Role of lipoprotein lipase variants in metabolic disorders and cardiovascular diseases

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Abstract

Lipoprotein lipase (LPL) is a glycoprotein that is produced and secreted into the interstitial space in various tissues, including the cardiac muscle, adipose tissue, macrophages, and skeletal muscle. LPL activity could be affected by genetic alterations which result in changes in lipid metabolism. This review article only focuses on reporting the recent studies which mainly explain the role of the LPL gene variants in metabolic syndrome and cardiovascular diseases. There are over 100 LPL gene variants, but this review article reported rs1801177, rs118204069, rs118204057, rs118204060, rs118204068, rs268, and rs328 as the most common in metabolic syndrome patients. In cardiovascular diseases, LPL variants rs1801177, rs268 and rs328 were the most prevalent. Therefore, it is suggested that further studies should be conducted to identify the LPL gene variants in other cardiovascular diseases, including cardiac arrhythmia. This review article concludes that LPL deficiency and dysfunction are associated with many diseases, such as obesity, insulin resistance, diabetes, chylomicronemia, atherosclerosis, myocardial infarction, coronary artery disease, and stroke.

Key words: lipoprotein lipase, metabolic syndrome, cardiovascular diseases, pathophysiology, mutation

Introduction

In 1929, Macheboeuf identified the lipoprotein as a highly lipid-rich formation that is easily soluble in water (1), whereas the human Lipoprotein Lipase (LPL*)* gene was isolated in 1970 (2). LPL, designated with the enzyme commission (EC) number EC 3.1.1.34, is a crucial extracellular enzyme in the metabolism of lipoproteins. It plays a significant role in the maturation of various classes of lipoprotein particles (3). LPL belongs to the mammalian lipase family including hepatic lipase, endothelial lipase, pancreatic lipase, and gastric lipase (4, 5). LPL is secreted from glycoprotein with 55 kDa and synthesized from numerous cell types, including muscle cells, adipocytes, and macrophages (6). The LPL protein plays a crucial role in lipid metabolism as a multifunctional glycoprotein enzyme. Following secretion, LPL attaches to the endothelial surface, facilitating the hydrolysis of triglycerides (TG) in circulating lipoproteins. This process involves the crucial step of eliminating lipoproteins, including those of endogenous origin, such as very-low density lipoproteins (VLDL), and exogenous sources like chylomicrons provided free fatty acids (FFAs) and glycerol for tissue use (7, 8). Another study demonstrated that LPL functions as a cleansing factor by efficiently hydrolyzing TG. LPL affects the serum concentrations of TG and the production of lipoprotein particles, which are processed by hepatic lipase. A recent study has investigated how LPL assists as the ligand for the protein which is associated with the low-density lipoprotein receptor (LDLR) and influences hepatic secretion and VLDL cholesterol (VLDL-C) and low-density lipoprotein cholesterol (LDL-C) capture (9). Moreover, the retention of VLDL and LDL particles by the subendothelial matrix of the arterial wall is increased by LPL, which promotes the transformation of these lipoproteins into more atherogenic forms (10). LPL activity could be affected by genetic modifications which result in changes in lipid metabolism: for example, an extended half-life of LDL-C, reduced production of high-density lipoprotein (HDL), and reduced hydrolysis of chylomicrons and VLDL-C (11, 12). Moreover, Augustus et al. (13) investigated various physiological roles of LPL using a mouse model. Firstly, they identified cardiac LPL as a crucial modulator of plasma TG levels. Secondly, the decreased uptake of lipoprotein-derived fatty acids led to reduced expression of genes involved in fatty acid oxidation. Thirdly, there was an elevation in cardiac glucose uptake without altering overall glucose homeostasis in the body. Fourthly, remarkably, the insulin-signaling pathway underwent changes, with a reduction in insulin receptor substrate 1 (IRS-1) expression and an increase in insulin receptor substrate 2 (IRS-2) expression. In summary, the authors reported, for the first time, that mice with a tissue-specific deletion of cardiac LPL demonstrated the importance of cardiac LPL in regulating plasma TG levels and clearing postprandial lipoproteins. The products of lipolysis generated by LPL influenced PPAR actions, and LPL activity played a role in metabolic switching between fatty acid uptake and glucose utilization. Moreover, the authors generated mice with acute depletion of LPL in the heart, resulting in similar changes in cardiac gene expression, heart function, and plasma lipids as observed with prenatal loss of

this enzyme in the heart. This confirmed the impact of LPL loss on cardiac function. The study indicated that the loss of this enzyme is not the primary cause of the metabolic and functional alterations seen with chronic LPL loss during development and in prenatal periods. Furthermore, it emphasized the importance of FFA in the adult heart, suggesting that interventions inhibiting the heart's ability to utilize FFA could have adverse effects. Acute loss of LPL could be induced by infection, and previous studies have reported reduced cardiac LPL activity in conditions such as diabetes and starvation. The authors speculated that changes in LPL actions might contribute to acute alterations in cardiac function (14). Atherosclerotic arteries were found to have higher LPL activity compared to normal arteries (15, 16). Considering the genetic, clinical, and biological significance, several investigators have noted the association of the rs328 variant with blood pressure and hypertension (17-19).

The LPL gene is located on the short arm of chromosome 8 and region 21.3 (8p21.3) that comprises 9 introns and 10 exons, encoding a protein consisting of 475 amino acids (20, 21). In 1960, Havel and Gordon reported the first cases of LPL deficiency in idiopathic hyperlipemia patients (22). Gaudet et al. (23) further highlighted that LPL deficiency is a rare inherited disease associated with severe hypertriglyceridemia, chylomicronemia, and the increased risk of recurrent pancreatitis, among other potential complications. Subsequent studies have identified various alteration in the LPL gene that are implicated in diverse metabolic disorders and cardiovascular conditions. Approximately 100 LPL gene variants have been documented, including rs1801177, rs118204069, rs118204057, rs118204060, rs118204068, rs268, and rs328. For instance, rs118204057 involves a G-to-A transition at nucleotide 818 in exon 5 (c.562G>A), resulting in a gly188-to-glu (p.G188E) substitution in the mature protein, and is associated with familial chylomicronemia syndrome characterized by markedly elevated triglyceride levels. Similarly, rs118204060, a C-to-T transition at nucleotide 875 in exon 5 (c.619C>T), leads to an amino acid substitution of leucine for proline-207 (p.P207L), also linked to familial chylomicronemia syndrome. Another variant, rs118204068, involves a G-to-A transition in exon 6 (c.749G>A), causing a substitution of asparagine for aspartic acid at residue 250 (p.D250N), and serves as the basis for familial chylomicronemia and hypertriglyceridemia cases. Additionally, rs268, a nucleotide substitution in exon 6 (c.872A>G), results in an asn291-to-ser substitution (p.N291S) associated with an increased risk of hypertriglyceridemia and cardiovascular diseases (CVDs). The rs118204069 variant, a T-to-C transition in exon 3 (c.257T>C), leads to a trp86-to-arg substitution (p.W86R), contributing to LPL deficiency and familial chylomicronemia syndrome. Finally, rs328 involves a C→G transversion at nucleotide 1595 within exon 9 (c.1339C>T). This alteration transforms the serine 447 codon (TCA) into a premature termination codon (TGA) (p.Ser447X), resulting in the generation of a truncated enzyme lacking the two carboxyl-terminal amino acids (Ser–Gly). The c.1339C>T variation is a common polymorphism with no functional significance, and it is not associated with variations in lipid metabolism risk. Studies

reported these mutations were common LPL mutations in metabolic syndrome (MetS) patients.

