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LIPOPROTEIN LIPASE: PHYSIOLOGY, BIOCHEMISTRY, AND MOLECULAR BIOLOGY

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1. ABSTRACT

Lipoprotein lipase (LpL) is the primary enzyme responsible for conversion of lipoprotein triglyceride into free fatty acids and monoglyderides. This permits their uptake into muscle and adipose. The roles of this enzyme in normal and altered physiology are reviewed. In addition, the relationship of LpL activity and genetic variations of LpL and human disease are summarized.

2. PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL FUNCTIONS

Over fifty years ago, a short paper appeared in the journal *Science* describing experiments studying fat absorption in dogs. The investigator, Hahn, noted that injection of heparin led to the rapid clearance of chylomicrons from plasma (1). Heparin releases two triglyceride hydrolyzing enzymes, lipoprotein lipase (LpL) and hepatic triglyceride lipase (HL), into the bloodstream. LpL is the major enzyme responsible for lipolysis of circulating lipoproteins, thereby producing free fatty acids. This is believed to be the major route for fatty acid accumulation by tissues as intact triglyceride is unable to dissolve in plasma and is thought to be incapable of transport across the cell membrane. In contrast, fatty acids enter cells via direct diffusion or fatty acid transporters such as CD36 (2).

Delivery of calories in the form of triglyceride and other lipophyllic substances such as cholesterol and fat-soluble vitamins is accomplished through the interactions of lipoprotein particles with cell surface receptors and with enzymes. On the luminal endothelial surface, lipoprotein triglyceride is hydrolyzed to free fatty acids that are taken-up by tissues and either used as energy or reassembled into triglyceride and stored (Figure 1). In tissues that do not have an intact endothelial cell barrier, or in situations in which the endothelial barrier permeability is altered is it likely that substantial amounts of these large lipoproteins leave the circulation and interact with parenchymal cells. While that is the conventional belief, studies of chylomicron uptake by tissues indicate that muscle and bone marrow may take up a significant amount of chylomicron core lipid (3). Several factors may alter the endothelial barrier function; one of these may be LpL generated free fatty acids. Endothelial barrier function *in vitro* (4, 5) and in perfused blood vessels (6) is disrupted by lipolysis products. Much of the LpL in tissues may be associated with the surface of LpL-expressing cells such as adipocytes and myocytes. Therefore if a substantial number of triglyceride-rich lipoproteins cross the endothelial barrier these LpLs could have significant physiological and pathophysiological effects.

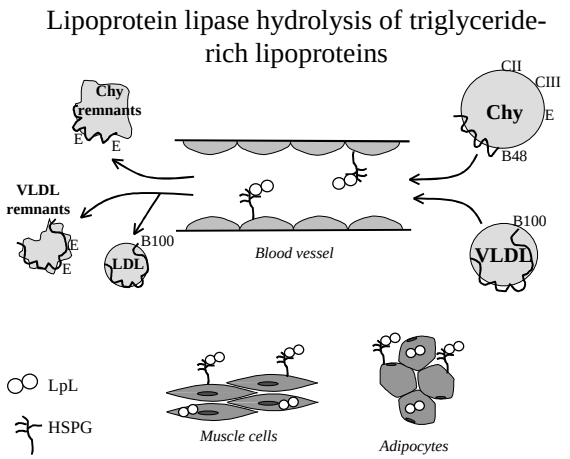

Figure 1. Lipoprotein lipase (LpL) shown as a dimer is thought to primarily hydrolyze circulating lipoproteins while it is associated with heparan sulfate proteoglycans (HSPG) on the luminal side of endothelial cells. This leads to conversion of VLDL to IDL and LDL and production of chylomicron remnants. In the process of this surface lipid and apoproteins dissociate from these particles and transfer to HDL. ApoCII on the triglyceride-rich lipoprotein is requires to fully activate LpL. ApoCIII, apoCI, and perhaps apoE may inhibit this process. The origin of vascular LpL is the underlying parenchymal cells, primarily myocytes and adipocytes. Thus the enzyme must transfer from its site of synthesis on these cells to the endothelial cells and then must translocate from the abluminal to the luminal side of this cell.

In several tissues unlipolyzed particles must directly interact with parenchymal cells. These are tissues that have portal blood supplies, such as liver, adrenal, and bone marrow. In the bone marrow of some animals there appears to be a mechanism for direct cellular uptake of non-lipolyzed large triglyceride-rich lipoproteins (7). This appears to be a non-LpL requiring process. In contrast lipoprotein uptake into the liver is clearly increased by LpL expression in that tissue (8).

3. CALORIC AND VITAMIN DISTRIBUTION BY LpL

Exclusive of its actions to alter the circulating levels of lipoproteins, LpL affects the distribution of calories between tissues. As a marker for adipocyte differentiation and fat stores, LpL is correlated with obesity (9). After weight loss, LpL activity increases (10). A number of adipose genes that are stimulated by greater insulin sensitive are increased after weight loss (11, 12). Although it has been postulated that genetic regulation of adipose LpL might, in fact, modulate the propensity to weight gain, LpL is likely to be but one of many factors important in this respect. Humans and genetically manipulated mice that have no adipose LpL do not have a defect in fat development (13). Although less plasma lipoprotein free fatty acids are internalized in LpL deficient fat, more de novo fatty acids are produced from carbohydrates. Mice that only excess LpL in muscles do have a decrease in weight gain when crossed onto the ob/ob background. Therefore, there appear to be conditions in animals, perhaps reproduced in humans, in which LpL may be limiting for fat accumulation.

Partitioning of more fatty acids into muscle occurs with exercise. This could increase fatty acid oxidation in muscle and modulate the development of obesity (14). Moreover, LpL-induced triglyceride accumulation that occurs in muscle LpL overexpressing mice leads to increased muscle triglyceride and fatty acids and a myositis that is akin to those associated with mitochondrial disorders (15). In addition, even lesser increases in muscle LpL and fat uptake will produce insulin resistance (16). Similarly, liver overexpression of LpL leads to hepatic resistance to insulin [16]. These types of animal experiments have shown that LpL modulation of the generation of fatty acids can play a central, but not necessarily essential, role in tissue fat and glucose metabolism.

The major fat-soluble vitamins that circulate in the bloodstream are vitamin A and vitamin E. Both vitamins are absorbed on chylomicrons; some of the chylomicron vitamin esters are delivery to peripheral tissues. For retinyl ester, the initial circulating form of vitamin A, that uptake is primarily into muscle and is modulated by the amount of LpL in the tissues (17). Retinyl ester that remains with the remnant particles arrives in the liver and is re-secreted as retinol bound to retinol binding protein (RBP). If RBP is knocked out in a mouse, the newborn pups are blind but develop sight presumable due to delivery of milk-derived vitamin A via the lipolysis route (17). LpL on the surface of cells will increase uptake of tocopheral (18). Moreover, mice that overexpress LpL in muscle have an increase in vitamin E (19). Like vitamin A, vitamin E also circulates in the bloodstream associated with a binding protein. Thus, the LpL mediated pathways for fat-soluble vitamin uptake may be physiologically important only under some conditions. In this regard, it should be noted that humans with a genetic deficiency of LpL are not clinically deficient in fat-soluble vitamins.

4. SYNTHESIS AND PROCESSING OF LIPASES

LpL is synthesized by a number of cells and tissues. The major sites of LpL synthesis are the skeletal and cardiac muscle and adipose; lesser amounts of LpL are made in the kidney, adrenal, brain, and macrophages (see below). LpL undergoes a series of intracellular processing events that control its activity; unglycosylated LpL is inactive. In addition, LpL is most active as a dimer. This dimerization process does not require the presence of heparan sulfate proteoglycans (20). Defects in LpL processing are the cause of severe hyperchylomicronemia and lack of LpL enzymatic activity in the cld (combined lipase deficiency) mouse (21).

Postheparin lipase enzymes must transfer from their cells of origin to the luminal surface of capillary endothelial cells that are exposed to the large triglyceride-

rich lipoproteins contained in the blood. Regulation of LpL appears to involve this transfer process as major changes in LpL activity and actions occur without alterations in LpL gene expression or translation (22). In part, this may involve changes in LpL activity that occur as the protein is released from the adipocyte or myocyte and moves to the luminal side of the endothelial cell.
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After its synthesis, LpL must undergo a series of extracellular movements to reach its site of physiological actions, on the luminal surface of endothelial cells. From tissue culture studies it appears that the newly synthesized protein is, as least in adipose, first associated with the surface of the cells. Some of this LpL is re-internalized and then degraded by the adipocytes (23, 24). The remainder is dissociated from the cell surface, perhaps via the actions of an endothelial cell heparanase (25). The newly released LpL, either alone or in tandem with a fragment of digested glycosaminoglycan, transfers to the endothelial cell. Aside from proteoglycans LpL also binds to members of the LDL-receptor superfamily. Therefore LpL transfer from the abluminal to the luminal side of endothelial cells could occur by moving around or non-specifically through the endothelial cells. Alternatively, a receptor like the VLDL receptor could be responsible for LpL movement across cells (26).

LpL association with the luminal endothelial surface and its release from these cells could affect its activity *in vivo*. Both LpL and hepatic lipase associate with highly negative charged molecules, heparan sulfate proteoglycans on the cell surface. In addition to heparan sulfate proteoglycans with specific sequences (27, 28). LpL associates with a number of other proteins including member of the LRP receptor family - including LRP (29-31) the VLDL receptor (32), gp330 (33) - and regions of apolipoprotein B (34). LpL will bind to a number of proteoglycans that are not associated with cell surfaces including perlecan, the major heparan sulfate in the subendothelial cell matrix (5, 35), and dermatan sulfate proteoglycans produced by macrophages and smooth muscle cells (36, 37). Perturbations of endothelium with tumor necrosis factor (38) and perhaps other cytokines, and lipolysis products (39) will release the bound LpL into the bloodstream. Some active LpL is found in the bloodstream associated with lipoproteins (40-42) and even more inactive LpL is present on lipoproteins in pre-heparin blood (41). Most of this LpL is rapidly removed by the liver (43, 44). Its uptake may be via LRP or proteoglycans. It is possible that by acting as a ligand for LRP, LpL will increase removal of associated lipoproteins (29).

5. LIPOPROTEINS AND REGULATION OF THE LIPOLYSIS REACTION

LpL controls the circulating levels of all classes of lipoproteins and is responsible for differences in size and composition of particles within the conventional lipoproteins classes. Although the hydrolysis of triglyceride within chylomicrons and VLDL is the most well known of the LpL actions, this is a complicated process that has only been partially reproduced by *in vitro* experiments.

The lipoproteins must physically come into contact with LpL for lipolysis to begin. The diameter of the vessel, its tortuosity, and the flow rate of the blood and any margination of the particles that allows them to contact the vessel wall must modulate this. Larger diameter particles are more likely to come into contact with the vessel wall and are also more likely to interact with multiple LpL molecules at once

LpL has enzymatic actions to hydrolyze triglyceride and phospholipids. Within the bloodstream, it is the essential enzyme required for clearance of chylomicrons. In addition, catabolism of larger VLDL and initiation of the conversion of VLDL to LDL requires LpL. VLDL and chylomicrons appears to compete for interaction with cell surface LpL, such that increases of VLDL above 5 umoles/ml, an amount that is near the saturation of the enzyme, will decrease both VLDL and chylomicron catabolism (45). In fact, lipolysis appears to require a number of steps that may represent the number of LpL proteins interacting with the lipoproteins or the number of separate associations of the lipoproteins with endothelial associated LpL. Thus, each triglyceride-rich lipoprotein has a competition between lipolysis and liver uptake of partially hydrolyzed lipoproteins. In the case of VLDL, this process determines the percent of VLDL that is converted to LDL; larger VLDL require more lipolysis and are less likely to be converted to LDL. A similar process is likely to occur for chylomicrons; smaller chylomicrons may generate more remnants that circulate in the postprandial period.

LpL will hydrolyze triglyceride and phospholipid on other circulating lipoproteins, LDL and HDL. Therefore it will convert triglyceride-rich LDL into smaller denser LDL. Triglyceride in HDL is also a substrate for LpL actions. Probably more importantly, removal of surface lipid from chylomicrons causes their transfer to HDL. This increases circulating HDL lipids. Moreover, larger, more lipid rich HDL are catabolized more slowly (46). For this reason, LpL activity is positively correlated with HDL (47-49). Although LpL will hydrolyze most triacylglycerols, its preferred fatty acid is oleate. Saturated fatty acids appear to be a less preferred substrate than unsaturated. Fatty acids in the 1 position of triglyceride and phsopholipids are hydrolyzed in preference to those in the 2 position (50).

6. APOLIPOPROTEINS

Maximal activation of lipoprotein lipase requires the presence of apolipoprotein CII. Both triglyceride-rich lipoproteins and HDL contain apoCII. Since newly formed chylomicrons that are isolated from the lymph before their entry into the circulation contain very little apoCII, chylomicron CII in the bloodstream must have transferred from other lipoproteins, most likely from HDL. The apoCII is a component of the surface of the triglyceride rich lipoproteins and increases the Vmax of the reaction (50).

