipolytic activity and a normal ApoC-II in plasma, suggesting that LPL deficiency was the cause for chylomicronemia in this patient. A diet restricted in fat (10–15% daily fat intake, supplemented with medium-chain fatty acids) resulted in a significant decrease in plasma triglycerides at discharge from hospital (TG = 370 mg/dl). At age 18 months, after a normal diet, abdominal pain ensued. On examination, hepatosplenomegaly, eruptive xanthomata, lipemia retinalis, and severe hypertriglyceridemia (TG = 2,900 mg/dl) were evident. At age 24 months, the same clinical manifestations were complicated this time with acute pancreatitis (TG = 6,000 mg/dl), necessitating hospital care for 2 months. A second episode of acute pancreatitis occurred 6 months later. Until the present age of 10 years, the patient has remained free of acute pancreatitis on a very-low-fat diet (< 5% of total kcal/day). Growth and development have been normal.

Proband 2 was the third offspring of a sibship of four and was born in December 1978. Her parents were first cousins and of Berber ancestry. The family originated from Agadir (South Morocco) and had emigrated to Holland in 1975. The proband was ascertained in May 1985, with a diagnosis of acute pancreatitis, from which she died 2 weeks later.

Biochemical Studies

Fasting lipid and lipoprotein profiles were determined by standard procedures previously described (Benlian et al., 1996). LPL enzymatic mass and activity were measured on fasting plasma before and 10 min after an intravenous injection of heparin, using previously described procedures (Benlian et al., 1996). The presence of ApoC-II was assessed by isoelectric focusing. ApoC-II activator function was analysed in proband 1's serum by the measure of lipolytic activity in the presence of exogenous LPL.

DNA Analysis

Genomic DNA was extracted from blood leukocytes by a phenol chloroform method in both families. When a gene variant was detected by single-strand conformation polymorphism (SSCP) on an exon of the *LPL* gene (Gagné et al., 1994), the corresponding polymerase chain reaction (PCR) product was sequenced directly after subcloning using previously reported procedures (Monsalve et al., 1990). Once the missense mutation was identified as novel, its functional effects were tested in vitro by site-directed mutagenesis (Bruin et al., 1993). Briefly, a 2.4-kb *Pst*I/*Xba*I fragment from an LPL-cDNA clone (a gift from Dr. R. Lawn, Stanford University, CA) containing the entire LPL coding sequence, was cloned into the pSelect-I phagemid vector (Promega, Madison, WI) and was used as a template for site-directed mutagenesis. Mutant and wild-type LPL cDNA clones were subcloned in the expression vector pcDNA-1 (Invitrogen, San Diego, CA) and used to transfect COS-B cells. Four separate transfections were performed using mutant and wild-type clones. LPL mass and activity were assayed on cell culture media (Babirak et al., 1989; Iverius et al., 1985). Four *LPL* gene polymorphisms were used for haplotyping. The VNTR in intron 6 was detected after radiolabeling (Zuliani and Hobbs, 1990) and intragenic RFLPs (*Pvu*II, *Hin*dIII, *Mnl*I) after enzymatic cleavage of PCR products (Hata et al., 1990; Gotoda et al., 1992).

RESULTS

Plasma lipids and lipoproteins in members from both families are shown in Table 1. In family 1, the father had combined hyperlipidemia, while the mother had a normal lipid profile. In family 2, the father and the proband's sibs had a normal lipid profile, while the mother proved to exhibit a high-triglyceride/low high-density lipoprotein (HDL) phenotype.

In proband 1, plasma ApoCII was present and functional. Plasma LPL activity was undetectable. LPL mass was normal in plasma; however, the LPL

TABLE 1. Clinical and Biological Data Observed in Probands (A) and Their Families (B)

A	Age (yr)	BMI	TC (mg/dl)	TG (mg/dl)	HDL (mg/dl)	Age of presentation (mo)	With pancreatitis (mo)	LPL in vivo Mass (ng/ml)	LPL in vivo Activity (IU/L)	LPL in vitro Mass (ng/ml)	LPL in vitro Activity (IU/L)
Proband 1	6	15.4	137 ±25 (105–165)	474 ±337 (170–795)	22 ±5 (15–27)	6	24, 30	308.6	1	466 ±56 mt	17.6 ±3.1 mt
Proband 2	†6.5	—	—	—	—	12	24, 77	—	—	639 ±49 wt	832 ±41 wt