Multiple restriction fragment length polymorphisms (RFLPs) have been detected within the LPL gene, including variants associated with *BamHI, PvuII, HindIII, BstNI, BstI, BglII, and XbaI*. Among these, the polymorphisms characterized by the *HindIII* and *PvuII* RFLP sites (located on introns 8 and 6 of the LPL gene, respectively) are the most prevalent and could be linked to significant modifications in plasma lipid levels. The *HindIII* polymorphism results from the occurrence or absence of a T→G transition at position +495 in intron 8 of the LPL gene, and is among the most prevalent polymorphisms. The *PvuII* polymorphism results from a C⇒T transition at the restriction site within intron 6 of the LPL gene, positioned 1.57 kb from the splice acceptor (SA) site. The region encompassing the *PvuII* site shares its homology with the splicing site, resembling the consensus sequence essential for 3′-splicing and lariat structure formation. This suggests that the C497→T (CAG CTG ⇒ TAG CTG) alteration may disrupt the accurate splicing of messenger RNA (mRNA) (24). In addition, these LPL variants, including rs1801177, rs268, rs1801177, and rs328, were also reported in patients affected with cardiovascular disorders. Therefore, this review article focuses exclusively on summarizing recent studies that primarily elucidate the role of these LPL gene mutations in MetS and CVDs, as explained in Figure 1 and Table I.
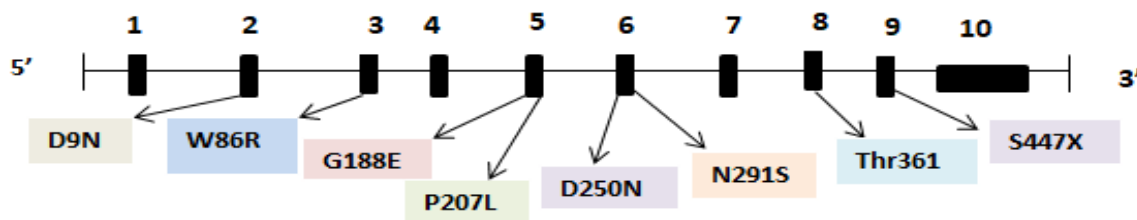

Figure 1. Common variants within the exonic region of the LPL gene resulting in protein substitutions, ultimately contributing to metabolic and cardiovascular disorders

Slika 1. Uobičajene varijante unutar egzonskog regiona LPL gena koje rezultiraju supstitucijama proteina, što na kraju doprinosi metaboličkim i kardiovaskularnim poremećajima

Table I Role of LPL gene variants in metabolic and cardiovascular disorders

Tabela I Uloga varijanti LPL gena u metaboličkim i kardiovaskularnim poremećajima

LPL Variants	Exon/ Intron	Nucleotide Change	Amino Acid Change	Mutation Type	Clinical Significance	Role of LPL variants in disorders
rs1801177	Exon 2	c.106G>A	p.Asp9Asn	Missense	Benign	familial hypertriglyceridemia, familial chylomicronemia, hypertriglyceridemia, atherosclerosis, coronary artery disease,
rs118204069	Exon 3	c.257T>C	p.Trp86Arg	Missense	Pathogenic	hypertriglyceridemia
rs118204057	Exon 5	c.562G>A	p.Gly188Glu	Missense	Pathogenic	familial hypertriglyceridemia, familial chylomicronemia, hypertriglyceridemia
rs118204060	Exon 5	c.619C>T	p.Pro207Leu	Missense	Pathogenic	hypertriglyceridemia
rs118204068	Exon 6	c.749G>A	p.Asp250Asn	Missense	Pathogenic	hypertriglyceridemia
rs268	Exon 6	c.872A>G	p.Asn291Ser	Missense	Benign	familial hypertriglyceridemia, familial chylomicronemia, hypertriglyceridemia, metabolic syndrome, atherosclerosis, coronary artery disease,
rs328	Exon 9	c.1339C>T	p.Ser447X	Nonsense	Benign	dyslipidemia, hypertension, atherosclerosis, obesity, type 2 diabetes, hypertriglyceridemia, coronary artery disease, atherosclerosis
rs316	Exon 8	c.1164C>A	p.Thr361	Silent	Synonymous	atherosclerosis
Pvull	Intron 6	IVS6+1595C>T	No change	NA	NA	myocardial infarction, atherosclerosis
HindIII	Intron 8	IVS6+481T>G	No change	NA	NA	type 2 diabetes, atherosclerosis, myocardial infarction, coronary artery disease, hypertension

NA: Not applicable

Methods

Literature survey and selection criteria

Google Scholar, Science Direct, and PubMed were used to review the literature. Numerous keywords were used for searching the literature, such as lipoprotein lipase, MetS, CVDs, and LPL variants. The language for the review of clinical studies was set to English. This review article only focuses on reporting the recent studies which mainly explained the pathophysiological aspects of the LPL gene variants in MetS and CVDs. The time frame was not limited, even though more recent studies were preferred.

Lipoprotein lipase (LPL) role in metabolic disorders

MetS is a combination of various conditions, such as elevated blood glucose, hypertension, increased serum TG, reduced serum HDL-C, and central obesity. The

presence of MetS is linked to an increased risk of developing type 2 diabetes (T2D) and CVD. MetS has been defined by different organizations, including the International Diabetes Federation, World Health Organization, National Cholesterol Education Programme Adult Treatment Panel III, American Association of Clinical Endocrinologists, and the European Group for the Study of Insulin Resistance (25, 26). LPL is centrally involved in the metabolism of both VLDL and HDL. Various diseases, such as obesity, atherosclerosis, dyslipidemia, insulin resistance (IR), diabetes, chylomicronemia, and Alzheimer's disease, have been associated with LPL dysfunction or deficiency (27). Moreover, the most prevalent variants in the LPL gene include rs118204057, rs1801177, and rs268.