Excess of a number of apolipoproteins inhibit LpL-mediated lipolysis either by displacing apoCII or by direct actions on the enzyme. This was first observed *in vitro* (51) and subsequently has been confirmed by studies in transgenic mice overexpressing apoCIII (52). ApoCIII

also decreases uptake of remnant lipoproteins by blocking their interaction with the LDL receptor related protein (LRP). It had been thought that apoCIII overexpression led to larger triglyceride-rich lipoproteins by blocking the actions of apoE. This is not the case, as the apoCIII transgene also caused hypertriglyceridemia in apoE knockout mice (53). It may be that excess apoproteins will block lipolysis. ApoCI (54), apoAIV (55), and even apoCII (56), the LpL activator, when overexpressed in mice lead to hypertriglyceridemia. ApoE if expressed in low concentrations will increase removal of triglyceride-rich lipoproteins, however at high concentrations it will lead to hypertriglyceridemia (57, 58). Although in part this effect may result from changes in lipoprotein production by the liver (59, 60), excess apoE may affect lipolysis. Although the reasons for this are not clear, it may be that excess apoproteins coat the surface of the lipoprotein and prevent LpL from having access to any triglyceride that normally is near the surface of the particle.

7. NON-ENZYMATIC ACTIONS OF LIPOPROTEIN LIPASE

LpL interacts with both lipoproteins and cell and matrix proteoglycans; therefore it can form a molecular bridge between these molecules. When circulating triglyceride-rich lipoproteins are hydrolyzed by LpL, the enzyme must interact with lipoproteins while it also is associated with the endothelial surface. Thus, it must provide a molecular bridge between triglyceride-rich lipoproteins and the cell surface. However, lipoproteins that are not its usual substrates will also be anchored to proteoglycans by LpL. LpL associated with matrix proteoglycans will increase LDL and oxidized LDL association with subendothelial matrix (5, 36, 61, 62). This does not require the LpL to be enzymatically active. Moreover, the interaction appears to involve an association between LpL and a region in the amino-terminal 20% of apoB (34). The physiologic and pathophysiological importance of the non-enzymatic effects of the lipases is currently an area of active investigation.

Non-enzymatic, actions of LpL can increase cellular lipoprotein uptake. LpL mediated increased lipoprotein uptake by cells may occur via a number of mechanisms. 1) LpL increases the effective concentrations of lipoproteins on the surface of cells by serving as a bridge between the lipoproteins and cell surface proteoglycans. 2) Lipoproteins are internalized along with recycling of the proteoglycans, or because the LpL serves as a ligand for the LRP family of cell surface receptors. 3) By increasing the proximity of the lipoprotein and cell membrane lipids, a transfer of lipids could occur. Overexpression of enzymatically inactive LpL leads to uptake of lipids into muscle (63), thus inactive LpL can function *in vivo*. In part, this may have occurred because the inactive LpL binds circulating lipoproteins and approximates them near active LpL (64).

8. STRUCTURE-FUNCTION ANALYSIS OF LIPOPROTEIN LIPASE

LpL belongs to a gene family that includes hepatic lipase, pancreatic lipase, and a newly described endothelial lipase. All members of this family have a similar active serine catalytic site. This site has been identified, mutated, and the inactive LpL has been used to create transgenic mice (see above). Difference in their substrates utilization is due to differences in the lipid binding regions of the proteins, e.g. substituting the hepatic lipase lid will cause the remaining LpL to function like hepatic lipase (65). This is a simplistic analysis and does not explain all the data. Monoclonal antibodies that are directly to the carboxyl terminal region of LpL also inhibit lipolysis (66). Therefore several regions may be required for full LpL activity or distant mutations or antibody interactions might alter the tertiary structure of the LpL sufficiently to affect its actions. In support of a role of the carboxyl-terminal region in LpL activity is the observation that a truncated form of LpL (serine 447 changed to a stop codon) is more active than the native lipase (see section 2).

LpL interaction with heparin plays a critical role in the metabolism and physiological actions of this enzyme. For this reason, the heparin-binding regions of LpL have been studied in some detail. There are a number of basic amino acid rich regions of LpL in both the amino and carboxyl terminal regions of the enzymes. Mutations in either site will decrease LpL interaction with heparin (67, 68). In an elegant study to determine why LpL has greater affinity for heparin than hepatic lipase, portions of LpL and hepatic lipase were interchanged. This study suggested that the carboxyl-terminal domains of the proteins modulate LpL high affinity interaction with heparin (69). The carboxyl terminal heparin-binding region of LpL appears to overlap with the region of LpL that binds to apoB (70). Recently a defective heparin-binding LpL has been produced in transgenic mice; the LpL was mutated in the carboxyl terminal heparin-binding region. This LpL lead to a greater amount of circulating LpL protein in the plasma and increased postprandial free fatty acids, presumably due to intravascular triglyceride lipolysis (71). Moreover, LpL that is defective in heparin binding is unstable. This confirms the previous observations that heparin association stabilizes LpL activity (20).

LpL is widely believed to be most active as a dimeric molecule that is composed of two identical subunits that are arranged in a head to tail configuration (72). When the molecule is allowed to monomerize, this leads to a decrease in heparin affinity and enzyme activity (73). The sites on the LpL protein that are involved in dimerization have not been identified. Moreover, the importance of monomerization per se versus the accompanying loss of heparin affinity has not been ascertained.

A final domain on LpL is that which interacts with apoCII. ApoCII activation is unique to LpL; hepatic lipase activity is not increased by apoproteins. In an in vitro assay, the addition of the detergent Triton will also increase LpL activity and negates the requirement for apoCII. It appears that apoCII may directly affect the interaction of the LpL and its substrates (50). The site on LpL that interacts with apoCII has not been defined.

Table 1. Mutations in the LpL gene possible with clinical relevance in found in humans

Ex	Amino Acid	Nucleotide	Clinical importance	References
2	Asp9Asn	GAC->AAC	HTG, low HDL	(81, 116-118, 122, 143, 144)
3	Val69Leu	GTG->CTG	Chylomicronemia	(81, 92, 145)
3	Arg75Ser	AGA->AGT	Chylomicronemia*	(146)
3	Trp86Arg	TGG->CGG	Chylomicronemia*	(81, 147, 148)
3	Trp86Gly	TGG->GGG	Chylomicronemia	(102)
4	His136Arg	CAT->CGT	Chylomicronemia*	(81, 147)
4	Gly139Ser	GGC->AGC	Chylomicronemia	(81, 92, 149)
4	Gly142Glu	GGA->GAA	Chylomicronemia	(81, 150, 151)
5	Gly154Ser	GGC->AGC	Chylomicronemia	(81, 92)
5	Asp156Asn	GAT->AAT	Chylomicronemia *	(81, 152)
5	Asp156Gly	GAT->GGT	Chylomicronemia	(81, 152, 153)
5	Pro157Arg	CCA->CGA	Chylomicronemia	(81, 154)
5	Ala158Thr	GCT->ACT	Chylomicronemia	(102)
5	Ser172Cys	TCT->TGT	Chylomicronemia only in pregnancy	(81, 92, 155)
5	Ala176Thr	GCA->ACA	Chylomicronemia	(81, 156)
5	Asp180Glu	GAC->GAG	Chylomicronemia	(157)
5	His183Gln	CAC->CA?	Chylomicronemia*, unknown second Allele	(102)
5	His183Asp	CAC->GAC	Chylomicronemia	(158)
5	Gly188Glu	GGG->GAG	Chylomicronemia	(81, 102, 145, 147, 159-165)
5	Ser193Arg	AGC->?G?	Chylomicronemia*	(102)
5	Ile194Thr	ATT->ACT	Chylomicronemia	(81, 147, 166-169)
5	Asp204Glu	GAC->GAG	Chylomicronemia	(81, 171)
5	Gly195Glu	GGA->GAA	Chylomicronemia	(170)
5	Ile205Ser	ATT->AGT	Chylomicronemia	(81, 147)
5	Pro207Leu	CCG->CTG	Chylomicronemia*	(81, 102, 168, 172)
5	Cys216Ser	TGT->AGT	Chylomicronemia*	(81, 152)
5	Ile225Thr	ATT->ACT	Chylomicronemia*	(81, 173, 174)
6	Glu242Lys	GAG->AAG	Chylomicronemia*, unknown second Allele	(175)
6	Arg243His	CGC->CAC	Chylomicronemia	(81, 169, 171)
6	Arg243Cys	CGC->TGC	Chylomicronemia	(81, 170)
6	Ser244Thr	TCC->ACC	Chylomicronemia*	(81, 176)
6	Asp250Asn	GAC->AAC	Chylomicronemia*	(81, 172, 177, 178)
6	Ser251Cys	TCT->TGT	Chylomicronemia*	(81, 92, 172)
6	Leu252Val	CTG->GTG	Chylomicronemia	(179, 180)
6	Leu252Arg	CTG->CGG	Chylomicronemia	(179)
6	Ser259Gly	AGT->GGT	Chylomicronemia*	(160)
6	Ser259Arg	AGT->AGA	Chylomicronemia	(181)
6	Ala261Thr	GCC->ACC	Chylomicronemia	(81, 92)
6	Tyr262His	TAC->CAC	Chylomicronemia, combined with Asp9Asn	(81, 121, 143)
6	Asn291Ser	AAT->AGT	Heterozygous, FCHL, CAD	(88, 89, 103-112, 167, 182)
6	Met301Thr	ATG->ACG	Chylomicronemia*, unknown second Allele	(102)
6	Leu303Pro	CTG->CCG	Chylomicronemia	(102)
7	Ser323Cys	TCT->TGT	only heterozygous, HTG	(183)
7	Ala334Thr	GCC->ACC	Chylomicronemia	(184)
8	Leu365Val	CTA->GTA	Chylomicronemia	(185)
9	Cys418Tyr	TGT->TAT	Chylomicronemia*	(186)
9	Glu421Lys	GAG->AAG	only heterozygous, HTG in pregnancy	(99)
Nonsense mutations				
Exon	**Amino Acid**	**Nucleotide**	**Clinical importance**	**References**
1	Trp-14stop	TGG->Stop	mild Chylomicronemia	(187)
3	Tyr61stop	TAT->TAA	Chylomicronemia	(81, 171, 188)
3	Tyr73stop	TAC->TAA	Chylomicronemia*	(146)
3	Trp64stop	TCG->TAG	Chylomicronemia*	(81, 168)
3	Glu106stop	CAG->TAG	Chylomicronemia	(81, 189)
6	Cys239stop	TGA->TGA	heterozygous HTG	(190)
6	Tyr262stop	TAC->TAA/G	Chylomicronemia	(81)
6	Tyr302stop	TAC->TAA	Chylomicronemia	(191)
8	Trp382stop	TGG->TGA	Chylomicronemia	(81, 159, 171, 192)
9	Ser447stop	TCA->TGA	only heterozygous, lower TG, increased HDL	(81, 93, 153, 193, 194)

Table 1. continued

Frameshift mutations and small insertions/deletions				
Exon	**Amino Acid**	**Nucleotide**	**Clinical importance**	**References**
2	Thr18del	ACC CCT GAA Gadel	Chylomicronemia*	(147)
2	Glu35ins	GAG->A+GAG	Chylomicronemia. (Uniparental disomy)	(195)
3	Thr101ins	ACC->ACT+GGGCT	Chylomicronemia	(81, 196)
5	Ala221del	GCT->CT	Chylomicronemia	(81, 188, 197, 198)
5	Gly229ins	GGA->GG+TAAATATT	Chylomicronemia	(81, 92)
6	Asn 291del	AAT->AT	Chylomicronemia*	(167)
6	Leu252del	CTG->2bp del	Chylomicronemia*	(102)
8	Ser396-Pro397 del	AGT CCCdel	linked to another mutation	(102)
Other mutations				
Location	**Mutation**		**Clinical importance**	**References**
6	2kb dupl		Chylomicronemia	(81, 102, 199, 200)
3-5	6kb del		Chylomicronemia	(81, 199)
9	3kb deletion		Chylomicronemia	(81)
intr. 1	–2 to –4 del, (skipping of exon 2)		Chylomicronemia	(158)
intr. 2	G->A (acceptor splice site)		Chylomicronemia*	(81, 176)
intr. 2	G->A (donor splice site)		Chylomicronemia	(81)
intr. 3	C->T (6bp 5' from acceptor)		Heterozygous, Hypertriglyceridemia	(81, 183, 187)
intr. 8	HIII Polymorphism (Linkage to Ser447Stop)		see Ser447Stop	(123, 201, 202)
Promoter Location	Clinical importance			References
-93T->G	Heterozygous FCHL and increased CAD; linkage to Asp9Asn			(118, 122, 131-133)
-53G->C	Decreased promoter activity, possible FCHL			(133, 203)
-39T->C	Decreased promoter activity, possibly FCHL			(133)
+13-+19 CC	Insertion in 5' untranslated region: decreased promoter activity			(133)

HTG: Hypertriglyceridemia. *Found as compound heterozygote Genotype.Missense mutations

9.GENETIC VARIATION IN LIPOPROTEIN LIPASE

The LpL gene spans about 30 kb on chromosome 8p22 and is divided into 10 exons (74, 75). The cDNA for human LpL codes for a mature protein of 448 amino acids resulting in a calculated molecular weight of 50,394 Daltons (76), an additional 8 percent of carbohydrates is assumed (77). The catalytic center consists of three amino acids, Ser132, Asp156, and His241 (5-7).