B	Age (yr)	BMI	TC (mg/dl)	TG (mg/dl)	HDL (mg/dl)	ApoB (g/L)	ApoA-I (g/L)
Family 1							
I-1	47	26.8	226 ±16 (205–245)	285 ±115 (140–415)	38 ±3 (35–43)	1.67 ±0.15 (1.55–1.90)	1.36 ±0.08 (1.25–1.45)
I-2	35	28.0	167 ± 28 (140–205)	62 ±3 (59–65)	63 ±8 (55–74)	0.77 ±0.07 (0.70–0.85)	1.68 ±0.09 (1.58–1.80)
II-1	15	23.6	130	85	47	0.67	1.21
II-2	12	20.2	210	75	59	0.95	1.46
II-3	9	17.7	190	95	60	1.00	1.55
Family 2							
I-1	49	—	273	159	40	1.69	1.42
I-2	41	—	203	227	31	1.31	1.25
II-1	22	—	196	109	44	1.32	1.44
II-2	6	—	172	88	40	1.05	1.24
II-4	8	—	200	58	46	1.15	1.45

†: died at the age 6 years and 5 months
mt indicates mutant
wt indicates wild-type

dimer-to-monomer ratio was profoundly decreased (46 ng/ml to 262 ng/ml = 0.17, normal = 2.85 ± 1.6). In first-degree relatives of proband 2, LPL mass was low normal (127.7 ± 44.5 ng/ml, n = 4, normal = 196 ± 59 ng/ml), whereas LPL activity was decreased (98 ± 21 IU/L, n = 4, normal = 220 ± 59 IU/L) to 45% of normal.

SSCP analysis revealed a bandshift in exon 6 as the only variation in the LPL-encoding gene sequence (not shown). DNA sequencing revealed substitution of an A for a T at nucleotide position 857, changing codon Ser259 to an Arg (Fig. 1). In vitro expression of mutant and normal alleles revealed that the mutation caused a profound decrease in LPL activity (< 2% of normal), whereas LPL mass was partially decreased to 73% of normal (Table 1A). Thus, in both families, early onset chylomicronemia and impaired in vivo LPL catalytic activity were caused by a Ser259Arg mutation in the *LPL* gene.

This mutation was novel and was seen on both chromosomes, homozygous in proband 1 and heterozygous in parents and sibs of proband 2, in whom homozygosity for the mutation was inferred from the clinical history and family data. This mutation does not disrupt or introduce any natural restriction site.

Analysis of polymorphic markers of the *LPL* gene revealed that haplotype P1V5H2 was present in both families, together with the Ser259Arg mutation (Fig. 2). Allele P1 of *Pvu*II and allele H2 of *Hin*dIII occur with respective frequencies of 0.24–0.41 and 0.63–0.73, in Caucasian and Japanese populations (Heinzmann et al., 1991; Gotoda et al., 1992; Ahn et al., 1993; Jemaa et al., 1995). Moreover, allele V5 of the VNTR corresponds to the 119-bp allele (according to Zuliani and Hobbs, 1990; Ahn et al., 1992), i.e., nine repeats of the TTTA motif in intron 6 of the *LPL* gene. This allele has been reported as the rarest in various populations (allele frequency = 0.02 to 0.08) in Caucasians, Asians, and Blacks (Ahn et al., 1992; Wall et al., 1993).

Therefore, a unique haplotype segregated with the Ser259Arg mutation, in both Moroccan families, who shared Berber ancestry. Despite a molecular and genetic heterogeneity of LPL mutations, the finding of the same unique mutations on a rare haplotype, suggests that a founder effect may be the cause for LPL deficiency in this population.

DISCUSSION

Two unrelated probands of Berber ancestry with familial chylomicronemia resulting from a homozygous Ser259Arg mutation in the *LPL* gene, are described. Nucleotide T^{857} and amino acid Ser259 are conserved in 10 animal species in which LPL cDNA sequence has been determined, including chicken (Hide et al., 1992). In addition, Ser259 is in the middle of a stretch of 10 amino acids conserved in mammalian species, and is conserved in hepatic li-