Role of LPL variants in familial chylomicronemia

Familial LPL deficiency is recognized as the most prevalent form of familial chylomicronemia syndrome, formerly referred to as type 1 hyperlipoproteinemia (OMIM# 609708). It follows an autosomal recessive inheritance pattern and is predominantly observed in children, with an approximate prevalence of one in 1,000,000 in the general population of the US (28). Familial LPL deficiency is characterized by severe hypertriglyceridemia, leading to recurrent acute pancreatitis, hepatosplenomegaly, episodes of abdominal pain, and eruptive cutaneous xanthomata. The impaired clearance of chylomicrons from the plasma results in the accumulation of TG in plasma, with concentrations exceeding 111.1 mmol/L in untreated states, giving it a milky appearance. The condition is identified through biallelic pathogenic variants in LPL via molecular genetic testing and is caused by homozygous pathogenic LPL variants (28). Familial chylomicronemia is associated with homozygous mutations, while the heterozygous mutation is significantly prevalent in the general population, ranging from 3-7%. Heterozygous mutations result in up to a 50% reduction in LPL activity, leading to elevated TG levels and reduced HDL-C levels. These lipid profile alterations increase the susceptibility to cardiovascular disease (29). The occurrence of homozygous LPL deficiency is approximately 1 per million individuals, and its primary functions involve the hydrolysis of TG and the peripheral uptake of FFA. Molecular characteristics of this condition encompass significantly reduced or completely absent LPL enzyme activity. The proportion of monogenic variants contributing to this condition is estimated to be 95% (30, 31). Moreover, mutations in the LPL gene result in partial enzyme deficiency, leading to elevated TG levels which form the basis of familial chylomicronemia, characterized by TG levels ranging from 16.7 mmol/L to 44.4 mmol/L, increases in VLDL-C, and decreased levels of LDL-C and HDL-C, manifesting as pure hypertriglyceridemia, with TC levels below 13 mmol/L. Various LPL variants involving amino acid replacements at specific positions of the LPL gene have been identified, such as rs1801177, rs268, and rs118204057 (32). Similarly, Pingitore et al. (33) suggested that two newly identified mutations lead to type 1 hyperlipoproteinemia attributed to LPL gene mutations, resulting in a decrease or absence of LPL secretion, along with a loss of LPL enzymatic activity. Additionally, a mutation in the Apolipoprotein C-II (ApoCII)

gene diminishes the enzymatic activity of LPL, an essential activator of LPL. Interestingly, mutations like R72T in the Apolipoprotein C-II gene result in severe hypertriglyceridemia and recurrent pancreatitis (34).

Role of LPL variants in obesity

Schwartz et al. (35) characterized and defined obesity as an excess of body fat mass. The study by Nuermaimalti et al. (36) illustrated adipogenesis as the process of lipid accumulation and adipocyte differentiation, with the expression of LPL messenger ribonucleic acid (mRNA) often considered an early indicator of adipocyte differentiation. Similarly, Kersten (37) demonstrated that, during adipogenesis, transcription of the LPL gene is stimulated by fatty acids, the adipogenic transcription factor peroxisome proliferator-activated receptor-gamma (PPARγ), and other PPARγ agonists in differentiated adipocytes. Additionally, Wang et al. (38) illustrated that insulin exerts a significant influence on LPL activity in adipose tissues during adipocyte differentiation by enhancing LPL gene transcription. Furthermore, in mature adipocytes, insulin not only elevates the level of LPL mRNA, but also regulates LPL activity through both posttranscriptional and posttranslational mechanisms (38). The LPL variants may influence the concentrations of plasma lipids. In children with uncomplicated obesity, body mass index (BMI) and plasma lipoproteins could potentially impact the distribution of subcutaneous fats (39). Likewise, Huang et al. (40) proposed that central obesity and the levels of serum lipids could be influenced by the LPL gene rs328 variants. This highlights the importance of reducing waist circumference to enhance serum lipids, particularly in individuals with central obesity, especially those with the rs328 genotype. Numerous studies on obesity in both humans and rodents have indicated increased LPL activity in adipose tissue (27). Similarly, obese individuals exhibit higher adipose tissue LPL activity per fat cell compared to lean control subjects (41).

Role of LPL variants in Type 2 Diabetes

LPL activity is frequently diminished in T2D, leading to a reduction in HDL-C levels and an elevation in serum TG levels (42-44). Furthermore, numerous studies have demonstrated the association between genetic variations in LPL and lipid metabolism in individuals with T2D (45-47). Ma et al. (46) documented a correlation between reduced levels of HDL cholesterol and elevated plasma TG levels, along with the presence of the H+ allele (risk allele) of the LPL HindIII polymorphism in Chinese individuals with early-onset T2D. Additional investigations have also indicated a connection between T2D complications and LPL polymorphisms (48-52). Additionally, Ng et al. (51) uncovered an association between rs328 and nephropathy in T2D patients. Moreover, in 2007 Radha et al. (53) demonstrated that polymorphisms in the promoter region, including G53C of the LPL gene, confer protection against T2D. Likewise, Cho et al.'s (54) study concluded that the LPL gene product, which regulates lipid levels in the blood, may be a significant genetic factor influencing the onset of T2D in the Korean population. LPL activity in both the skeletal muscle and adipose tissue is insulin-dependent and varies in diabetes mellitus based on ambient insulin levels and insulin sensitivity (55). Taskinen et al. (55) indicated

that modifications in lipoproteins could influence LPL activity in individuals with diabetes. These modifications encompass low HDL and low LPL activity in conditions of insulin deficiency, high TG and high VLDLs, normal or low VLDLs and increased HDLs in chronically insulin-treated patients with elevated LPL activity, and low HDLs in untreated T2D patients. In white adipose tissue, heightened LPL activity observed in obese and T2D individuals shares a common characteristic – hypertriglyceridemia, which is positively linked to adverse lipid accumulation in tissues (56, 57). Insulin regulates the production and expression of LPL in adipocytes and in the skeletal muscle (58). The levels of pre-heparin LPL decrease in tandem with the worsening of MetS, exhibiting a negative correlation with TG, fasting blood glucose, body weight, and IR, while positively correlating with HDL-C (58). Moreover, individuals with T2D exhibit lower circulating preheparin LPL mass and reduced LPL production compared to their healthy counterparts, along with an inverse correlation between LPL and glycated hemoglobin in T2D (58).