About 80 naturally occurring mutations in the LpL gene have been described in humans, the majority of which are missense (Table 1). LpL mutations are spread over most exons; the most frequent sites of these mutations are in exons 5 and 6. Most of these mutations are rare and lead to LpL deficiency if they are present as homozygote or compound heterozygotes. However, for some mutations a linkage to increased triglycerides, decreased HDL-cholesterol, familiar combined hyperlipidemia (FCHL) and premature coronary artery disease (CAD) has been found in the heterozygous state.

10. HOMOZYGOTE LpL DEFICIENCY: THE FAMILIAR CHYLOMICRONEMIA SYNDROME

Homozygote or compound heterozygote mutations in the LpL gene leading to a complete loss of LpL activity result in the familiar chylomicronemia syndrome. Due to lack of plasma triglyceride hydrolysis, a dramatic increase of chylomicrons is found resulting in triglyceride levels far over 1000 mg/dl and extremely low HDL-cholesterol. Patients usually suffer from recurrent abdominal pain, pancreatitis, memory loss, xanthomas and/or dyspnea (81). Case reports with a wide range of severity of symptoms have been described, and occasionally patients present for the first time during pregnancy or following dietary excess (81). It has been suggested, that LpL deficiency can lead to premature atherosclerosis (82). The prevalence of this disease has been estimated to be 1:1,000,000 (83), however, considering the frequency of heterozygote LpL mutations (see below), many cases may have been missed due to inapparent symptoms.

If the disease is suspected, the diagnosis is made by measuring LpL activity in post heparin plasma (84); however, no standardized assay for LpL activity is available to date. LpL mass measured by ELISA (77) may be low, normal, or even increased, depending on whether the mutation alters LpL structure and production. Defects have been demonstrated or are proposed to affect catalytic activity, protein transport or translocation, heparin binding, or dimerization. The structure-function relationship of LpL has been extensively studied *in vitro*.

A disease to differentiate from primary LpL deficiency is a deficiency of apoCII, the apoprotein necessary for full LpL activity. Since the clinical features for this syndrome are less severe but the same as in LpL deficiency, the diagnosis can be made by using the patient's serum as an activator from a standard source of LpL (81), only if apoCII is present will full activity be found.

11. HETEROZYGOTE MUTATIONS IN THE LpL GENE AND ATHEROSCLEROSIS

Homozygous LpL deficiency can lead to a dramatic disease, chylomicronemia, however, the relation of mutations in the LpL gene and premature atherosclerosis may be of great importance for a broad range of populations in all cultures. Although it seems clear that a reduction of LpL activity should lead to increased triglycerides, decreased HDL and therefore possibly premature atherosclerosis (85), only a part of the clinical studies were able to show this connection, and sometimes the findings were contradictory. Generally, it seems to be accepted, that the presence or absence of LpL mutations is able to modulate the development of familiar combined hyperlipidemia and premature atherosclerosis, but LpL mutations fail to be a major defect directly leading to these diseases. Other factors - which are likely to be partially unknown genes, or factors like hyperinsulinemia, adiposity (86) or apo E2/E2 (87) - may modify the effects of LpL mutations.

The frequency of individual mutations differs widely between populations. It is expected, that the frequency of heterozygous LpL deficiency may be as high as 3-7% (82), with Asn291Ser most common, in some Caucasian populations (88, 89). In the French Canadian population, an especially high rate of LpL mutation carriers up to 17% of the population was found, with Pro207Leu, Gly188Glu, and Asp250Asn being the most abundant (90. 91). In other Caucasian groups, Gly188Glu is also widely present (92), however, Pro207Leu and Asp250Asn has rarely been found. Based on a recent meta-analysis, at least one mutation, Ser447Stop (93) seems to be beneficial in terms of lipid metabolism and CAD (94).

Mutations in the LpL gene have also been linked to other diseases: A recent population study shows a relation of LpL mutations to Alzheimer's disease [Ser447-Stop may prevent and Asn291Ser may contribute to its development (95)]. Although clinical studies found a linkage between hypertension and the LpL gene locus (96-98), the importance of this relationship is still unclear. Occasionally, severe hyperlipidemia due to heterozygote LpL mutations may develop during pregnancy [e.g. Glu421Lys (99), Gly188Glu (100)]. Furthermore, carriers of Asn291Ser or combined Asp9Asn/T-93G mutations in the LpL gene may have an increased risk of pre-eclampsia (101).

11.1. Asn291Ser

Asn291Ser is a common mutation in the LpL gene. Heterozgote frequency in the normal population has been estimated to be about 2-5% in Caucasian population (88, 89). This mutation was reported to be heterozygous in a patient with chylomicronemia and an unknown second allele (102). However, it is quite unlikely that the reduced LpL activity found in Asn291Ser-LpL (103) causes chylomicronemia alone; the high frequency of this mutation would lead to much more disease than is commonly found.

Heterozygosity for Asn291Ser was found widely in patients with FCHL and premature CAD (104-108). Based on a meta-analysis, triglycerides were increased 31%, HDL-cholesterol was decreased 0.12 mmol/l (4.8 mg/dl), and a 1.2 fold increased risk in ischemic heart disease was found (94). Some data suggested that the Asn291Ser mutation affects especially postprandial lipemia (89, 105). An association with other genetic factors such as apoE-3 deficiency or familial hypercholesterolemia (FH) may increase the effect of this mutation on plasma lipids and coronary artery disease (88, 109, 110) and worsen the FCHL phenotype (107, 110-112).

11.2. Asp9Asn

Asp9Asn has been frequently linked to hypertriglyceridemia, low HDL, small dense LDL, FCHL and increased risk of CAD, especially if combined with other risk factors (113-119). Its heterozygous frequency has been estimated as being up to 4.5% (114, 117, 120). Homozygotes with Asn291Ser, Asp9Asn do not have chylomicronemia. However, a patient who was a compound heterozygote for Tyr262His and Asp9Asn had this disease and a 20% decrease in specific LpL activity (117, 121). According to a meta-analysis by Wittrup, triglycerides were increased 20%, HDL-cholesterol was decreased 0.8 mmol/l (3.2 mg/dl), and the risk of ischemic heart disease was 1.4 fold increased (94). However, in Caucasian populations Asp9Asn is strongly linked to the promoter mutation T-93G, which also leads to decreased LpL activity (118, 122). Unlike T–93G, the frequency of Asp9Asn did not differ between American Blacks and Hispanics (122). In the Copenhagen city heart study, double-heterozygous carrier status of both mutations was associated with elevated plasma triglycerides and an increased risk of CAD in men (120). However, the effect of the mutation Asp9Asn without additional promoter mutation has not been estimated at this time.

11.3. Gly188Glu

Although the Gly188Glu mutation is most frequent among French Canadians in Quebec, it is widely spread among populations (92). Heterozygote carriers have 78% increased triglycerides, 0.25 mmol (10 mg/dl) decreased HDL-cholesterol, and a 4.9 fold increased risk of coronary heart disease (94). A preliminary report also found higher systolic blood pressure in heterozygote carriers of Gly188Glu and Pro207Leu (97), however, these data have not yet been confirmed.

11.4. Ser447Stop

The Ser447Stop mutation is a common gene defect (up to 20% heterozygous carriers), resulting in a truncation of the LpL protein by two amino acids (EARS study, 123). The HindIII polymorphism of intron 8 in the LpL gene is associated with this mutation (123). Based on clinical data from the Framingham Offspring study, that this mutation in heterozygous carriers results in decreased plasma triglycerides and higher HDL, combined with a decreased risk of CAD (124). Other studies have supported these findings (93, 125-129). In a meta-study of 9 studies an 8% reduction of triglycerides, a slight (0.04 mmol/l = 1.6 mg/dl) increase in HDL cholesterol, and a 0.8 fold reduced risk in ischemic heart disease was found (94). Interestingly, the beneficial effect of the mutation seems to be most abundant in patients using beta-blockers (126).

In vitro and *in vivo* studies found that the Ser447Stop-LpL leads a higher LpL activity due to higher LpL expression (126, 130). In addition, LpL bridging, dimer conformation or LpL lipid binding could be affected.

11.5. T-93G

The variant T-93G is a promoter variant. The highest frequency was found in South African Blacks (76.4%); it was less present in Caucasian population (1.7%, 131). Near complete linkage disequilibrium between the –93G and the Asp9Asn mutation was observed in the Caucasian population, but not in South African Blacks (118, 122, 131). Individuals homozygous for the G allele showed mildly decreased triglycerides compared with individuals homozygous for the T allele (131). It is suggested, that the –93T variant has a lower promoter activity than the –93G (132, 133).

12. ANIMAL MODELS OF GENETIC VARIANTS OF LpL

Several animal models of muted LpL have been established. The naturally combined lipase deficiency (cld/cld) mutation mouse line (134-136) as well as homozygote LpL deficiency in two independent mouse lines developed by homologous recombination (137, 138) result in a dramatic chylomicronemia, decreased HDL cholesterol and neonatal death after 1-2 days of life. LpL deficient cats also develop chylomicronemia; they have reduced body mass and lower growth rates. However, they survive until adulthood as do humans (139). Originally it was thought that chylomicronemia and obstruction of lung capillaries caused the neonatal demise of the LpL deficient mice (137). However, data from liver LpL expressing mice show that LpL deficient mice have an energy substrate deficiency and appear to die from hypoglycemia (140). Heterozygote LpL deficient mice suffered from mild hypertriglyceridemia and have impaired VLDL clearance (137). Based on data from these mice it has been suggested, that a reduction in endothelial LpL may be protective against atherosclerosis (141). Experiments in mice overexpressing mutated, inactive LpL (Asp156Asn-LpL) in the muscle revealed, that mutated LpL might still increase lipoprotein and cholesterol ester uptake into organs (142). Therefore, LpL mutations causing a complete destruction of one LpL gene may have different clinical implications than mutations causing complete LpL deficiency for instance by changing the catalytic center.

13. REFERENCES

1. Hahn, P.F.: Abolishment of alimentary lipemia following injection of heparin. *Science* 98, 19-20 (1943)

2. Febbraio, M., N.A. Abumrad, D.P. Hajjar, K. Sharma, W. Cheng, S.F. Pearce, R.L. Silverstein: A null mutation in murine CD36 reveals an important role in fatty acid and lipoprotein metabolism. *J Biol Chem* 274(27), 19055-62 (1999)

3. Hultin, M., C. Carneheim, K. Rosenqvist, T. Olivecrona: Intravenous lipid emulsions: removal mechanisms as compared to chylomicrons. *J Lipid Res* 36(10), 2174-84 (1995)

4. Hennig, B., D.M. Shasby, A.B. Fulton, A.A. Spector: Exposure to free fatty acid increases the transfer of albumin across cultured endothelial monolayers. *Arteriosclerosis* 4(5), 489-97 (1984)

5. Saxena, U., M.G. Klein, T.M. Vanni and I.J. Goldberg: Lipoprotein lipase increases low density lipoprotein (LDL) retention by subendothelial cell matrix. *J Clin Invest* 89**,** 373-380 (1992)

6. Rutledge, J., M.M. Woo, A.A. Rezai, L.K. Curtiss and I.J. Goldberg: Lipoprotein lipase increases lipoprotein binding to the artery wall and increases endothelial layer permeability by formation of lipolysis products. *Circ Res* 80**,** 819-828 (1997)

7. Hussain, M.M., I.J. Goldberg, K.H. Weisgraber, R.W. Mahley and T.L. Innerarity: Uptake of chylomicrons by the liver, but not by the bone marrow, is modulated by lipoprotein lipase activity. *Arterioscler Thromb Vasc Biol* 17(7), 1407-13 (1997)

8. Merkel, M., P.H. Weinstock, T. Chajek-Shaul, H. Radner, B. Yin, J.L. Breslow and I.J. Goldberg: Lipoprotein lipase expression exclusively in liver. A mouse model for metabolism in the neonatal period and during cachexia. *J Clin Invest* 102(5), 893-901 (1998)

9. Pykalisto, O.J., P.H. Smith and J.D. Brunzell: Determinants of human adipose tissue lipoprotein lipase. Effect of diabetes and obesity on basal- and diet-induced activity. *J Clin Invest* 56(5), 1108-17 (1975)