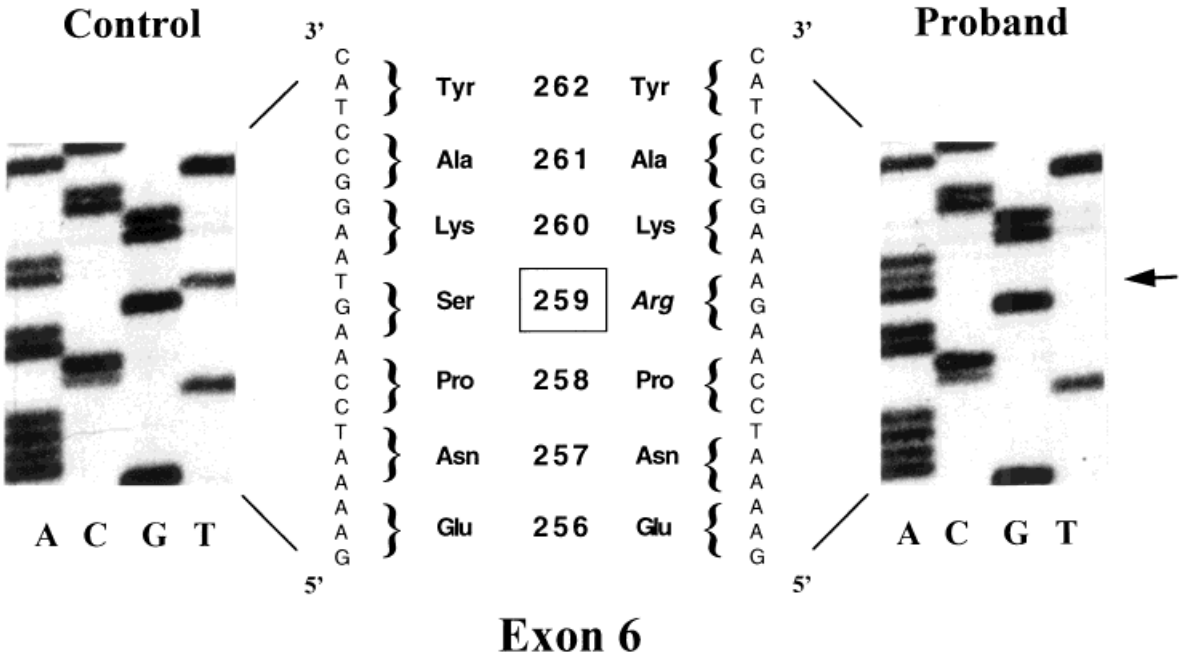

FIGURE 1. DNA sequencing of exon 6 of the *LPL* gene. Wild-type sequence (*left*) and mutant sequence (*right*). *Arrow*, mutation.