Role of LPL variants in Metabolic Syndrome

Genetic studies have identified numerous variants within the LPL gene, some of which confer protective effects, while others have deleterious consequences. Heparin stimulates the activity of lipoprotein lipase (LPL), leading to increased plasma lipolytic activity and higher levels of free fatty acids in the blood. Assessing post-heparin lipoprotein lipase activities helps identify underlying disorders related to triglyceride and HDL-cholesterol metabolism. In one study, carriers of the rs328 variant exhibit elevated levels of post-heparin LPL activity and increased lipolytic activity. The presence of the rs328 variant is associated with small increases in HDL-C levels, low levels of TG, and a moderate reduction in cardiovascular risk (58). Additionally, carriers of this variant, as reported by Groenemeijer et al. (59), show increased blood glucose and TG levels compared to non-carriers. These findings suggest that the benefits of this mutation may be limited in individuals of normal weight under the assessed conditions (59). Moreover, Daoud et al. (60) determined that distinct genotype frequencies existed between the control and patient groups, although no statistically significant differences were identified between these groups. However, the authors did observe notable variations in plasma levels of TG, LDL-C, TC, and HDL-C in association with the LPL genotype. This observation suggests a correlation between the polymorphisms and lipid profiles in patients with CAD. The interplay of environmental and genetic factors may contribute to the complexity of CAD, potentially influencing the disease onset. Similarly, Goodarzi et al. (61) demonstrated that haplotype structure of the 3' end of the LPL gene was analyzed by genotyping several LPL 3' end single nucleotide polymorphisms (SNPs) in the Mexican American population. Associations between polymorphisms in this region, notably *HindIII*, and surrogate indicators of insulin resistance and atherosclerosis were investigated. *HindIII* variant is associated with dyslipidemia, hypertension, atherosclerosis, and obesity. Additionally, the authors assessed insulin sensitivity in the Mexican American population, finding a direct correlation with variations in the *LPL*

gene through a haplotype-based approach. The authors recommended further investigations in the Mexican American population to delve into the connection between the LPL gene and components of the insulin syndrome. Similarly, Barg (62) elucidated the central role of LPL in the development of MetS and dyslipidemia. The polymorphisms in the LPL gene have been implicated in disturbances of lipid metabolism and the pathogenesis of CAD. Carriers of the X allele of Ser447X polymorphism were associated with a reduced risk of CAD, lower TG levels, and elevated levels of HDL-C. Common LPL mutations such as rs1801177, rs118204069, rs118204057, rs118204060, rs118204068, rs268, and rs328 were identified in patients with hypertriglyceridemia. LPL plays a significant role in various aspects of normal metabolism, including body weight regulation, atherosclerosis, insulin action, and energy balance. Numerous physiological factors and daily conditions, such as fasting and exercise, intricately regulate LPL activity. Moreover, various diseases can impact human metabolism and LPL function. Obesity, osteoporosis, T2D, dyslipidemia, and MetS stand out as prevalent metabolic disorders (63-65). Consequently, MetS is a heterogeneous entity with various synonymous terms, including the Reaven syndrome, plurimetabolic syndrome, atherothrombogenic syndrome, and syndrome X (66-68). Two common LPL gene variants, rs268 and rs328, are associated with MetS due to their impact on low HDL-C and high TG (69). Brunzell et al. (70) demonstrated that individuals with homozygous LPL deficiency, recognized as familial chylomicron syndrome, exhibit severe hypertriglyceridemia, elevated chylomicron levels, and recurrent pancreatitis. However, they did not observe any association with an elevated risk of CAD, as large circulating chylomicrons were incapable of infiltrating the arterial wall (71, 72). Nordestgaard (73) demonstrated that individuals with heterozygous LPL deficiency exhibit impaired lipolysis, resulting in the accumulation of circulating chylomicron remnants and intermediate-density lipoproteins rich in both cholesterol and TG. However, they did not establish a confirmed link to an increased risk of CAD. Conversely, in a cross-sectional study involving CAD case-control studies, Khera et al. (74) reported that gene sequencing identified deleterious alterations in the LPL gene in 188 out of 46,891 individuals (0.4%). These mutations were significantly associated with higher levels of TG and an increased presence of CAD. As per Cagatay et al.'s research (75), the Pvull polymorphism has been associated with reduced levels of HDL-C and elevated TG levels. A meta-analysis has indicated that this polymorphism is correlated with a decreased risk of experiencing a heart attack or myocardial infarction (76). Consequently, it demonstrates a protective effect against cerebrovascular accidents (76).

Role of LPL variants in Atherosclerosis

Increased atherosclerosis and early atherogenic processes are associated with the expression of LPL found on macrophages and other cells within vascular walls. Moreover, overexpression of LPL is correlated with IR and hypertension due to heightened inflammation, vascular remodeling, oxidative stress, sympathetic nervous system activation, vasoconstriction, and sodium retention (77-79). In the Central

European Caucasian population, dyslipidemia in subjects with MetS has indicated that the S1 allele of apolipoprotein C-III (APOC3) SstI polymorphism arising from a substitution of C to G at position 3238 in the 3′ untranslated region of exon 4 in the APOC3 gene, situated on the long arm of chromosome 11, along with the H-allele of LPL HindIII polymorphism, may have a marginal impact on apoB levels (80). The increased risk of premature arteriosclerosis is connected to the accumulation of triglyceride-rich lipoproteins as an independent factor. Among hypertriglyceridemia patients, approximately 20% carry common mutations in the LPL gene, such as rs1801177, rs118204069, rs118204057, rs118204060, rs118204068, rs268, and rs328, which are associated with hypertriglyceridemia. It is advisable to conduct genotyping for these LPL gene mutations, especially in individuals at a high risk of premature arteriosclerosis. Additionally, a significant number of individuals carry silent mutations, including Thr361 (one novel mutation was observed: C1338A in exon 8 of the LPL gene, which is a silent mutation at Thr361), and common mutations, such as rs328, which are associated with less favorable lipid profiles (81).

Role of LPL variants in cardiovascular diseases

Elevated levels of TG are a well-established factor for CVD. LPL plays a crucial role in the hydrolysis of TG, ensuring an adequate supply of fatty acids, primarily to adipose tissue. When there is a deficiency in LPL or an imbalance in tissue-specific LPL activities, this leads to hypertriglyceridemia. Various regulators influence LPL, including angiopoietin-like (ANGPTL) proteins (such as ANGPTL8, ANGPTL4, ANGPTL3) and certain apolipoproteins (including apolipoprotein A5, apolipoprotein C3, and apolipoprotein C2). These regulators collaboratively modulate LPL activity and the utilization of TG (57, 58, 82).

In the Mexican population, Muñoz-Barrios et al. (83) demonstrated an association between the HindIII polymorphism and hypertension. Likewise, Tanguturi et al. (84) reported that individuals with a homozygous genotype for the common allele (H+/H+) of the LPL gene are at an increased risk of experiencing their first myocardial infarction. In contrast, Imeni et al. (85) found no statistically significant association between CAD and the genotypic distribution of the HindIII polymorphism. Additionally, Muñoz-Barrio's study indicated an elevated risk of stroke in individuals with LPL gene variations, particularly in the HindIII polymorphism (83).