10. Bessesen, D.H., A.D. Robertson and R.H. Eckel: Weight reduction increases adipose but decreases cardiac LPL in reduced- obese Zucker rats. *Am J Physiol* 261(2 Pt 1), E246-51 (1991)

11. Schwartz, R.S. and J.D. Brunzell: Increase of adipose tissue lipoprotein lipase activity with weight loss. *J Clin Invest* 67(5) 1425-30 (1981)

12. Eckel, R.H. and T.J. Yost: Weight reduction increases adipose tissue lipoprotein lipase responsiveness in obese women. *J Clin Invest* 80(4), 992-7 (1987)

13. Weinstock, P.H., S. Levak-Frank, L.C. Hudgins, H. Radner, J.M. Friedman, R. Zechner and J.L. Breslow: Lipoprotein lipase controls fatty acid entry into adipose tissue, but fat mass is preserved by endogenous synthesis in mice deficient in adipose tissue lipoprotein lipase. *Proc Natl Acad Sci USA* 94(19), 10261-6 (1997)

14. Jensen, D.R., I.R. Schlaepfer, C.L. Morin, D.S. Pennington, T. Marcell, S.M. Ammon, A. Gutierrez-Hartmann and R.H. Eckel: Prevention of diet-induced obesity in transgenic mice overexpressing skeletal muscle lipoprotein lipase. *Am J Physiol* 273(2 Pt 2), R683-9 (1997)

15. Levak-Frank, S., H. Radner, A. Walsh, R. Stollberger, G. Knipping, G. Hoefler, W. Sattler, P.H. Weinstock, J.L.

Breslow and R. Zechner: Muscle-specific overexpression of lipoprotein lipase causes a severe myopathy characterized by proliferation of mitochondria and peroxisomes in transgenic mice. *J Clin Invest* 96(2) 976-86 (1995)

16. Kim, J., W. Velez-Carrasco, Y. Kako, J. Fillmore, Y. Chen, P. Perret, I. Goldberg, J. Breslow and G Shulman: Effect of muscle specific overexpression of lipoprotein lipase on insulin action. Presented at American Diabetes Association, Manuscript submitted (2000)

17. van Bennekum, A.M., Y. Kako, P.H. Weinstock, E.H. Harrison, R.J. Deckelbaum, I.J. Goldberg and W.S. Blaner: Lipoprotein lipase expression level influences tissue clearance of chylomicron retinyl ester. *J Lipid Res* 40(3), 565-74 (1999)

18. Traber, M.G., T. Olivecrona and H.J. Kayden: Bovine milk lipoprotein lipase transfers tocopherol to human fibroblasts during triglyceride hydrolysis *in vitro*. *J Clin Invest* 75(5), 1729-34 (1985)

19. Sattler, W., S. Levak-Frank, H. Radner, G.M. Kostner and R. Zechner: Muscle-specific overexpression of lipoprotein lipase in transgenic mice results in increased alpha-tocopherol levels in skeletal muscle. *Biochem J* 318(Pt 1), 15-9 (1996)

20. Berryman, D.E. and A. Bensadoun: Heparan sulfate proteoglycans are primarily responsible for the maintenance of enzyme activity, binding, and degradation of lipoprotein lipase in Chinese hamster ovary cells. *J Biol Chem* 270(41), 24525-31 (1995)

21. Davis, R.C., O. Ben-Zeev, D. Martin M.H. Doolittle: Combined lipase deficiency in the mouse. Evidence of impaired lipase processing and secretion. *J Biol Chem* 265(29), 17960-6 (1990)

22. Ong, J.M. and P.A. Kern: Effect of feeding and obesity on lipoprotein lipase activity, immunoreactive protein, and messenger RNA levels in human adipose tissue. *J Clin Invest* 84(1), 305-11 (1989)

23. Cupp, M., A. Bensadoun, and K. Melford: Heparin decreases the degradation rate of lipoprotein lipase in adipocytes. *J Biol Chem* 262(13), 6383-8 (1987)

24. Obunike, J.C., P. Sivaram, L. Paka, M.G. Low and I.J. Goldberg: Lipoprotein lipase degradation by adipocytes: receptor-associated protein (RAP)-sensitive and proteoglycan-mediated pathways. *J Lipid Res* 37(11), 2439-49 (1996)

25. Pillarisetti, S., L. Paka, A. Sasaki, T. Vanni-Reyes, B. Yin, N. Parthasarathy, W.D. Wagner and I.J. Goldberg: Endothelial cell heparanase modulation of lipoprotein lipase activity. Evidence that heparan sulfate oligosaccharide is an extracellular chaperone. *J Biol Chem* 272(25), 15753-9 (1997)

26. Obunike, J., L. Paka, T. Kapotopodis, Z. Li, D. Strickland, S. Pillarisetti and I. Goldberg: Lipoprotein lipase transcytosis across endothelial cells is mediated by a receptor associated protein (RAP)-sensitive mechanism. *Circ* 100, I-329 (1999)

27. Parthasarathy, N., I.J. Goldberg, P. Sivaram, B. Mulloy, D.M. Flory and W. D. Wagner: Oligosaccharide sequences of endothelial cell surface heparan sulfate proteoglycan with affinity for lipoprotein lipase. *J Biol Chem* 269(35), 22391-6 (1994)

28. Lookene, A., O. Cheveruil, P. Ostergaard and G. Oloivercrona: Interaction of lipoprotein lipase with heparin fragments and with heparan sulfate: stoichiometry, stabilization, and kinetics. *Biochemistry* 35(37), 12155-63 (1996)

29. Beisiegel, U., W. Weber and G. Bengtsson-Olivecrona: Lipoprotein lipase enhances the binding of chylomicrons to low density lipoprotein receptor-related protein. *Proc Natl Acad Sci USA* 88(19), 8342-6 (1991)

30. Chappell, D.A., G.L. Fry, M.A. Waknitz, P.H. Iverius, S.E. Williams and D.K. Strickland: The low density lipoprotein receptor-related protein/alpha 2- macroglobulin receptor binds and mediates catabolism of bovine milk lipoprotein lipase. *J Biol Chem* 267(36), 25764-7 (1992)

31. Willnow, T.E., J.L. Goldstein, K. Orth, M.S. Brown and J. Herz: Low density lipoprotein receptor-related protein and gp330 bind similar ligands, including plasminogen activator-inhibitor complexes and lactoferrin, an inhibitor of chylomicron remnant clearance. *J Biol Chem* 267(36), 26172-80 (1992)

32. Argraves, K.M., F.D. Battey, C.D. MacCalman, K.R. McCrae, M. Gafvels, K.F. Kozarsky, D.A. Chappell, J.F. Strauss and D.K. Strickland: The very low density lipoprotein receptor mediates the cellular catabolism of lipoprotein lipase and urokinase-plasminogen activator inhibitor type I complexes. *J Biol Chem* 270(44), 26550-7 (1995)

33. Kounnas, M.Z., D.A. Chappell, D.K. Strickland and W.S. Argraves: Glycoprotein 330, a member of the low density lipoprotein receptor family, binds lipoprotein lipase *in vitro*. *J Biol Chem* 268(19), 14176-81 (1993)

34. Sivaram, P., S.Y. Choi, L.K. Curtiss and I.J. Goldberg: An amino-terminal fragment of apolipoprotein B binds to lipoprotein lipase and may facilitate its binding to endothelial cells. *J Biol Chem* 269(13), 9409-12 (1994)

35. Fuki, I.V., R.V. Iozzo, and K.J. Williams: Perlecan Heparan Sulfate Proteoglycan. A novel receptor that mediates a distinct pathway for ligand catabolism. *J Biol Chem* 275(33), 25742-25750 (2000)

36. Olin, K.L., S. Potter-Perigo, P.H. Barrett, T.N. Wright and A. Chait: Lipoprotein lipase enhances the binding of native and oxidized low density lipoproteins to versican and biglycan synthesized by cultured arterial smooth muscle cells [In Process Citation]. *J Biol Chem* 274(49), 34629-36 (1999)

37. Edwards, I.J., H. Xu, J.C. Obunike, I.J. Goldberg and W.D. Wagner: Differentiated macrophages synthesize a heparan sulfate proteoglycan and an oversulfated chondroitin sulfate proteoglycan that bind lipoprotein lipase. *Arterioscler Thromb Vasc Biol* 15(3), 400-9 (1995)

38. Saxena, U., L.D. Witte, and I.J. Goldberg: Tumor necrosis factor induced release of endothelial cell lipoprotein lipase. *Arteriosclerosis* 10(3), 470-6 (1990)

39. Saxena, U., L.D. Witte and I.J. Goldberg: Release of endothelial cell lipoprotein lipase by plasma lipoproteins and free fatty acids. *J Biol Chem* 264(8), 4349-55 (1989)

40. Goldberg, I.J., J.J. Kandel, C.B. Blum and H.N. Ginsberg: Association of plasma lipoproteins with postheparin lipase activities. *J Clin Invest* 78(6), 1523-8 (1986)

41. Vilella, E., J. Joven, M. Fernandez, S. Vilaro, J.D. Drunzell, T. Olivercrona and G. Bengtsson-Olivecrona: Lipoprotein lipase in human plasma is mainly inactive and associated with cholesterol-rich lipoproteins. *J Lipid Res*, 1993. 34(9): p. 1555-1564 (1993)

42. Zambon, A., I. Schmidt, U. Beisiegel and J.D. Brunzell: Dimeric lipoprotein lipase is bound to triglyceride-rich plasma lipoproteins. *J Lipid Res* 37(11), 2394-404 (1996)

43. Wallinder, L., G. Bengtsson and T. Olivecrona: Rapid removal to the liver of intravenously injected lipoprotein lipase. *Biochim Biophys Acta* 575(1), 166-73 (1979)

44. Wallinder, L., J. Peterson, T. Olivecrona and G. Bengtsson-Olivecrona: Hepatic and extrahepatic uptake of intravenously injected lipoprotein lipase. *Biochim Biophys Acta* 795(3), 513-24 (1984)

45. Brunzell, J.D., W.R. Hazzard, D. Porte and E.L. Bierman: Evidence for a common, saturable, triglyceride removal mechanism for chylomicrons and very low density lipoproteins in man. *J Clin Invest* 52(7), 1578-85 (1973)

46. Horowitz, B.S., I.J. Goldberg, J. Merab, T.M. Vanni, R. Ramakrishnan and H.N. Ginsberg: Increased plasma and renal clearance of an exchangeable pool of apolipoprotein A-I in subjects with low levels of high density lipoprotein cholesterol. *J Clin Invest* 91(4), 1743-52 (1993)

47. Clee, S.M., H. Zhang, N. Bissada, L. Miao, E. Ehrenborg, P. Benlian, G.X. Shen, A. Angel, R.C. LeBoeuf and M.R. Hayden: Relationship between lipoprotein lipase and high density lipoprotein cholesterol in mice: modulation by cholesteryl ester transfer protein and dietary status. *J Lipid Res* 38(10), 2079-89 (1997)

48. Magill, P., S.N. Rao, N.E. Miller, A. Nicoll, J. Brunzell. J. St. Hilaire and B. Lewis: Relationships between the metabolism of high-density and very-low-density lipoproteins in man: studies of apolipoprotein kinetics and adipose tissue lipoprotein lipase activity. *Eur J Clin Invest* 12(2), 113-20 (1982)

49. Patsch, J.R., S. Prasad, A.M. Gotto, Jr. and W. Patsch: High density lipoprotein2. Relationship of the plasma levels of this lipoprotein species to its composition, to the magnitude of postprandial lipemia, and to the activities of lipoprotein lipase and hepatic lipase. *J Clin Invest*, 1987. 80(2): p. 341-7 (1987)

50. Olivecrona, T.: Lipoprotein lipase from milk - the model enzyme in lipoprotein lipase research. In Lipoprotein Lipase, Ed: J. Borensztajn, Evener: Chicago. 15-58 (1987)

51. Brown, W.V. and M.L. Baginsky: Inhibition of lipoprotein lipase by an apoprotein of human very low density lipoprotein. *Biochem Biophys Res Commun* 46**,** 375-381 (1972)

52. Aalto-Setala, K., E.A. Fisher, X. Chen, T. Chajek-Shaul, T. Hayek, R. Zechner, A. Walsh, R. Ramakrishnan, H.N. Ginsberg and J.L. Breslow: Mechanism of hypertriglyceridemia in human apolipoprotein (apo) CIII transgenic mice. Diminished very low density lipoprotein fractional catabolic rate associated with increased apo CIII and reduced apo E on the particles. *J Clin Invest* 90(5), 1889-900 (1992)

53. Ebara, T., R. Ramakrishnan, G. Steiner and N.S. Shachter: Chylomicronemia due to apolipoprotein CIII overexpression in apolipoprotein E-null mice. Apolipoprotein CIII-induced hypertriglyceridemia is not mediated by effects on apolipoprotein. *E J Clin Invest* 99(11) 2672-81 (1997)

