REVIEW

Dyslipidemia: Genetics, lipoprotein lipase and HindIII polymorphism [version 1; peer review: 1 approved, 1 approved with reservations]

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Abstract

The direct link between lipid metabolism alterations and the increase of cardiovascular risk are well documented. Dyslipidemias, including isolated high LDL-c or mixed dyslipidemia, such as those seen in diabetes (hypertriglyceridemia, high LDL-c or low HDL-c), correlate with a significant risk of cardiovascular and cerebrovascular disease worldwide. This review analyzes the current knowledge concerning the genetic basis of lipid metabolism alterations, emphasizing lipoprotein lipase gene mutations and the HindIII polymorphism, which are associated with decreased levels of triglycerides and LDL-c, as well as higher levels of HDL-c. These patterns would be associated with decreased global morbidity and mortality, providing protection against cardiovascular and cerebrovascular diseases.

Keywords

Dyslipidemia, Polymorphisms, HindIII, Lipoprotein Lipase, coronary artery disease

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Dyslipidemia: The current status

The relationship between dyslipidemia and atherosclerosis continues to be an area of active research, since the prevalence of atherosclerosis and associated cardiovascular complications continue to increase in the industrialized world¹. Cardiovascular disease (CVD) constitutes the greatest cause of morbidity and mortality globally with a high incidence in countries of all economic categories². Evidence supporting a causal relationship between lipid profile abnormalities and the risk of coronary artery disease (CAD) is overwhelming, confirming that hypercholesterolemia is an independent risk factor for CVD³⁻⁵. In addition, hypertriglyceridemia and mixed dyslipidemias have been associated with the aggregation of metabolic risk factors, like hypertension (HTN)⁶ and obesity⁷.

Dyslipidemias are a group of metabolic derangements characterized by any or a combination of the following: elevated low density lipoprotein (LDL-c) (>130mg/dL), elevated total cholesterol (>200 mg/dL), elevated TG (>150mg/dL), or low high density lipoprotein (HDL-c) (<40mg/dL in men and <50mg/dL in women)⁸.

The worldwide prevalence of dyslipidemia varies between different individuals, depending on race, age, socio-economic and cultural factors, lifestyle and genetics. This prevalence has increased significantly in growing cities with economic growth⁹. According to the National Health and Nutrition Examination Survey (NHANES) 2003–2006, 53.0% of the adult population in United States has some form dyslipidemia¹⁰; however, a lower prevalence have been reported for other countries, for example Canada and South Korea, with 45% and 44.1%, respectively^{8,11}. De Souza *et al.* studied a sample of 1,039 patients and reported that the most common dyslipidemias in Brazil were isolated low HDL-c (18.3%), hypertriglyceridemia (17.1%), and isolated hypercholesterolemia (4.2%)¹². These results are similar to those reported by Aguilar-Salinas *et al.*, in which the incidence of dyslipidemia in a group of 4,040 Mexican patients was 60.3%, from which low HDL-c represented 60.3%, hypercholesterolemia 43.6% and hypertriglyceridemia 31.5%¹³. Another cross-sectional and descriptive study carried out in 318 patients from Cuenca, Ecuador, found that 82.4% of individuals (86.8% in females and 76.5% in males) had some type of dyslipidemia. Isolated low HDL-c was the most prevalent abnormality and it was significantly associated with obesity (OR: 3.99. CI: 95%. 1.65-9.36; $p < 0.01$)¹⁴.

In Venezuela, the CARMELA study evaluated the prevalence of lipid metabolism disorders in the city of Barquisimeto of Lara state, reporting one of the highest percentages in the country, with a 50.4% prevalence of dyslipidemia in this population¹⁵. Nevertheless, a study by Linares *et al.*¹⁶ with a sample of 2,230 individuals from Maracaibo City, Venezuela, identified the overall dyslipidemia prevalence was even higher at 84.8% ($n=1892$), where 88% of females and 81.4% of males were found to have dyslipidemia. High LDL-c was the most frequent abnormality found in this population (20%), followed by the combination of low HDL-c with high LDL-c (19%) and hypertriglyceridemia with high LDL-c and low HDL (16.2%). Bermúdez *et al.*¹⁷

found that low HDL-c was statistically associated with obesity, ethnic group, alcohol consumption, and elevated TG.