Similarly, He et al. (86) explored a reduced risk of stroke in individuals with the HindIII polymorphism carrying the G allele, and this association was observed in both hemorrhagic and ischemic stroke patients. Likewise, in another study (87), an investigation into the association between the distribution of HindIII polymorphism genotypes and the risk of CAD revealed no statistically significant differences between patients with a history of CAD and healthy individuals in Iran.

Likewise, Ma et al. (88) performed a meta-analysis, indicating an increased risk of CAD associated with the LPL rs1801177 polymorphism. However, the LPL HindIII and rs328 polymorphisms demonstrated a protective role against CAD. Additionally, the

authors did not identify any association between the LPL Pvull polymorphism, as well as rs268, and susceptibility to CAD.

Similarly, Xie et al. (89) conducted a meta-analysis on LPL polymorphism and its association with the risk of CAD. The authors concluded that the risk of CAD was associated with the homozygous H+ H+ genotype and H+ allele genotypes of the LPL HindIII polymorphism. Additionally, the risk of CAD was significantly linked to the rs328 XX genotype. However, the risk of CAD was not associated with the Pvull polymorphism. Finally, the authors suggested that the LPL HindIII polymorphism could serve as a potential biomarker for CAD risk.

Similarly, Spence et al. (90) elucidated that the predictor for the baseline carotid plaque area was significantly associated with the LPL rs1801177 genotype, and this association might be influenced by BMI. Furthermore, over a one-year period, plaque progression showed a strong correlation with the rs1801177 genotype. The authors propose that the rs1801177 genotype, as assessed by the progression of carotid plaque area, could be a determinant of atherosclerosis.

Furthermore, Gagné et al. (91) highlighted the connection between genetic variation at the LPL locus and the influence of plasma lipids in modulating the risk of coronary heart disease (CHD). The authors concluded that the rs328 variant could potentially offer significant protection against elevated TG levels, premature CHD, and low HDL-C in the studied subjects. Similarly, Guan et al. (92) examined the association between LPL gene variants rs328, rs1801177, and rs268 polymorphisms and the development of CVDs in children with obesity. In summary, the authors concluded that rs1801177, rs268, and rs328 gene mutations might not be associated with CVD risk in children with obesity.

Conclusion

This review article concludes that LPL deficiency and dysfunction are associated with various disorders, such as obesity, IR, T2D, chylomicronemia, atherosclerosis, myocardial infarction, CAD, and stroke. There are around 100 LPL gene variants, but this review article reported that LPL polymorphisms such as rs1801177, rs118204069, rs118204057, rs118204060, rs118204068, rs268, and rs328 were the common variants present among metabolic syndrome patients. On the other hand, rs1801177, rs268, rs1801177, and rs328 polymorphisms were common in CAD affected patients. Therefore, it is suggested that further studies should be conducted to identify the LPL gene variants in other CVDs, including cardiac arrhythmia.

Conflicts of Interest

The authors declare no conflict of interest.

Acknowledgments

Authors' Contributions

All authors contributed to the conception and design of this study. The first draft of the manuscript was written by Sana and Sara Rafaqat. Data collection was performed by Sana and Sara Rafaqat, SS and AK. AK critically revised the manuscript. All authors have read and approved the final version of the manuscript.

Availability of Data

Not applicable.

References

1. Mann GV. A short history of lipoproteins. In: Homburger F, Bernfeld P, editors. The Lipoproteins. Methods and Clinical Significance. Basel, Switzerland: Karger; 1958; pp. 7-13.

2. Gaudet D, Méthot J, Kastelein J. Gene therapy for lipoprotein lipase deficiency. Curr Opin Lipidol. 2012;23(4):310-20.

3. Wion KL, Kirchgessner TG, Lusis AJ, Schotz MC, Lawn RM. Human lipoprotein lipase complementary DNA sequence. Science. 1987;235(4796):1638-41.

4. Persson B, Bengtsson-Olivecrona G, Enerbäck S, Olivecrona T, Jörnvall H. Structural features of lipoprotein lipase. Lipase family relationships, binding interactions, non-equivalence of lipase cofactors, vitellogenin similarities and functional subdivision of lipoprotein lipase. Eur J Biochem. 1989;179(1):39-45.

5. Rader DJ, Jaye M. Endothelial lipase: a new member of the triglyceride lipase gene family. Curr Opin Lipidol. 2000;11:141–147.

6. Emmerich J, Beg OU, Peterson J, Previato L, Brunzell JD, Brewer HB Jr, Santamarina-Fojo S. Human lipoprotein lipase. Analysis of the catalytic triad by site-directed mutagenesis of Ser132, Asp-156, and His-241. J Biol Chem. 1992;267:4161–4165.

7. Eckel RH. Lipoprotein lipase. A multifunctional enzyme relevant to common metabolic diseases. N Engl J Med. 1989;320(16):1060-8.

8. Wang H, Eckel RH. Lipoprotein lipase: from gene to obesity. Am J Physiol Endocrinol Metab. 2009;297(2):E271-88.

9. Fernández-Borja M, Bellido D, Vilella E, Olivecrona G, Vilaró S. Lipoprotein lipase-mediated uptake of lipoprotein in human fibroblasts: evidence for an LDL receptor-independent internalization pathway. J Lipid Res. 1996;37(3):464-81.

10. Daoud MS, Ataya FS, Fouad D, Alhazzani A, Shehata AI, Al-Jafari AA. Associations of three lipoprotein lipase gene polymorphisms, lipid profiles and coronary artery disease. Biomed Rep. 2013;1(4):573-582.

11. Gerdes C, Gerdes LU, Hansen PS, Faergeman O. Polymorphisms in the lipoprotein lipase gene and their associations with plasma lipid concentrations in 40-year-old Danish men. Circulation. 1995;92(7):1765-9.

12. Heizmann C, Kirchgessner T, Kwiterovich PO, Ladias JA, Derby C, Antonarakis SE, Lusis AJ. DNA polymorphism haplotypes of the human lipoprotein lipase gene: possible association with high density lipoprotein levels. Hum Genet. 1991;86(6):578-84.

13. Augustus A, Yagyu H, Haemmerle G, Bensadoun A, Vikramadithyan RK, Park SY, et al. Cardiac-specific knock-out of lipoprotein lipase alters plasma lipoprotein triglyceride metabolism and cardiac gene expression. J Biol Chem. 2004;279(24):25050-7.

14. Noh HL, Okajima K, Molkentin JD, Homma S, Goldberg IJ. Acute lipoprotein lipase deletion in adult mice leads to dyslipidemia and cardiac dysfunction. Am J Physiol Endocrinol Metab. 2006;291(4):E755-60.

15. Goldberg IJ. Lipoprotein lipase and lipolysis: central roles in lipoprotein metabolism and atherogenesis. J Lipid Res. 1996; 37(4):693-707.