54. Shachter, N.S., T. Ebara, R. Ramakrishnan, G. Steiner, J.L. Breslow, H.N. Ginsberg and J.D. Smith: Combined hyperlipidemia in transgenic mice overexpressing human apolipoprotein Cl. *J Clin Invest* 98(3), 846-55 (1996)

55. Aalto-Setala, K., C.L. Bisgaier, A Ho, K.A. Kieft, M.G. Traber, H.J. Kayden, R. Ramakrishnan, A. Walsh, A.D. Essenburg and J.L. Breslow: Intestinal expression of human apolipoprotein A-IV in transgenic mice fails to influence dietary lipid absorption or feeding behavior. *J Clin Invest* 93(4) 1776-86 (1994)

56. Shachter, N.S., T. Hayek, T. Leff, J.D. Smith, D.W. Rosenberg, A. Walsh, R. Ramakrishnan, I.J. Goldberg, H.N. Ginsberg and J.L. Breslow: Overexpression of apolipoprotein CII causes hypertriglyceridemia in transgenic mice. *J Clin Invest* 93(4), 1683-90 (1994)

57. Jong, M.C., V.E. Dahlmans, M.H. Hofker and L.M. Havekes: Nascent very-low-density lipoprotein triacylglycerol hydrolysis by lipoprotein lipase is inhibited by apolipoprotein E in a dose-dependent manner. *Biochem J* 328(Pt 3), 745-50 (1997)

58. Huang, Y., X.Q. Liu, S.C. Rall Jr., J.M. Taylor, A. von Eckardstein, G. Assmann and R.W. Mahley: Overexpression and accumulation of apolipoprotein E as a cause of hypertriglyceridemia [In Process Citation]. *J Biol Chem* 273(41), 26388-93 (1998)

59. Kuipers, F., M.C. Jong, Y. Lin, M. Eck, R. Havinga, V. Bloks, H.J. Verkade, M.H. Hofker, H. Moshage, T.J. Berkel, R.J. Vonk and L.M. Havekes: Impaired secretion of very low density lipoprotein-triglycerides by apolipoprotein E- deficient mouse hepatocytes. *J Clin Invest* 100(11), 2915-22 (1997)

60. Mensenkamp, A.R., M. C. Jong, H. van Goor, M.J. van Luyn, V. Bloks, R. Havinga, P.J. Voshol, M.H. Hofker, K.W. van Dijk, L.M. Havekes and F. Kuipers: Apolipoprotein E participates in the regulation of very low density lipoprotein-triglyceride secretion by the liver. *J Biol Chem* 274(50), 35711-8 (1999)

61. Pentikainen, M.O., K. Oorni and P.T. Kovanen: Lipoprotein lipase (LPL) strongly links native and oxidized low density lipoprotein particles to decorin-coated collagen. Roles for both dimeric and monomeric forms of LPL. *J Biol Chem* 275(8), 5694-701 (2000)

62. Wang, X., J. Greilberger, S. Levak-Frank, R. Zimmermann, R. Zechner and G. Jurgens: Endogenously produced lipoprotein lipase enhances the binding and cell association of native, mildly oxidized and moderately oxidized low- density lipoprotein in mouse peritoneal macrophages. *Biochem J* 343 Pt 2, 347-53 (1999)

63. Merkel, M., Y. Kako, H. Radner, I.S. Cho, R. Ramasamy, J.D. Brunzell, I.J. Goldberg and J.L. Breslow: Catalytically inactive lipoprotein lipase expression in muscle of transgenic mice increases very low density lipoprotein uptake: direct evidence that lipoprotein lipase bridging occurs in vivo [In Process Citation]. *Proc Natl Acad Sci USA* 95(23), 13841-6 (1998)

64. Merkel, M., W. Dudeck, F. Rininger, J. Heeren, H. Radner, R. Zechner, I.J. Goldberg, J.L. Breslow and H. Greten: Catalytically inactive lipoprotein lipase solely expressed in muscle mediates selective cholesterol ester uptake from chylomicrons. *Circ* 102, Abstract, in press (2000)

65. Kobayashi, J., D. Applebaum-Bowden, K.A. Dugi, D.R. Brown, V.S. Kashyap, C. Parrott, C. Duarte, N. Maeda and S. Santamarina-Fojo Analysis of protein structure-function *in vivo*. Adenovirus-mediated transfer of lipase lid mutants in hepatic lipase-deficient mice. *J Biol Chem* 271(42), 26296-301 (1996)

66. Chang, S.F., B. Reich, J.D. Brunzell and H. Will: Detailed characterization of the binding site of the lipoprotein lipase-specific monoclonal antibody 5D2. *J Lipid Res* 39(12), 2350-9 (1998)

67. Hata, A., D.N. Ridnger, S. Sutherland, M. Emi, Z. Shuhua, R.L. Myers, K. Ren, T. Cheng, I. Inoue and D.E. Wilson: Binding of lipoprotein lipase to heparin. Identification of five critical residues in two distinct segments of the amino-terminal domain. *J Biol Chem* 268(12), 8447-57 (1993)

68. Sendak, R.A. and A. Bensadoun: Identification of a heparin-binding domain in the distal carboxyl- terminal region of lipoprotein lipase by site-directed mutagenesis. *J Lipid Res* 39(6), 1310-5 (1998)

69. Hill, J.S., D. Yang, J. Nikazy, L.K. curtiss, J.T. Sparrow and H. Wong: Subdomain chimeras of hepatic lipase and lipoprotein lipase. Localization of heparin and cofactor binding. *J Biol Chem*, 1998. 273(47): p. 30979-84.

70. Hussain, M.M., J.C. Obunike, A. Shaheen, M.J. Hussain, G.S. Shelness and I.J. Goldberg: High affinity binding between lipoprotein lipase and lipoproteins involves multiple ionic and hydrophobic interactions, does not require enzyme activity, and is modulated by glycosaminoglycans. *J Biol Chem* July 5, online, In press (2000)

71. Lutz, E.P., M. Merkel, Y. Kako, K. Melford, H. Radner, J.L. Breslow, A. Bensadoun and I.J. Goldberg: Mice expressing only mutated heparin-binding defective lipoprotein lipase have increase postprandial free fatty aicds and deceased tissue lipid uptake: direct evidence that the carboxyl terminal heparan sulfate binding region is essential for normal LpL phsyiological functions. *Circ* 102, abstact, in press (2000)

72. Wong, H., D. Yang, J.S. Hill, R.C. Davis, J. Nikazy and M.C. Schotz: A molecular biology-based approach to resolve the subunit orientation of lipoprotein lipase. *Proc Natl Acad Sci USA/* 94(11), 5594-8 (1997)

73. Osborne, J.C., Jr., G. Bengtsson-Olivecrona, N.S. Lee and T. Olivecrona: Studies on inactivation of lipoprotein lipase: role of the dimer to monomer dissociation. *Biochemistry* 24(20), 5606-11 (1985)

74. Kirchgessner, T.G., J.C. Chuat, C. Heinzmann, J. Etienne, S. Guilhot, K. Svenson, D. Ameis, C. Pilon, L. d'Auriol, A. Andalibi, M.C. Schotz, F. Galibert and A.J. Lusis: Organization of the human lipoprotein lipase gene and evolution of the lipase gene family. *Proc Natl Acad Sci USA* 86, 9647-9651 (1989)

75. Sparkes, R.S., S. Zollman, I. Klisak, T.G. Kirchgessner, M.C. Komaromy, T. Mohandas, M.C. Schotz and A.J. Lusis: Human genes involved in lipolysis of plasma lipoproteins: mapping of loci for lipoprotein lipase to 8p22 and hepatic lipase to 15q21. *Genomics* 1, 138-44 (1987)

76. Wion, K.L., T.G. Kirchgessner, A.J. Lusis, M.C. Schotz and R.M. Lawn: Human lipoprotein lipase complementary DNA sequence. *Science* 235, 1638-1641 (1987)

77. Peterson, J., W.Y. Fujimoto and J.D. Brunzell: Human lipoproteinlipase: Relationship of activity, heparin affinity and conformation as studied with monoclonal antibodies. *J Lipid Res* 33, 1165-1171 (1992)

78. Ma, Y. H., T. Bruin, S. Tuzgol, B. I. Wilson, G. Roederer, M. S. Liu, J. Davignon, J. J. Kastelein, J. D. Brunzell and M. R. Hayden: Two naturally occurring mutations at the first and second bases of codon aspartic acid 156 in the proposed catalytic triad of human

lipoprotein lipase. In vivo evidence that aspartic acid 156 is essential for catalysis. *J Biol Chem* 267, 1918-1923 (1992)

79. Faustinella, F., L.C. Smith, C.F. Semenkovich and L. Chan: Structural and functional roles of highly conserved serines in human lipoprotein lipase. Evidence that serine 132 is essential for enzyme catalysis. *J Biol Chem* 266, 9481-5 (1991)

80. Emmerich, J., O.U. Beg, J. Peterson, L. Previato, J.D. Brunzell, H.B. Brewer, Jr. and S. Santamarina-Fojo: Human lipoprotein lipase. Analysis of the catalytic triad by site-directed mutagenesis of Ser-132, Asp-156, and His-241. *J Biol Chem* 267, 4161-4165 (1992)

81. Brunzell, J.D.: Familial lipoprotein lipase deficiency and other causes of the chylomicronemia syndrome. In The metabolic and molecular bases of inherited disease: Eds: C.R. Scriver, A.L. Beaudet, W.S. Sly, and D. Valle, McGraw-Hill, New York 1913-1932 (1995)

82. Benlian, P., J.L. De Gennes, L. Foubert, H. Zhang, S.E. Gagne and M. Hayden: Premature atherosclerosis in patients with familial chylomicronemia caused by mutations in the lipoprotein lipase gene. *N Engl J Med* 335, 848-54 (1996)

83. Fredrickson, D.S., J.L. Goldstein and M.S. Brown: The familial hyperlipoproteinemias. In The Metabolic Basis of Inherited Disease: Eds: J.B. Stanbury, J.B. Wyngaarden, and D.S. Fredrickson, McGraw-Hill, New York 604-655 (1978)

84. Nilsson-Ehle, P. and M.C. Schotz: A stable, radioactive substrate emulsion for assay of lipoprotein lipase. *J Lipid Res* 17, 536-41 (1976)

85. Henderson, H.E., J.J. Kastelein, A.H. Zwinderman, E. Gagne, J.W. Jukema, P.W. Reymer, B.E. Groenemeyer, K.I. Lie, A.V. Bruschke, M.R. Hayden and H. Jansen: Lipoprotein lipase activity is decreased in a large cohort of patients with coronary artery disease and is associated with changes in lipids and lipoproteins. *J Lipid Res* 40, 735-43 (1999)

86. Julien, P., M.C. Vohl, D. Gaudet, C. Gagne, G. Levesque, J.P. Despres, F. Cadelis, L.D. Brun, A. Nadeau and M.R. Ven Murthy: Hyperinsulinemia and abdominal obesity affect the expression of hypertriglyceridemia in heterozygous familial lipoprotein lipase deficiency. *Diabetes* 46, 2063-8 (1997)

87. Brummer, D., D. Evans, D. Berg, H. Greten, U. Beisiegel and W.A. Mann: Expression of type III hyperlipoproteinemia in patients homozygous for apolipoprotein E-2 is modulated by lipoprotein lipase and postprandial hyperinsulinemia. *J Mol Med* 76, 355-64 (1998)

88. Wittekoek, M.E., S.N. Pimstone, P.W. Reymer, L. Feuth, G.J. Botma, J.C. Defesche, M. Prins, M. R. Hayden and J.J. Kastelein: A common mutation in the lipoprotein lipase gene (N291S) alters the lipoprotein phenotype and risk for cardiovascular disease in patients with familial hypercholesterolemia. *Circulation* 97, 729-35 (1998)

89. Pimstone, S.N., S.M. Clee, S.E. Gagne, L. Miao, H. Zhang, E.A. Stein and M.R. Hayden: A frequently occurring mutation in the lipoprotein lipase gene (Asn291Ser) results in altered postprandial chylomicron triglyceride and retinyl palmitate response in normolipidemic carriers. *J Lipid Res* 37, 1675-84 (1996)

90. Minnich, A., A. Kessling, M. Roy, C. Giry, G. DeLangavant, J. Lavigne, S. Lussier-Cacan and J. Davignon: Prevalence of alleles encoding defective lipoprotein lipase in hypertriglyceridemic patients of French Canadian descent. *J Lipid Res* 36, 117-24 (1995)

91. Normand, T., J. Bergeron, T. Fernandez-Margallo, A. Bharucha, M.R. Ven Murthy, P. Julien, C. Gagne, C. Dionne, M. De Braekeleer, R. Ma and et al.: Geographic distribution and genealogy of mutation 207 of the lipoprotein lipase gene in the French Canadian population of Quebec. *Hum Genet* 89, 671-5 (1992)

92. Hayden, M.R., J.J. Kastelein, H. Funke, J.D. Brunzell and Y. Ma: Phenotypic variation of mutations in the human lipoprotein-lipase gene. *Biochem Soc Trans* 21, 506-9 (1993)