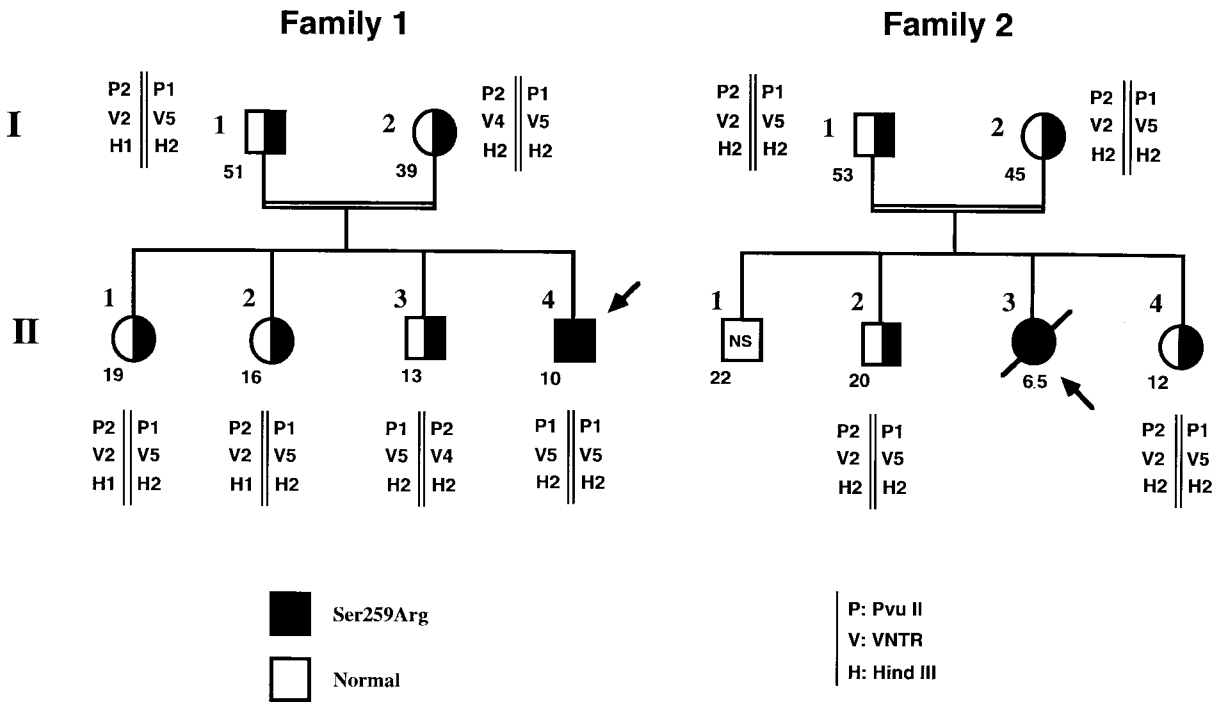

FIGURE 2. **Pedigrees of families 1 and 2. Age is given in years below symbols. Arrows, probands. Only informative polymorphic markers are shown. Alleles are numbered according to decreasing band size. *Pvu*II is localed in intron 6. VNTR is a TTTA tandem repeat sequence in intron 6 (V2 = 12 repeats; V3 = 11 repeats; V4 = 10 repeats; V5 = 9 repeats). *Hind*III is localised in intron 8. NS, not studied.**

pase (Kirchgessner et al., 1989). Exon encodes His241 of the Ser132–His241–Asp156 catalytic triad, a triad surrounded by a hydrophobic domain with a unique and highly conserved three-dimensional structure among the gene family of lipases (Van Tilbeurgh et al., 1994). In addition, part of the lipid-recognition loop (Cys216–Cys239), as well as a heparin binding site (Arg263–Arg282), are encoded by exon 6 (Dugi et al., 1992; Henderson et al., 1993). Therefore, the introduction of a charged residue such as Arg at this position is predicted to profoundly alter the overall catalytic properties of LPL.

Computer modeling of the three-dimensional structure of the region that includes Ser259, using a molecular model of human LPL (T. Bruin, personal communication) has shown that the Ser259 residue is located inside a hydrophobic loop, between α-helix-7 and α-helix-8. This loop is stabilised by hydrogen bonds Asn254–257 and Asn257–Ser259. The substitution of an Arg-residue for Ser259 would be predicted to disrupt LPL conformation significantly. A conformational change (as well as a change of charge) appears as the most plausible explanation for the complete loss of catalytic activity induced by the Ser259Arg mutation.

Both families came from rural areas of South Morocco, near Agadir and Taroudannt, towns located about 50 km apart, and had immigrated to France (family 1) and to Holland (family 2) a decade earlier. In both instances, parents were first cousins of Berber ancestry. In rural populations from North Africa, specific traditions encourage marriage between first cousins in order to preserve the patrimony (mainly land and cattle) within the family. As a consequence, consanguineous marriages are particularly common in rural populations of North Africa. In addition, Berbers constitute a unique subgroup in Arabic populations, with specific customs and traditions that limit admixture with neighbouring populations. The mutation was novel and segregated with a unique haplotype, rarely observed in Caucasians. Therefore, one could anticipate that other families of Berber ancestry in South Morocco may also carry this mutation, suggesting that a founder effect may underlie LPL deficiency in Moroccan Berbers.

The finding that a specific mutation causes LPL deficiency in Berber families from Morocco, has interesting implications. As described for the Pro207Leu in French Canadians, a simple and nonradioactive PCR-based genetic screening can be designed to detect this variant (Bijvoet and Hayden, 1992). Such an analysis may further determine if this mutation is present in Berbers from other parts of North Africa. Finally,

it has been shown that heterozygotes for LPL deficiency have an altered lipoprotein profile (Babirak et al., 1989; Wilson et al., 1990; Bijvoet et al., 1996), which may be aggravated by environmental (Miesenböck et al., 1993; Wilson et al., 1993) or other genetic factors (Zhang et al., 1995) in subjects of Northern European origin. It would be interesting to evaluate whether these variants have the same phenotypic consequences in populations with a different lifestyle.