16. Preiss-Landl K, Zimmermann R, Hämmerle G, Zechner R. Lipoprotein lipase: the regulation of tissue specific expression and its role in lipid and energy metabolism. Curr Opin Lipidol. 2002;13(5):471-81.

17. Yang W, Huang J, Yao C, Su S, Liu D, Ge D, et al. Linkage and linkage disequilibrium analysis of the lipoprotein lipase gene with lipid profiles in Chinese hypertensive families. Clin Sci (Lond). 2005;108:137–142.

18. Yang W, Huang J, Ge D, Yao C, Duan X, Shen Y, et al. Lipoprotein lipase gene is in linkage with blood pressure phenotypes in Chinese pedigrees. Hum Genet. 2004;115:8–12.

19. Henderson HE, Kastelein JJ, Zwinderman AH, Gagné E, Jukema JW, Reymer PW, et al. 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. 1999;40:735–743.

20. Oka K, Tkalcevic GT, Nakano T, Tucker H, Ishimura-Oka K, Brown WV. Structure and polymorphic map of human lipoprotein lipase gene. Biochim Biophys Acta. 1990;1049(1):21–6.

21. Deeb SS, Peng RL. Structure of the human lipoprotein lipase gene. Biochemistry. 1989;28(10):4131–5.

22. Havel RJ, Gordon RS. Idiopathic hyperlipemia: metabolic studies in an affected family. J Clin Invest. 1960;39(12):1777-90.

23. Gaudet D, Méthot J, Kastelein J. Gene therapy for lipoprotein lipase deficiency. Curr Opin Lipidol. 2012;23(4):310-20.

24. Duman BS, Türkoğlu Ç, Akpınar B, Güden M, Vertii A, Dak E, et al. Lipoprotein lipase gene polymorphism and lipid profile in coronary artery disease. Arch Pathol Lab Med. 2004;128(8):869-74.

25. Alberti K, Zimmet P, Shaw J. Metabolic syndrome—A new world-wide definition. A consensus statement from the International Diabetes Federation. Diabetic Med. 2006;23:469–80.

26. Kaur J. A comprehensive review on metabolic syndrome. Cardiol Res Pract. 2014;2014:943162.

27. Mead JR, Irvine SA, Ramji DP. Lipoprotein lipase: structure, function, regulation, and role in disease. J Mol Med. 2002;80:753-69.

28. Burnett JR, Hooper AJ, Hegele RA. Familial Lipoprotein Lipase Deficiency [Internet]. 1999 Oct 12 [updated 2017 Jun 22; cited]. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, et al, editors. GeneReviews. Seattle (WA): University of Washington, Seattle; 1993–2023. Available from: https://pubmed.ncbi.nlm.nih.gov/20301485/, 2023 December 01.

29. Petrescu-Dănilă E, Voicu PM, Ionescu CR. Aspecte mutagenice la nivelul genei lipoprotein lipazei [Mutagenic aspects of the lipoprotein lipase gene]. Rev Med Chir Soc Med Nat Iasi. 2006;110(1):173-7. (in Romanian).

30. Gotoda T, Shirai K, Ohta T, Kobayashi J, Yokoyama S, Oikawa S, et al. Diagnosis and management of type I and type V hyperlipoproteinemia. J Atheroscler Thromb. 2012;19:1–12.

31. Martín-Campos JM, Julve J, Roig R, Martínez S, Errico TL, Martínez-Couselo S, et al. Molecular analysis of chylomicronemia in a clinical laboratory setting: diagnosis of 13 cases of lipoprotein lipase deficiency. Clin Chim Acta. 2014;429:61–8.

32. Parson W, Kraft HG, Niederstätter H, Lingenhel AW, Köchl S, Fresser F, Utermann G. A common nonsense mutation in the repetitive Kringle IV-2 domain of human apolipoprotein(a) results in a truncated protein and low plasma Lp(a). Hum Mutat. 2004;24(6):474-80.

33. Pingitore P, Lepore SM, Pirazzi C, Mancina RM, Motta BM, Valenti L, et al. Identification and characterization of two novel mutations in the LPL gene causing type I hyperlipoproteinemia. J Clin Lipidol. 2016;10(4):816-23.

34. Eller P, Schgoer W, Mueller T, Tancevski I, Wehinger A, Ulmer H, et al. Hepatic lipase polymorphism and increased risk of peripheral arterial disease. J Intern Med. 2005;258(4):344-8.

35. Schwartz MW, Seeley RJ, Zeltser LM, Drewnowski A, Ravussin E, Redman LM, Leibel RL. Obesity pathogenesis: an endocrine society scientific statement. Endocr Rev. 2017;38(4):267-96.

36. Nuermaimaiti N, Liu J, Liang X, Jiao Y, Zhang D, Liu L, et al. Effect of lncRNA HOXA11-AS1 on adipocyte differentiation in human adipose-derived stem cells. Biochem Biophys Res Commun. 2018;495(2):1878-84.

37. Kersten S. Physiological regulation of lipoprotein lipase. Biochim Biophys Acta. 2014;1841(7):919-33.

38. Wang H, Eckel RH. Lipoprotein lipase: from gene to obesity. Am J Physiol Endocrinol Metab. 2009;297(2):E271-88.

39. Guo X, Chen R, Mo B, Liu Q. [Effect of lipoprotein lipase gene polymorphism on plasma lipid levels,BMI and subcutaneous fat distribution in simple obesity children]. Zhonghua Yi Xue Yi Chuan Xue Za Zhi. 2000;17(2):105-7. (in Chinese).

40. Huang AQ, Hu YH, Zhan SY, Xu B, Pang ZC, Cao WH, et al. Lipoprotein lipase gene S447X polymorphism modulates the relation between central obesity and serum lipids, a twin study. Int J Obes (Lond). 2006;30(12):1693-701.

41. Schwartz RS, Brunzell JD. Increase of adipose tissue lipoprotein lipase activity with weight loss. J Clin Invest. 1981;67(5):1425-30.

42. Taskinen MR. Lipoprotein lipase in diabetes. Diabetes Metab Rev. 1987;3:551-70.

43. Klannemark M, Suurinkeroinen L, Orho-Melander M, Groop L, Taskinen MR. Interaction between the Asn291Ser variant of the LPL gene and insulin resistance on dyslipidaemia in high risk individuals for Type 2 diabetes mellitus. Diabet Med. 2000;17:599-605.

44. Kalmar T, Seres I, Balogh Z, Kaplar M, Winkler G, Paragh G. Correlation between the activities of lipoprotein lipase and paraoxonase in type 2 diabetes mellitus. Diabetes Metab. 2005;31:574-80.

45. Marcais C, Bernard S, Merlin M, Ulhmann M, Mestre B, Rochet-Mingret L, et al. Severe hypertriglyceridaemia in Type II diabetes: involvement of apoC-III Sst-I polymorphism, LPL mutations and apo E3 deficiency. Diabetologia. 2000;43:1346-52.