93. Galton, D.J., R. Mattu, E.W. Needham and J. Cavanna: Identification of putative beneficial mutations for lipid transport. *Z Gastroenterol* 34 Suppl 3, 56-8 (1996)

94. Wittrup, H.H., A. Tybjaerg-Hansen and B.G. Nordestgaard: Lipoprotein lipase mutations, plasma lipids and lipoproteins, and risk of ischemic heart disease. A meta-analysis. *Circulation* 99, 2901-7 (1999)

95. Baum, L., L. Chen, E. Masliah, Y.S. Chan, H.K. Ng and C.P. Pang: Lipoprotein lipase mutations and Alzheimer's disease. *Am J Med Genet* 88, 136-9 (1999)

96. Wu, D.A., X. Bu, C.H. Warden, D.D. Shen, C.Y. Jeng, W.H. Sheu, M.M. Fuh, T. Katsuya, V.J. Dzau, G.M. Reaven, A.J. Lusis, J.I. Rotter and Y.D. Chen: Quantitative trait locus mapping of human blood pressure to a genetic region at or near the lipoprotein lipase gene locus on chromosome 8p22. *J Clin Invest* 97, 2111-8 (1996)

97. Sprecher, D.L., B.V. Harris, E.A. Stein, P.S. Bellet, L.M. Keilson and L.A. Simbartl: Higher triglycerides, lower high-density lipoprotein cholesterol, and higher systolic blood pressure in lipoprotein lipase-deficient heterozygotes. A preliminary report. *Circulation* 94, 3239-45 (1996)

98. O'Connor, D.T., M.T. Kailasam and R.J. Parmer: Complex trait genetics: new methods yield a result for essential hypertension. *J Clin Invest* 97, 1997-8 (1996)

99. Henderson, H., F. Leisegang, F. Hassan, M. Hayden and D. Marais: A novel Glu421Lys substitution in the

lipoprotein lipase gene in pregnancy-induced hypertriglyceridemic pancreatitis. *Clin Chim Acta* 269, 1-12 (1998)

100. Keilson, L.M., C.P. Vary, D.L. Sprecher and R. Renfrew: Hyperlipidemia and pancreatitis during pregnancy in two sisters with a mutation in the lipoprotein lipase gene. *Ann Intern Med* 124, 425-8 (1996)

101. Hubel, C.A., J.M. Roberts and R.E. Ferrell: Association of pre-eclampsia with common coding sequence variations in the lipoprotein lipase gene. *Clin Genet* 56, 289-96 (1999)

102. Mailly, F., J. Palmen, D.P. Muller, T. Gibbs, J. Lloyd, J. Brunzell, P. Durrington, K. Mitropoulos, J. Betteridge, G. Watts, H. Lithell, F. Angelico, S.E. Humphries and P.J. Talmud: Familial lipoprotein lipase (LpL) deficiency: a catalogue of LpL gene mutations identified in 20 patients from the UK, Sweden, and Italy. *Hum Mutat* 10, 465-73 (1997)

103. Busca, R., J. Peinado, E. Vilella, J. Auwerx, S.S. Deeb, S. Vilaro and M. Reina: The mutant Asn291-->Ser human lipoprotein lipase is associated with reduced catalytic activity and does not influence binding to heparin. *FEBS Lett* 367, 257-62 (1995)

104. de Bruin, T.W., F. Mailly, H.H. van Barlingen, R. Fisher, M. Castro Cabezas, P. Talmud, G.M. Dallinga-Thie and S.E. Humphries: Lipoprotein lipase gene mutations D9N and N291S in four pedigrees with familial combined hyperlipidaemia. *Eur J Clin Invest* 26, 631-9 (1996)

105. Gerdes, C., R.M. Fisher, V. Nicaud, J. Boer, S.E. Humphries, P.J. Talmud and O. Faergeman: Lipoprotein lipase variants D9N and N291S are associated with increased plasma triglyceride and lower high-density lipoprotein cholesterol concentrations: studies in the fasting and postprandial states: the European Atherosclerosis Research Studies. *Circulation* 96, 733-40 (1997)

106. Kastelein, J.J., J.M. Ordovas, M.E. Wittekoek, S.N. Pimstone, W.F. Wilson, S.E. Gagne, M.G. Larson, E.J. Schaefer, J.M. Boer, C. Gerdes and M.R. Hayden: Two common mutations (D9N, N291S) in lipoprotein lipase: a cumulative analysis of their influence on plasma lipids and lipoproteins in men and women. *Clin Genet* 56, 297-305 (1999)

107. Reymer, P.W., B.E. Groenemeyer, E. Gagne, L. Miao, E.E. Appelman, J.C. Seidel, D. Kromhout, S.M. Bijvoet, K. van de Oever, T. Bruin and et al.: A frequently occurring mutation in the lipoprotein lipase gene (Asn291Ser) contributes to the expression of familial combined hyperlipidemia. *Hum Mol Genet* 4, 1543-9 (1995)

108. Reymer, P.W., E. Gagne, B.E. Groenemeyer, H. Zhang, I. Forsyth, H. Jansen, J.C. Seidell, D. Kromhout, K.E. Lie, J. Kastelein and et al.: A lipoprotein lipase mutation (Asn291Ser) is associated with reduced HDL cholesterol levels in premature atherosclerosis. *Nat Genet* 10, 28-34 (1995)

109. Zhang, H., P.W. Reymer, M.S. Liu, I.J. Forsythe, B.E. Groenemeyer, J. Frohlich, J.D. Brunzell, J.J. Kastelein, M.R. Hayden and Y. Ma: Patients with apoE3 deficiency (E2/2, E3/2, and E4/2) who manifest with hyperlipidemia have increased frequency of an Asn 291-->Ser mutation in the human LpL gene. *Arterioscler Thromb Vasc Biol* 15, 1695-703 (1995)

110. Fisher, R.M., F. Mailly, R.E. Peacock, A. Hamsten, M. Seed, J.S. Yudkin, U. Beisiegel, G. Feussner, G. Miller, S.E. Humphries and et al.: Interaction of the lipoprotein lipase asparagine 291-->serine mutation with body mass index determines elevated plasma triacylglycerol concentrations: a study in hyperlipidemic subjects, myocardial infarction survivors, and healthy adults. *J Lipid Res* 36, 2104-12 (1995)

111. Syvanne, M., M. Antikainen, S. Ehnholm, H. Tenkanen, S. Lahdenpera, C. Ehnholm and M.R. Taskinen: Heterozygosity for Asn291-->Ser mutation in the lipoprotein lipase gene in two Finnish pedigrees: effect of hyperinsulinemia on the expression of hypertriglyceridemia. *J Lipid Res* 37, 727-38 (1996)

112. Hoffer, M.J., S.J. Bredie, D.I. Boomsma, P.W. Reymer, J.J. Kastelein, P.D. Knijff, P.N. Demacker, A.F. Stalenhoef, L.M. Havekes and R.R. Frants: The lipoprotein lipase (Asn291-->Ser) mutation is associated with elevated lipid levels in families with familial combined hyperlipidaemia. *Atherosclerosis* 119, 159-67 (1996)

113. Hokanson, J.E., J.D. Brunzell, G.P. Jarvik, E.M. Wijsman and M.A. Austin: Linkage of low-density lipoprotein size to the lipoprotein lipase gene in heterozygous lipoprotein lipase deficiency. *Am J Hum Genet* 64, 608-18 (1999)

114. Wittekoek, M.E., E. Moll, S.N. Pimstone, M.D. Trip, P.J. Lansberg, J.C. Defesche, J.J. van Doormaal, M.R. Hayden and J.J. Kastelein: A frequent mutation in the lipoprotein lipase gene (D9N) deteriorates the biochemical and clinical phenotype of familial hypercholesterolemia. *Arterioscler Thromb Vasc Biol* 19, 2708-13 (1999)

115. Jukema, J.W., A.J. van Boven, B. Groenemeijer, A.H. Zwinderman, J.H. Reiber, A.V. Bruschke, J.A. Henneman, G.P. Molhoek, T. Bruin, H. Jansen, E. Gagne, M.R. Hayden and J.J. Kastelein: The Asp9 Asn mutation in the lipoprotein lipase gene is associated with increased progression of coronary atherosclerosis. *Circulation* 94, 1913-8 (1996)

116. Mailly, F., R. M. Fisher, V. Nicaud, L. A. Luong, A. E. Evans, P. Marques-Vidal, G. Luc, D. Arveiler, J.M. Bard, O. Poirier, P.J. Talmud and S.E. Humphries: Association between the LpL-D9N mutation in the lipoprotein lipase gene and plasma lipid traits in myocardial infarction survivors from the ECTIM Study. *Atherosclerosis* 122, 21-8 (1996)

117. Mailly, F., Y. Tugrul, P.W. Reymer, T. Bruin, M. Seed, B.F. Groenemeyer, A. Asplund-Carlson, D. Vallance, A.F. Winder, G.J. Miller and et al.: A common variant in the gene for lipoprotein lipase (Asp9-->Asn). Functional implications and prevalence in normal and hyperlipidemic subjects. *Arterioscler Thromb Vasc Biol* 15, 468-78 (1995)

118. Kastelein, J.J., B.E. Groenemeyer, D.M. Hallman, H. Henderson, P.W. Reymer, S.E. Gagne, H. Jansen, J.C. Seidell, D. Kromhout, J.W. Jukema, A.V. Bruschke, E. Boerwinkle and M.R. Hayden: The Asn9 variant of lipoprotein lipase is associated with the -93G promoter mutation and an increased risk of coronary artery disease. *Clin Genet* 53, 27-33 (1998)

119. Hoffer, M.J., S.J. Bredie, H. Snieder, P.W. Reymer, P.N. Demacker, L.M. Havekes, D.I. Boomsma, A.F. Stalenhoef, R.R. Frants and J.J. Kastelein: Gender-related association between the -93T-->G/D9N haplotype of the lipoprotein lipase gene and elevated lipid levels in familial combined hyperlipidemia. *Atherosclerosis* 138, 91-9 (1998)

120. Wittrup, H.H., A. Tybjaerg-Hansen, R. Steffensen, S.S. Deeb, J.D. Brunzell, G. Jensen and B.G. Nordestgaard: Mutations in the lipoprotein lipase gene associated with ischemic heart disease in men. The Copenhagen city heart study. *Arterioscler Thromb Vasc Biol* 19, 1535-40 (1999)

121. Rouis, M., P. Lohse, K.A. Dugi, O.U. Beg, R. Ronan, G.D. Talley, J.D. Brunzell and S. Santamarina-Fojo: Homozygosity for two point mutations in the lipoprotein lipase (LpL) gene in a patient with familial LpL deficiency: LpL(Asp9-->Asn, Tyr262-- >His). *J Lipid Res* 37, 651-61 (1996)

122. Talmud, P.J., S. Hall, S. Holleran, R. Ramakrishnan, H.N. Ginsberg and S.E. Humphries: LpL promoter -93T/G transition influences fasting and postprandial plasma triglycerides response in African-Americans and Hispanics. *J Lipid Res* 39, 1189-96 (1998)

123. Humphries, S.E., V. Nicaud, J. Margalef, L. Tiret and P.J. Talmud: Lipoprotein lipase gene variation is associated with a paternal history of premature coronary artery disease and fasting and postprandial plasma triglycerides: the European Atherosclerosis Research Study (EARS). *Arterioscler Thromb Vasc Biol* 18, 526-34 (1998)

124. Gagne, S.E., M.G. Larson, S.N. Pimstone, E.J. Schaefer, J.J. Kastelein, P.W. Wilson, J.M. Ordovas and M.R. Hayden: A common truncation variant of lipoprotein lipase (Ser447X) confers protection against coronary heart disease: the Framingham Offspring Study. *Clin Genet* 55, 450-4 (1999)

125. Kuivenhoven, J.A., B.E. Groenemeyer, J.M. Boer, P.W. Reymer, R. Berghuis, T. Bruin, H. Jansen, J.C. Seidell and J.J. Kastelein: Ser447stop mutation in lipoprotein lipase is associated with elevated HDL cholesterol levels in normolipidemic males. *Arterioscler Thromb Vasc Biol* 17, 595-9 (1997)

126. Groenemeijer, B.E., M.D. Hallman, P.W. Reymer, E. Gagne, J.A. Kuivenhoven, T. Bruin, H. Jansen, K.I. Lie, A.V. Bruschke, E. Boerwinkle, M.R. Hayden and J.J. Kastelein: Genetic variant showing a positive interaction with beta-blocking agents with a beneficial influence on lipoprotein lipase activity, HDL cholesterol, and triglyceride levels in coronary artery disease patients. The Ser447-stop substitution in the lipoprotein lipase gene. REGRESS Study Group. *Circulation* 95, 2628-35 (1997)