ACKNOWLEDGMENTS

This work was supported by grant 91CN45 from INSERM (to P.B.) and by grants from MRC Canada (to M.R.H.) L.F. was the recipient of a grant from ARCOL. P.B. was the recipient of a grant from the French Ministry of Foreign Affairs (Bourse Lavoisier) and of a Fellowship from the International Atherosclerosis Society. E.E. was supported by a grant from the Swedish Society of Medicine. We are indebted to Jean Pierre Lagarde, Leila Zekraoui, and Alain Raisonnier for helpful contributions.

REFERENCES

Ahn YI, Kamboh MI, Ferrell RE (1992) Two new alleles in the tetranucleotide repeat polymorphism at the lipoprotein lipase (LPL) locus. Hum Genet 90:184.

Ahn YI, Kamboh MI, Hamman RF, Cole SA, Ferrell RE (1993) Two DNA polymorphisms in the lipoprotein lipase gene and their associations with factors related to cardiovascular disease. J Lipid Res 34:421–428.

Babirak S, Iverius PH, Fujimoto WY, Brunzell JD (1989) Detection and characterization of the heterozygote state for lipoprotein lipase deficiency. Arteriosclerosis 9:326–334.

Benlian P, Foubert L, Gagné E, Bernard L, De Gennes J-L, Langlois S, Robinson W, Hayden MR (1996) Complete paternal isodisomy for chromosome 8 unmasked by lipoprotein lipase deficiency. Am J Hum Genet 59:431–436.

Bijvoet S, Hayden MR (1992) Mismatch PCR: A rapid method to screen for the Pro207→Leu mutation in the lipoprotein lipase (LPL) gene. Hum Mol Genet 1:541.

Bijvoet S, Gagné SE, Moorjani S, Gagné C, Henderson HE, Fruchart J-C, Dallongeville J, Alaupovic P, Prins M, Kastelein JJP, Hayden MR (1996) Alterations in plasma lipoproteins and apolipoproteins before the age of 40 in heterozygotes for lipoprotein lipase deficiency. J Lipid Res 37:640–650.

Bruin T, Tuzgol S, Van Diermen DE, Hoogerbrugge-Van der Linden N, Brunzell JD, Hayden MR, Kastelein JJP (1993) Recurrent pancreatitis and chylomicronemia in an extended kindred is caused by a Gly154→Ser substitution in lipoprotein lipase. J Lipid Res 34:2109–2119.

Brunzell JD (1995) Familial lipoprotein lipase deficiency and other causes of the chylomicronemia syndrome. In Scriver CR, Beaudet AL, Sly WS, Valle D (eds): The Metabolic Basis of Inherited Disease. 7th Ed. Highstown NJ: McGraw-Hill, pp 1913–1932.

Dugi KA, Dichek HL, Talley GD, Brewer HB Jr, Santamarina-Fojo S (1992) Human lipoprotein lipase: The loop covering the catalytic site is essential for interaction with lipid substrates. J Biol Chem 267:25086–25091.

Fojo SS (1992) Genetic dyslipoproteinemias: Role of lipoprotein lipase and apolipoprotein C-II. Curr Opin Lipidol 3:186–195.

Gagné E, Genest J Jr, Zhang H, Clarke LA, Hayden MR (1994) Analysis of DNA changes in the LPL gene in patients with familial combined hyperlipidemia. Arterioscler Thromb 14:1250–1257.

Gotoda T, Yamada N, Murase T, Shimano H, Shimada M, Harada K, Kawamura M, Kozaki K, Yazaki Y (1992) Detection of three separate DNA polymorphisms in the human lipoprotein gene by gene amplification and restriction endonuclease. J Lipid Res 33:1067–172.

Hata A, Robertson M, Emi M, Lalouel JM (1990) Direct detection and automated sequencing of alleles after electrophoretic strand separation: Identification of a common nonsense mutation in exon 9 of the human lipoprotein lipase gene. Nucleic Acids Res 18:5407–5411.

Hayden MR, Ma Y, Brunzell J, Henderson HE (1991) Genetic variants affecting human lipoprotein and hepatic lipases. Curr Opin Lipidol 2:104–109.

Heinzmann C, Kirchgessner T, Kwiterovich PO, Ladias JA, Derby C, Antonarakis SE, Lusis AJ (1991) DNA polymorphism haplotypes of the human lipoprotein lipase gene: Possible association with high density lipoprotein levels. Hum Genet 86:578–584.

Henderson HE, Ma Y, Liu MS, Clark-Lewis I, Maeder DL, Kastelein JJP, Brunzell JD, Hayden MR (1993) Structure-function relationships of lipoprotein lipase: Mutation analysis and mutagenesis of the loop region. J Lipid Res 34:1593–1602.