46. Ma YQ, Thomas GN, Ng MC, Critchley JA, Chan JC, Tomlinson B. The lipoprotein lipase gene HindIII polymorphism is associated with lipid levels in early-onset type 2 diabetic patients. Metabolism. 2003;52:338-43.

47. Socquard E, Durlach A, Clavel C, Nazeyrollas P, Durlach V. Association of HindIII and PvuII genetic polymorphisms of lipoprotein lipase with lipid metabolism and macrovascular events in type 2 diabetic patients. Diabetes Metab Rev. 2006;32:262-9.

48. Ukkola O, Savolainen MJ, Salmela PI, von Dickhoff K, Kesaniemi YA. DNA polymorphisms at the lipoprotein lipase gene are associated with macroangiopathy in type 2 (non-insulin-dependent) diabetes mellitus. Atherosclerosis. 1995;115:99-05.

49. Mattu RK, Trevelyan J, Needham EW, Khan M, Adiseshiah MA, Richter D, et al. Lipoprotein lipase gene variants relate to presence and degree of microalbuminuria in Type II diabetes. Diabetologia. 2002;45:905-13.

50. Solini A, Passaro A, Fioretto P, Nannipieri M, Ferrannini E. Lipoprotein lipase gene variants and progression of nephropathy in hypercholesterolaemic patients with type 2 diabetes. J Intern Med. 2004;256:30-6.

51. Ng MC, Baum L, So WY, Lam VK, Wang Y, Poon E, et al. Association of lipoprotein lipase S447X, apolipoprotein E exon 4, and apoC3 -455T＞C polymorphisms on the susceptibility to diabetic nephropathy. Clin Genet. 2006;70:20-8.

52. Javorsky M, Kozarova M, Salagovic J, Tkac I. Relationship among urinary albumin excretion rate, lipoprotein lipase PvuII polymorphism and plasma fibrinogen in type 2 diabetic patients. Physiol Res. 2006;55:55-62.

53. Radha V, Vimaleswaran KS, Ayyappa KA, Mohan V. Association of lipoprotein lipase gene polymorphisms with obesity and type 2 diabetes in an Asian Indian population. Int J Obes (Lond). 2007;31:913-8.

54. Cho YS, Go MJ, Han HR, Cha SH, Kim HT, Min H, et al. Association of lipoprotein lipase (LPL) single nucleotide polymorphisms with type 2 diabetes mellitus. Exp Mol Med. 2008;40(5):523-32.

55. Taskinen MR. Lipoprotein lipase in diabetes. Diabetes Metab Rev. 1987;3(2):551-70.

56. Reccia I, Kumar J, Akladios C, Virdis F, Pai M, Habib N, Spalding D. Non-alcoholic fatty liver disease: a sign of systemic disease. Metabolism. 2017;72:94-108.

57. Heo JH, Jo SH. Triglyceride-Rich Lipoproteins and Remnant Cholesterol in Cardiovascular Disease. J Korean Med Sci. 2023;38(38):e295.

58. Kimura T, Tsunekawa K, Nagasawa T, Aoki T, Miyashita K, Yoshida A, et al. Circulating levels of lipoprotein lipase and glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1: new markers for cardiovascular diseases among noncommunicable diseases: a brief narrative review. J Lab Precis Med. 2023;8:18.

59. Groenemeijer BE, Hallman MD, Reymer PW, Gagné E, Kuivenhoven JA, Bruin T, et al. 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. 1997;95(12):2628-35.

60. Daoud MS, Ataya FS, Fouad D, Alhazzani A, Shehata AI, Al-Jafari AA. Associations of three lipoprotein lipase gene polymorphisms, lipid profiles and coronary artery disease. Biomed Rep. 2013;1(4):573-582.

61. Goodarzi MO, Guo X, Taylor KD, Quinones MJ, Saad MF, Yang H, et al. Lipoprotein lipase is a gene for insulin resistance in Mexican Americans. Diabetes. 2004;53(1):214-20.

62. Barg E. Polimorfizmy genu lipazy lipoproteinowej i ich udział w procesach metabolicznych [Polymorphisms of lipoprotein lipase gene and their participation in metabolic processes]. Pediatr Endocrinol Diabetes Metab. 2011;17(2):107-12. (in Polish).

63. Rohini A, Agrawal N, Kumar H, Kumar V. Emerging role of branched chain amino acids in metabolic disorders: a mechanistic review. PharmaNutrition. 2018;6:47-54.

64. Tabatabaei-Malazy O, Larijani B, Abdollahi M. Targeting metabolic disorders by natural products. J Diabetes Metab Disord. 2015;14:57.

65. Dehghan M, Pourahmad-Jaktaji R, Farzaneh Z. Calcitonin receptor AluI (rs1801197) and Taq1 calcitonin genes polymorphism in 45-and over 45-year-old women and their association with bone density. Acta Inform Med. 2016;24:239-243.

66. Kina-Tanada M, Sakanashi M, Tanimoto A, Kaname T, Matsuzaki T, Noguchi K, et al. Long-term dietary nitrite and nitrate deficiency causes the metabolic syndrome, endothelial dysfunction and cardiovascular death in mice. Diabetologia. 2017;60:1138-1151.

67. Muller CJF, Malherbe CJ, Chellan N, Yagasaki K, Miura Y, Joubert E. Potential of rooibos, its major C-glucosyl flavonoids, and Z-2-(β-D-glucopyranosyloxy)-3-phenylpropenoic acid in prevention of metabolic syndrome. Crit Rev Food Sci Nutr. 2018;58(2):227-246.

68. Leslie BR. Metabolic syndrome: historical perspectives. Am J Med Sci. 2005;330:264-268.

69. Vishram JK, Hansen TW, Torp-Pedersen C, Madsbad S, Jørgensen T, Fenger M, et al. Relationship Between Two Common Lipoprotein Lipase Variants and the Metabolic Syndrome and Its Individual Components. Metab Syndr Relat Disord. 2016;14(9):442-448.

70. Brunzell JD, Deeb SS. Familial lipoprotein lipase deficiency, apo CII deficiency and hepatic lipase deficiency. In: Scriver CR, Beaudet AI, Sly WS, Valle D, editors. The Metabolic and Molecular Basis of Inherited Disease. 8th ed. New York, NY: McGraw-Hill; 2000; pp. 2789-2816.

71. Nordestgaard BG, Stender S, Kjeldsen K. Reduced atherogenesis in cholesterol-fed diabetic rabbits: giant lipoproteins do not enter the arterial wall. Arteriosclerosis. 1988;8(4):421-428.

72. Nordestgaard BG. Triglyceride-rich lipoproteins and atherosclerotic cardiovascular disease: new insights from epidemiology, genetics, and biology. Circ Res. 2016;118(4):547-563.