127. Stocks, J., J.A. Thorn and D.J. Galton: Lipoprotein lipase genotypes for a common premature termination codon mutation detected by PCR-mediated site-directed mutagenesis and restriction digestion. *J Lipid Res* 33, 853-7 (1992)

128. Mattu, R.K., E.W. Needham, R. Morgan, A. Rees, A.K. Hackshaw, J. Stocks, P.C. Elwood and D.J. Galton: DNA variants at the LpL gene locus associate with angiographically defined severity of atherosclerosis and serum lipoprotein levels in a Welsh population. *Arterioscler Thromb* 14, 1090-7 (1994)

129. Jemaa, R., F. Fumeron, O. Poirier, L. Lecerf, A. Evans, D. Arveiler, G. Luc, J.P. Cambou, J.M. Bard, J.C. Fruchart and et al.: Lipoprotein lipase gene polymorphisms: associations with myocardial infarction and lipoprotein levels, the ECTIM study. Etude Cas Temoin sur l'Infarctus du Myocarde. *J Lipid Res* 36, 2141-6 (1995)

130. Zhang, H., H. Henderson, S.E. Gagne, S.M. Clee, L. Miao, G. Liu and M.R. Hayden: Common sequence variants of lipoprotein lipase: standardized studies of in vitro expression and catalytic function. *Biochim Biophys Acta* 1302, 159-66 (1996)

131. Ehrenborg, E., S.M. Clee, S.N. Pimstone, P.W. Reymer, P. Benlian, C.F. Hoogendijk, H.J. Davis, N. Bissada, L. Miao, S.E. Gagne, L.J. Greenberg, R. Henry, H. Henderson, J.M. Ordovas, E.J. Schaefer, J.J. Kastelein, M.J. Kotze and M.R. Hayden: Ethnic variation and in vivo effects of the -93t-->g promoter variant in the lipoprotein lipase gene. *Arterioscler Thromb Vasc Biol* 17, 2672-8 (1997)

132. Yang, W.S. and S.S. Deeb: Sp1 and Sp3 transactivate the human lipoprotein lipase gene promoter through binding to a CT element: synergy with the sterol regulatory element binding protein and reduced transactivation of a naturally occurring promoter variant. *J Lipid Res* 39, 2054-64 (1998)

133. Yang, W.S., D.N. Nevin, L. Iwasaki, R. Peng, B.G. Brown, J.D. Brunzell and S.S. Deeb: Regulatory mutations in the human lipoprotein lipase gene in patients with familial combined hyperlipidemia and coronary artery disease. *J Lipid Res* 37, 2627-37 (1996)

134. Davis, R.C., O. Ben-Zeev, D. Martin and M.H. Doolittle: Combined lipase deficiency in the mouse. Evidence of impaired lipase processing and secretion. *J Biol Chem* 265, 17960-6 (1990)

135. Yacoub, L.K., T.M. Vanni and I.J. Goldberg: Lipoprotein lipase mRNA in neonatal and adult mouse tissues: comparison of normal and combined lipase deficiency (cld) mice assessed by *in situ* hybridization. *J Lipid Res* 31, 1845-1852 (1990)

136. Blanchette-Mackie, E.J., M.G. Wetzel, S.S. Chernick, J.R. Paterniti, Jr., W.V. Brown and R.O. Scow: Effect of the

combined lipase deficiency mutation (cld/cld) on ultrastructure of tissues in mice. Diaphragm, heart, brown adipose tissue, lung, and liver. *Lab Invest* 55, 347-62 (1986)

137. Weinstock, P.H., C.L. Bisgaier, K. Aalto-Setala, H. Radner, R. Ramakrishnan, S. Levak-Frank, A.D. Essenburg, R. Zechner and J.L. Breslow: Severe hypertriglyceridemia, reduced high density lipoprotein, and neonatal death in lipoprotein lipase knockout mice. *J Clin Invest* 96, 2555-2568 (1995)

138. Coleman, T., R.L. Seip, J.M. Gimble, D. Lee, N. Maeda and C.F. Semenkovich: COOH-terminal disruption of lipoprotein lipase in mice is lethal in homozygotes, but heterozygotes have elevated triglycerides and impaired enzyme activity. *J Biol Chem* 270, 12518-12525 (1995)

139. Ginzinger, D.G., S.M. Clee, J. Dallongeville, M.E. Lewis, H.E. Henderson, E. Bauje, Q.R. Rogers, D.R. Jensen, R.H. Eckel, R. Dyer, S. Innis, B. Jones, J.C. Fruchart and M.R. Hayden: Lipid and lipoprotein analysis of cats with lipoprotein lipase deficiency. *Eur J Clin Invest* 29, 17-26 (1999)

140. Merkel, M., P.H. Weinstock, T. Chajek-Shaul, H. Radner, B. Yin, J.L. Breslow and I.J. Goldberg: Lipoprotein lipase expression exclusively in liver: A mouse model for metabolism in the neonatal period and during cachexia. *J Clin Invest* 102, 893-901 (1998)

141. Semenkovich, C.F., T. Coleman and A. Daugherty: Effects of heterozygous lipoprotein lipase deficiency on diet-induced atherosclerosis in mice. *J Lipid Res* 39, 1141-1151 (1998)

142. Merkel, M., Y. Kako, H. Radner, I.S. Cho, R. Ramasamy, J.D. Brunzell, I.J. Goldberg and J.L. Breslow: Catalytically inactive lipoprotein lipase expression in muscle of transgenic mice increases VLDL uptake. Direct evidence that LpL bridging occurs *in vivo*. *Proc Natl Acad Sci U S A* 95, 13841-13846 (1998)

143. Lohse, P., O.U. Beg, J.D. Brunzell, S. Santamarina-Fojo and H.B. J. Brewer: Familial chylomicronemia: Identification of a unique patient homozygote for two separate mutations in the LpL gene. *Atherosclerosis* 11, 1415a (abstr.) (1991)

144. Nevin, D.N., J.D. Brunzell and S.S. Deeb: The LpL gene in individuals with familial combined hyperlipidemia and decreased LpL activity. *Arterioscler Thromb* 14, 869-73 (1994)

145. Bruin, T., S. Tuzgol, W.J. Mulder, A.E. van den Ende, H. Jansen, M.R. Hayden and J.J. Kastelein: A compound heterozygote for lipoprotein lipase deficiency, Val69-->Leu and Gly188-->Glu: correlation between in vitro LpL activity and clinical expression. *J Lipid Res* 35, 438-45 (1994)

146. Wilson, D.E., A. Hata, L.K. Kwong, A. Lingam, J. Shuhua, D.N. Ridinger, C. Yeager, K.C. Kaltenborn, P.H. Iverius and J.M. Lalouel: 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, 203-11 (1993)

147. Reina, M., J.D. Brunzell and S.S. Deeb: Molecular basis of familial chylomicronemia: mutations in the lipoprotein lipase and apolipoprotein C-II genes. *J Lipid Res* 33, 1823-32 (1992)

148. Ishimura-Oka, K., F. Faustinella, S. Kihara, L.C. Smith, K. Oka and L. Chan: A missense mutation (Trp86----Arg) in exon 3 of the lipoprotein lipase gene: a cause of familial chylomicronemia. *Am J Hum Genet* 50, 1275-80 (1992)

149. Bijvoet, S.M., T. Bruin, S. Tuzgol, H.D. Bakker, M.R. Hayden and J.J. Kastelein: Homozygosity for a mutation in the lipoprotein lipase gene (Gly139-- >Ser) causes chylomicronaemia in a boy of Spanish descent. *Hum Genet* 93, 339-43 (1994)

150. Ameis, D., J. Kobayashi, R.C. Davis, O. Ben-Zeev, M.J. Malloy, J.P. Kane, G. Lee, H. Wong, R. J. Havel and M.C. Schotz: Familial chylomicronemia (type I hyperlipoproteinemia) due to a single missense mutation in the lipoprotein lipase gene. *J Clin Invest* 87, 1165-70 (1991)

151. Busca, R., M. Martinez, E. Vilella, P. Pognonec, S. Deeb, J. Auwerx, M. Reina and S. Vilaro: The mutation Gly142-->Glu in human lipoprotein lipase produces a missorted protein that is diverted to lysosomes. *J Biol Chem* 271, 2139-46 (1996)

152. Ma, Y.H., T. Bruin, S. Tuzgol, B.I. Wilson, G. Roederer, M.S. Liu, J. Davignon, J.J. Kastelein, J.D. Brunzell and M.R. Hayden: Two naturally occurring mutations at the first and second bases of codon aspartic acid 156 in the proposed catalytic triad of human lipoprotein lipase. In vivo evidence that aspartic acid 156 is essential for catalysis. *J Biol Chem* 267, 1918-23 (1992)

153. Faustinella, F., A. Chang, J.P. Van Biervliet, M. Rosseneu, N. Vinaimont, L.C. Smith, S.H. Chen and L. Chan: Catalytic triad residue mutation (Asp156----Gly) causing familial lipoprotein lipase deficiency. Co-inheritance with a nonsense mutation (Ser447----Ter) in a Turkish family. *J Biol Chem* 266, 14418-24 (1991)

154. Bruin, T., J.J. Kastelein, D.E. Van Diermen, Y. Ma, H.E. Henderson, P.M. Stuyt, A.F. Stalenhoef, A. Sturk, J.D. Brunzell and M.R. Hayden: A missense mutation Pro157 Arg in lipoprotein lipase (LpLNijmegen) resulting in loss of catalytic activity. *Eur J Biochem* 208, 267-72 (1992)

155. Ma, Y., M.S. Liu, D. Ginzinger, J. Frohlich, J.D. Brunzell and M.R. Hayden: Gene-environment interaction in the conversion of a mild-to-severe phenotype in a patient homozygous for a Ser172-->Cys mutation in the lipoprotein lipase gene. *J Clin Invest* 91, 1953-8 (1993)

156. Beg, O.U., M.S. Meng, S.I. Skarlatos, L. Previato, J.D. Brunzell, H.B. Brewer, Jr. and S.S. Fojo: Lipoprotein lipaseBethesda: a single amino acid substitution (Ala-176--- -Thr) leads to abnormal heparin binding and loss of enzymic activity. *Proc Natl Acad Sci U S A* 87, 3474-8 (1990)

157. Haubenwallner, S., G. Horl, N. Shachter, E. Presta, S.K. Fried, G. Hofler, G.M. Kostner, J.L. Breslow and R. Zechner: A novel missense mutation in the gene for lipoprotein lipase resulting in a highly conservative amino acid substitution (Asp180-->Glu) causes familial chylomicronemia (type I hyperlipoproteinemia). *Genomics* 18, 392-396 (1993)

158. Holzl, B., H.G. Kraft, H. Wiebusch, A. Sandhofer, J. Patsch, F. Sandhofer and B. Paulweber: Two novel mutations in the lipoprotein lipase gene in a family with marked hypertriglyceridemia in heterozygous carriers. Potential interaction with the polymorphic marker D1S104 on chromosome 1q21-q23. *J Lipid Res* 41, 734-41 (2000)

159. Takagi, A., Y. Ikeda, K. Tachi, T. Shinozuka and A. Yamamoto: Identification of compound heterozygous mutations (G188E/W382X) of lipoprotein lipase gene in a Japanese infant with hyperchylomicronemia: the G188E mutation was newly identified in Japanese. *Clin Chim Acta* 285, 143-54 (1999)

160. Evans, D., D. Wendt, S. Ahle, A. Guerra and U. Beisiegel: Compound heterozygosity for a new (S259G) and a previously described (G188E) mutation in lipoprotein lipase (LpL) as a cause of chylomicronemia. *Hum Mutat* 12, 217 (1998)

161. Emi, M., D.E. Wilson, P.H. Iverius, L. Wu, A. Hata, R. Hegele, R.R. Williams and J.M. Lalouel: Missense mutation (Gly----Glu188) of human lipoprotein lipase imparting functional deficiency. *J Biol Chem* 265, 5910-6 (1990)

162. Wilson, D.E., M. Emi, P.H. Iverius, A. Hata, L.L. Wu, E. Hillas, R.R. Williams and J.M. Lalouel: Phenotypic expression of heterozygous lipoprotein lipase deficiency in the extended pedigree of a proband homozygous for a missense mutation. *J Clin Invest* 86, 735-50 (1990)

163. Monsalve, M.V., H. Henderson, G. Roederer, P. Julien, S. Deeb, J.J. Kastelein, L. Peritz, R. Devlin, T. Bruin, M.R. Murthy and et al.: 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, 728-34 (1990)

164. Paulweber, B., H. Wiebusch, G. Miesenboeck, H. Funke, G. Assmann, B. Hoelzl, M.J. Sippl, W. Friedl, J.R. Patsch and F. Sandhofer: Molecular basis of lipoprotein lipase deficiency in two Austrian families with type I hyperlipoproteinemia. *Atherosclerosis* 86, 239-50 (1991)

165. Henderson, H.E., F. Hassan, G.M. Berger and M.R. Hayden: The lipoprotein lipase Gly188----Glu mutation in South Africans of Indian descent: evidence suggesting common origins and an increased frequency. *J Med Genet* 29, 119-22 (1992)