Hide WA, Chan L, Li W-H (1992) Structure and evolution of the lipase superfamily. J Lipid Res 33:167–178.

Iverius PH, Brunzell JD (1985) Human adipose lipoprotein lipase: Changes with feeding and relationship to postheparin plasma enzyme. Am J Physiol 249:E107–E114.

Jemaa R, Fumeron F, Poirier O, Lecerf L, Evans A, Arveiler D, Luc G, Cambou JP, Bard JM, Fruchart JC, Apfelbaum M, Cambien F, Tiret L (1995) Lipoprotein lipase gene polymorphisms: Associations with myocardial infarction and lipoprotein levels, the ECTIM study. J Lipid Res 36:2141–2146.

Kirchgessner TG, Chuat JC, Heinzmann C, Etienne J, Guilhot S, Svenson K, Ameis D, Pilon C, D'auriol L, Andalibi A, Schotz M, Galibert F, Lusis AJ (1989) Organization of the human lipoprotein lipase gene and evolution of the lipase gene family. Proc Natl Acad Sci USA 86:9647–9651.

Ma Y, Henderson HE, Ven Murthy MR, Roederer G, Monsalve MV, Clarke LA, Normand T, Julien P, Gagné C, Lambert M, Davignon J, Lupien PJ, Brunzell J, Hayden MR (1991) A mutation in the lipoprotein lipase gene as the most common cause of familial chylomicronemia in French Canadians. N Engl J Med 324:1761–1766.

Miesenböck G, Hölzl B, Föger B, Brandstätter E, Paulweber B, Sandhofer F, Patsch JR (1993) Heterozygous lipoprotein lipase deficiency due to a missense mutation as the cause of impaired triglyceride tolerance with multiple lipoprotein abnormalities. J Clin Invest 91:448–455.

Monsalve MV, Henderson H, Roederer G, Deeb S, Kastelein JJP, Peritz L, Devlin R, Bruin T, Murthy MRV, Gagné C, Davignon J, Lupien PJ, Brunzell JD, Hayden MR (1990) A missense mutation at codon 188 of the human lipoprotein lipase gene is a frequent cause of lipoprotein lipase deficiency in persons of different ancestries. J Clin Invest 86:728–734.

Olivcrona T, Bengstsson-Olivecrona G (1993) Lipoprotein lipase and hepatic lipase. Curr Opin Lipidol 4:187–196.

Van Tilbeurgh H, Roussel A, Lalouel J-M, Cambillau C (1994) Lipoprotein lipase. Molecular model based on the pancreatic lipase X-Ray structure: Consequences for heparin binding and catalysis. J Biol Chem 269:4626–4633.

Wall WJ, Williamson R, Petrou M, Papioannou D, Parkin BH (1993) Variation of short tandem repeats within and between populations. Hum Mol Genet 2:1023–1029.

Wilson DE, Emi M, Iverius P-H, Hata A, Wu LL, Hillas E, Williams

RR, Lalouel JM (1990) Phenotypic expression of heterozygous lipoprotein lipase deficiency in the extended pedigree of a proband homozygous for a missense mutation. J Clin Invest 86:735–750.

Wilson DE, Hata A, Kwong LK, Lingam A, Shuhua J, Ridinger DN, Yeager C, Kaltenborn KC, Iverius PH, Lalouel JM (1993) Mutations in exon 3 of the lipoprotein lipase gene segregating in a family with hypertriglyceridemia, pancreatitis and non-insulin-dependent diabetes. J Clin Invest 92:203–211.

Wood S, Schertzer M, Hayden MR, Ma Y (1993) Support for a founder effect for two lipoprotein lipase (LPL) gene mutations in French Canadians by analysis of GT microsatellites flanking the LPL gene. Hum Genet 91:312–316.

Zhang H, Reymer PWA, Liu M-S, Forsythe IJ, Groenemeyer BE, Frohlich J, Brunzell JD, Kastelein JJP, Hayden MR, Ma Y (1995) Patients with apo E3 deficiency (E2/2, E3/2, and E4/2) who manifest with hyperlipidemia have increased frequency of an Asn291→Ser mutation in the human LPL gene. Arterioscler Thromb Vasc Biol 15:1695–1703.

Zuliani G, Hobbs HH (1990) Tetranucleotide repeat polymorphism in the LPL gene. Nucleic Acids Res 18:4958.