73. Nordestgaard BG, Abildgaard S, Wittrup HH, Steffensen R, Jensen G, Tybjaerg-Hansen A. Heterozygous lipoprotein lipase deficiency: frequency in the general population, effect on plasma lipid levels, and risk of ischemic heart disease. Circulation. 1997;96(6):1737-1744.

74. Khera AV, Won HH, Peloso GM, O'Dushlaine C, Liu D, Stitziel NO, et al; Myocardial Infarction Genetics Consortium, DiscovEHR Study Group, CARDIoGRAM Exome Consortium, and Global Lipids Genetics Consortium. Association of Rare and Common Variation in the Lipoprotein Lipase Gene with Coronary Artery Disease. JAMA. 2017;317(9):937-946.

75. Cagatay P, Susleyici-Duman B, Ciftci C. Lipoprotein lipase gene PvuII polymorphism serum lipids and risk for coronary artery disease: metaanalysis. Dis Markers. 2007;23(3):161–6.

76. Sayad A, Noruzinia M, Zamani M, Harirchian MH, Kazemnejad A. Lipoprotein Lipase HindIII Intronic Polymorphism in a Subset of Iranian Patients with Late-Onset Alzheimer's Disease. Cell J. 2012;14(1):67-72.

77. Goodarzi MO, Guo X, Taylor KD, Quiñones MJ, Saad MF, Yang H, et al. Lipoprotein lipase is a gene for insulin resistance in Mexican Americans. Diabetes. 2004;53(1):214-20.

78. Mead JR, Cryer A, Ramji DP. Lipoprotein lipase, a key role in atherosclerosis? FEBS Lett. 1999;462(1–2):1–6.

79. McFarlane SI, Banerji M, Sowers JR. Insulin resistance and cardiovascular disease. J Clin Endocrinol Metab. 2001;86(2):713–8.

80. Stancáková A, Baldaufová L, Javorský M, Kozárová M, Salagovic J, Tkác I. Effect of gene polymorphisms on lipoprotein levels in patients with dyslipidemia of metabolic syndrome. Physiol Res. 2006;55(5):483-490.

81. Gehrisch S. Common mutations of the lipoprotein lipase gene and their clinical significance. Curr Atheroscler Rep. 1999;1(1):70-8.

82. Wen Y, Chen YQ, Konrad RJ. The Regulation of Triacylglycerol Metabolism and Lipoprotein Lipase Activity. Adv Biol (Weinh). 2022;6(10):e2200093.

83. Muñoz-Barrios S, Guzmán-Guzmán IP, Muñoz-Valle JF, Salgado-Bernabé AB, Salgado-Goytia L, Parra-Rojas I. Association of the HindIII and S447X polymorphisms in LPL gene with hypertension and type 2 diabetes in Mexican families. Dis Markers. 2012;33(6):313-20.

84. Tanguturi PR, Pullareddy B, Rama Krishna BS, Murthy DK. Lipoprotein lipase gene HindIII polymorphism and risk of myocardial infarction in South Indian population. Indian Heart J. 2013;65(6):653-7.

85. Imeni M, Hasanzad M, Naji T, Poopak B, Babanejad M, Sanati HR, et al. Analysis of the association Hind III Polymorphism of Lipoprotein Lipase gene on the risk of coronary artery disease. Res Mol Med. 2013;1(3):19–24.

86. He T, Wang J, Deng WS, Sun P. Association between Lipoprotein Lipase Polymorphism and the Risk of Stroke: A Meta-analysis. J Stroke Cerebrovasc Dis. 2017;26(11):2570–2578.

87. Palacio Rojas M, Prieto C, Bermúdez V, Garicano C, Núñez Nava T, Martínez MS, et al. Dyslipidemia: Genetics, lipoprotein lipase and HindIII polymorphism. F1000Res. 2017;6:2073.

88. Ma YQ, Thomas GN, Ng MC, Critchley JA, Chan JC, Tomlinson B. The lipoprotein lipase gene HindIII polymorphism is associated with lipid levels in early-onset type 2 diabetic patients. Metabolism. 2003;52:338-43.

89. Xie L, Li YM. Lipoprotein Lipase (LPL) Polymorphism and the Risk of Coronary Artery Disease: A Meta-Analysis. Int J Environ Res Public Health. 2017;14(1):84.

90. Spence JD, Ban MR, Hegele RA. Lipoprotein lipase (LPL) gene variation and progression of carotid artery plaque. Stroke. 2003;34(5):1176-80.

91. Gagné SE, Larson MG, Pimstone SN, Schaefer EJ, Kastelein JJ, Wilson PW, Ordovas JM, Hayden MR. A common truncation variant of lipoprotein lipase (Ser447X) confers protection against coronary heart disease: the Framingham Offspring Study. Clin Genet. 1999;55(6):450-4.

92. Guan YM, Gui YH, Luo FH, Shen SX, Yang Y. [Lipoprotein lipase gene mutations and the risk of cardiovascular diseases in children with obesity]. Zhongguo Dang Dai Er Ke Za Zhi. 2010;12(3):161-4. (in Chinese).

Uloga varijanti lipoprotein lipaze u metaboličkim poremećajima i kardiovaskularnim oboljenjima

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Kratak sadržaj

Lipoproteinska lipaza (LPL) je glikoprotein koji se proizvodi i sekretuje u intersticijalni prostor različitih tkiva, uključujući srčani mišić, masno tkivo, makrofage i skeletne mišiće. Aktivnost LPL može biti pod uticajem genetskih modifikacija koje rezultiraju promenama u metabolizmu lipida. Ovaj revijski članak sadrži podatke o nedavnim studijama koje uglavnom objašnjavaju patofiziološke aspekte mutacije gena za LPL u metaboličkom sindromu i kardiovaskularnim bolestima. Zabeleženo je oko 100 mutacija gena za LPL, ali ovaj revijski članak prikazuje rs1801177, rs118204069, rs118204057, rs118204060, rs118204068, rs268 i rs328, koje su najčešći nosioci mutacije gena za LPL kod pacijenata sa metaboličkim sindromom. Kod kardiovaskularnih bolesti, varijante LPL rs1801177, rs268 and rs328 su najučestalije. Potrebne su buduće studije kako bi se ispitale mutacije gena za LPL u drugim kardiovaskularnim bolestima, uključujući srčanu aritmiju. Ovaj revijski članak zaključuje da su deficit i disfunkcija LPL povezane sa bolestima kao što su gojaznost, insulinska rezistencija, dijabetes, hilomikronemija, ateroskleroza, infarkt miokarda, koronarna arterijska bolest i moždani udar.

Ključne reči: lipoproteinska lipaza, metabolički sindrom, kardiovaskularne bolesti, patofiziologija, mutacija