166. Henderson, H.E., Y. Ma, M.F. Hassan, M.V. Monsalve, A.D. Marais, F. Winkler, K. Gubernator, J. Peterson, J.D. Brunzell and M.R. Hayden: Amino acid substitution (Ile194----Thr) in exon 5 of the lipoprotein lipase gene causes lipoprotein lipase deficiency in three unrelated probands. Support for a multicentric origin. *J Clin Invest* 87, 2005-11 (1991)

167. Kobayashi, J., I. Nagashima, K. Taira, M. Hikita, K. Tamura, H. Bujo, N. Morisaki and Y. Saito: A novel frameshift mutation in exon 6 (the site of Asn 291) of the lipoprotein lipase gene in type I hyperlipidemia. *Clin Chim Acta* 285, 173-82 (1999)

168. Sprecher, D.L., J. Kobayashi, M. Rymaszewski, I.J. Goldberg, B.V. Harris, P.S. Bellet, D. Ameis, R.L. Yunker, D.M. Black, E.A. Stein and et al.: Trp64----nonsense mutation in the lipoprotein lipase gene. *J Lipid Res* 33, 859-66 (1992)

169. Dichek, H.L., S.S. Fojo, O.U. Beg, S.I. Skarlatos, J.D. Brunzell, G.B. Cutler, Jr. and H.B. Brewer, Jr.: Identification of two separate allelic mutations in the lipoprotein lipase gene of a patient with the familial hyperchylomicronemia syndrome. *J Biol Chem* 266, 473-7 (1991)

170. Hata, A., D.N. Ridinger, S.D. Sutherland, M. Emi, L.K. Kwong, J. Shuhua, A. Lubbers, B. Guy-Grand, A. Basdevant, P.H. Iverius and et al.: Missense mutations in exon 5 of the human lipoprotein lipase gene. Inactivation correlates with loss of dimerization. *J Biol Chem* 267, 20132-9 (1992)

171. Gotoda, T., N. Yamada, M. Kawamura, K. Kozaki, N. Mori, S. Ishibashi, H. Shimano, F. Takaku, Y. Yazaki, Y. Furuichi and et al.: Heterogeneous mutations in the human lipoprotein lipase gene in patients with familial lipoprotein lipase deficiency. *J Clin Invest* 88, 1856-64 (1991)

172. Bijvoet, S., S.E. Gagne, S. Moorjani, C. Gagne, H.E. Henderson, J.C. Fruchart, J. Dallongeville, P. Alaupovic, M. Prins, J.J. Kastelein and M.R. Hayden: Alterations in plasma lipoproteins and apolipoproteins before the age of 40 in heterozygotes for lipoprotein lipase deficiency. *J Lipid Res* 37, 640-50 (1996)

173. Henderson, H.E., Y. Ma, M.S. Liu, I. Clark-Lewis, D.L. Maeder, J.J. Kastelein, J.D. Brunzell and M.R. Hayden: Structure-function relationships of lipoprotein lipase: mutation analysis and mutagenesis of the loop region. *J Lipid Res* 34, 1593-602 (1993)

174. Henderson, H.E., S.M. Bijvoet, M.A. Mannens, T. Bruin, D. W. Erkelens, M.R. Hayden and J.J. Kastelein: Ile225Thr loop mutation in the lipoprotein lipase (LpL) gene is a de novo event. *Am J Med Genet* 78, 313-6 (1998)

175. Shen, J., R. Chen, W. Hu, K.E. Bingshen, L. Li, Y. Du and Y. Liu: A gene analysis of familial lipoprotein lipase deficiency in China. *Chung Hua I Hsueh I Chuan Hsueh Tsa Chih* 16, 233-5 (1999)

176. Hata, A., M. Emi, G. Luc, A. Basdevant, P. Gambert, P.H. Iverius and J. M. Lalouel: Compound heterozygote for lipoprotein lipase deficiency: Ser----Thr244 and transition in 3' splice site of intron 2 (AG----AA) in the lipoprotein lipase gene. *Am J Hum Genet* 47, 721-6 (1990)

177. Ma, Y., B.I. Wilson, S. Bijvoet, H.E. Henderson, E. Cramb, G. Roederer, M.R. Ven Murthy, P. Julien, H.D.

Bakker, J.J. Kastelein and et al.: A missense mutation (Asp250----Asn) in exon 6 of the human lipoprotein lipase gene causes chylomicronemia in patients of different ancestries. *Genomics* 13, 649-53 (1992)

178. Ishimura-Oka, K., C.F. Semenkovich, F. Faustinella, I.J. Goldberg, N. Shachter, L.C. Smith, T. Coleman, W.A. Hide, W.V. Brown, K. Oka and et al.: A missense (Asp250----Asn) mutation in the lipoprotein lipase gene in two unrelated families with familial lipoprotein lipase deficiency. *J Lipid Res* 33, 745-54 (1992)

179. Chan, L., Y. Mak, B. Tomlinson, L. Baum, X. Wu, J. Masarei and C. Pang: Compound heterozygosity of Leu252Val and Leu252Arg causing lipoprotein lipase deficiency in a chinese patient with hypertriglyceridemia. *Eur J Clin Invest* 30, 33-40 (2000)

180. Kao, J.T., W.H. Hsiao, C.J. Yu and F.T. Chiang: Newly identified missense mutation reduces lipoprotein lipase activity in Taiwanese patients with hypertriglyceridemia. *J Formos Med Assoc* 98, 606-12 (1999)

181. Foubert, L., T. Bruin, J.L. De Gennes, E. Ehrenborg, J. Furioli, J. Kastelein, P. Benlian and M. Hayden: A single Ser259Arg mutation in the gene for lipoprotein lipase causes chylomicronemia in Moroccans of Berber ancestry. *Hum Mutat* 10, 179-85 (1997)

182. Knudsen, P., S. Murtomaki, M. Antikainen, S. Ehnholm, S. Lahdenpera, C. Ehnholm and M.R. Taskinen: The Asn-291-->Ser and Ser-477-->Stop mutations of the lipoprotein lipase gene and their significance for lipid metabolism in patients with hypertriglyceridaemia. *Eur J Clin Invest* 27, 928-35 (1997)

183. Li, J., K. Kobori, A. Kondo, O. Yonekawa and T. Kanno: The application of end user computing (EUC) for detection of lipoprotein lipase gene abnormality. *Rinsho Byori* 47, 737-43 (1999)

184. Kobayashi, J., N. Sasaki, J. Tashiro, H. Inadera, Y. Saito and S. Yoshida: A missense mutation (Ala334-->Thr) in exon 7 of the lipoprotein lipase gene in a case with type I hyperlipidemia. *Biochem Biophys Res Commun* 191, 1046-54 (1993)

185. Pepe, G., G. Chimienti, F. Resta, V. Di Perna, C. Tarricone, M. Lovecchio, A.M. Colacicco and A. Capurso: A new Italian case of lipoprotein lipase deficiency: a Leu365-> Val change resulting in loss of enzyme activity. *Biochem Biophys Res Commun* 199, 570-6 (1994)

186. Henderson, H.E., F. Hassan, D. Marais and M.R. Hayden: A new mutation destroying disulphide bridging in the C-terminal domain of lipoprotein lipase. *Biochem Biophys Res Commun* 227, 189-94 (1996)

187. Nakamura, T., T. Suehiro, N. Yasuoka, M. Yamamoto, H. Ito, T. Yamano and K. Hashimoto: A novel nonsense mutation in exon 1 and a transition in intron 3 of the lipoprotein lipase gene. *J Atheroscler Thromb* 3, 17-24 (1996)

188. Gotoda, T., N. Yamada, T. Murase, S. Miyake, R. Murakami, M. Kawamura, K. Kozaki, N. Mori, H. Shimano, M. Shimada and et al.: A newly identified null allelic mutation in the human lipoprotein lipase (LpL) gene of a compound heterozygote with familial LpL deficiency. *Biochim Biophys Acta* 1138, 353-6 (1992)

189. Emi, M., A. Hata, M. Robertson, P.H. Iverius, R. Hegele and J.M. Lalouel: Lipoprotein lipase deficiency resulting from a nonsense mutation in exon 3 of the lipoprotein lipase gene. *Am J Hum Genet* 47, 107-11 (1990)

190. Takagi, A., Y. Ikeda, A. Mori, Z. Tsutsumi, K. Oida, T. Nakai and A. Yamamoto: A newly identified heterozygous lipoprotein lipase gene mutation (Cys239-->stop/TGC972-->TGA; LpLobama) in a patient with primary type IV hyperlipoproteinemia. *J Lipid Res* 35, 2008-18 (1994)

191. Bertolini, S., M.L. Simone, G.M. Pes, M. Ghisellini, M. Rolleri, A. Bellocchio, N. Elicio, P. Masturzo and S. Calandra: Pseudodominance of lipoprotein lipase (LpL) deficiency due to a nonsense mutation (Tyr302>Term) in exon 6 of LpL gene in an Italian family from Sardinia (LpL(Olbia)). *Clin Genet* 57, 140-7 (2000)

192. Suga, S., N. Tamasawa, I. Kinpara, H. Murakami, N. Kasai, T. Onuma, Y. Ikeda, A. Takagi and T. Suda: Identification of homozygous lipoprotein lipase gene mutation in a woman with recurrent aggravation of hypertriglyceridaemia induced by pregnancy. *J Intern Med* 243, 317-21 (1998)

193. Hata, A., M. Robertson, M. Emi and J.M. Lalouel: Direct detection and automated sequencing of individual alleles after electrophoretic strand separation: identification of a common nonsense mutation in exon 9 of the human lipoprotein lipase gene. *Nucleic Acids Res* 18, 5407-11 (1990)

194. Kobayashi, J., T. Nishida, D. Ameis, G. Stahnke, M. C. Schotz, H. Hashimoto, I. Fukamachi, K. Shirai, Y. Saito and S. Yoshida: A heterozygous mutation (the codon for Ser447----a stop codon) in lipoprotein lipase contributes to a defect in lipid interface recognition in a case with type I hyperlipidemia. *Biochem Biophys Res Commun* 182, 70-7 (1992)

195. Benlian, P., L. Foubert, Gagne, L. Bernard, J.L. De Gennes, S. Langlois, W. Robinson and M. Hayden: Complete paternal isodisomy for chromosome 8 unmasked by lipoprotein lipase deficiency. *Am J Hum Genet* 59, 431-6 (1996)

196. Henderson, H.E., R. Devlin, J. Peterson, J.D. Brunzell and M.R. Hayden: Frameshift mutation in exon 3 of the lipoprotein lipase gene causes a premature stop codon and lipoprotein lipase deficiency. *Mol Biol Med* 7, 511-7 (1990)

197. Yamana, K., H. Yanagi, C. Hirano, K. Kobayashi, M. Tanaka, S. Tomura, S. Tsuchiya and H. Hamaguchi: Genetic polymorphisms and mutations of the lipoprotein lipase gene in Japanese schoolchildren with hypoalphalipoproteinemia. *J Atheroscler Thromb* 4, 97-101 (1998)

198. Takagi, A., Y. Ikeda, Z. Tsutsumi, T. Shoji and A. Yamamoto: Molecular studies on primary lipoprotein lipase (LpL) deficiency. One base deletion (G916) in exon 5 of LpL gene causes no detectable LpL protein due to the absence of LpL mRNA transcript. *J Clin Invest* 89, 581-91 (1992)

199. Langlois, S., S. Deeb, J. D. Brunzell, J.J. Kastelein and M. R. Hayden: A major insertion accounts for a significant proportion of mutations underlying human lipoprotein lipase deficiency. *Proc Natl Acad Sci U S A* 86, 948-52 (1989)

200. Devlin, R.H., S. Deeb, J. Brunzell and M.R. Hayden: Partial gene duplication involving exon-Alu interchange results in lipoprotein lipase deficiency. *Am J Hum Genet* 46, 112-9 (1990)

201. Senti, M., M. Bosch, C. Aubo, R. Elosua, R. Masia and J. Marrugat: Relationship of abdominal adiposity and dyslipemic status in women with a common mutation in the lipoprotein lipase gene. The REGICOR investigators. *Atherosclerosis* 150, 135-41 (2000)

202. Nicklas, B.J., R.E. Ferrell, E.M. Rogus, D.M. Berman, A.S. Ryan, K.E. Dennis and A.P. Goldberg: Lipoprotein lipase gene variation is associated with adipose tissue lipoprotein lipase activity, and lipoprotein lipid and glucose concentrations in overweight postmenopausal women. *Hum Genet* 106, 420-4 (2000)

203. Yang, W.S., D.N. Nevin, R. Peng, J.D. Brunzell and S.S. Deeb: A mutation in the promoter of the lipoprotein lipase (LpL) gene in a patient with familial combined hyperlipidemia and low LpL activity. *Proc Natl Acad Sci U S A* 92, 4462-6 (1995)

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