Dyslipidemia genetics

The association between family history of dyslipidemia and the risk of CVD is supported by a large body of evidence¹⁸⁻²². Additionally, the great advancement in DNA analysis techniques has aided research surrounding CVD and related genetics and epigenetics. Understanding gene mutations or polymorphisms involved in the synthesis, transport, and metabolism of lipoproteins allows recognition of potential therapeutic targets and alternative treatments through identification of new molecules^{1,3,20}.

Dyslipidemia is one of the most well characterized cardiovascular risk factors^{19,20}. This not only depends on diet, but also on the synthesis and metabolism of lipoproteins conditioned by gene expression. Given the importance and the great diversity of proteins that participate in lipid metabolism, one might expect that a single defect in any step of gene expression would affect the quantity or quality of the product and potentially predispose to dyslipidemias and CVD¹⁹.

One genetic abnormalities associated with low HDL-c and increased CVD risk is the *Taq IB* polymorphism located in chromosome 16q21. This gene alters cholesteryl ester protein transferase (CEPT), which decreases HDL-c concentration²³. Some deletions, inversions, and substitutions of the *APO AI-IV*, *CII*, and *CIII* genes are also associated with both premature CVD and low HDL-c^{24,25}. Total deficiency of lecithin cholesterol acyl transferase (LCAT) can be seen after transition of C→T in codon 147 of exon 4 (W147R), G→A in codon 293 of exon 6 (M293I), as well as partial deficiencies of LCAT due to transition of C→T. Additionally, the substitution of threonine for isoleucine in codon 123 (T123I) causes decreased HDL-c and higher cholesterol in the intima of arterial vessels^{26,27}.

Below, some of the genetic alterations associated with low levels of HDL-c and a higher risk of CVD are highlighted:

1. *CETP*. The transcript of this gene mediates the exchange of lipids between lipoproteins, resulting in a net transference of cholesteryl esters from HDL to other lipoproteins and the capture of cholesterol in the liver. High levels of *CETP* lead to HDLs rich in TG, making a substrate for hepatic lipases, so that TG are hydrolyzed and ApoA-I is degraded in renal tubule cells. The subsequent decrease in HDL-c concentration creates a pro-atherogenic environment²⁸. This occurs when *CETP* reaches a high level of expression in some individuals with polymorphisms in the codifying *CETP* gene (16q21). Being the most frequently occurring and best characterized polymorphism on intron 1, *TaqIB* is associated with the development of early atherosclerosis²³.
2. *Familial hypoalphalipoproteinemia and HDL-C deficiency*. Approximately 50% of HDL-c alterations are explained by polygenic defects in various chromosomal loci that control apolipoprotein expression (*A-I*, *A-II*, *C-II*, *C-III* and *Apo A-IV*) and LCAT. Multiple genetic defects have been

reported, such as deletions, inversions and substitutions on codifying genes of apolipoproteins, which are all associated with premature arterial disease^{24,25}.

3. *LCAT*. This liver-synthesized enzyme circulates in plasma forming complexes with HDL and participating in the inverse transport of cholesterol. An *LCAT* deficiency results in the accumulation of free cholesterol on tissues. Insertions and substitutions in the *LCAT* gene may cause inactivation of the protein. Some of the reported mutations are C→T transitions on codon 147 of exon 4 (W147R), G→A on codon 293 of exon 6 (M293I), and the insertion of 3 pair of bases on exon 4, introducing a glycine on a helicoidally region of the protein and a substitution N228K^{24,25}. The best characterized mutation is a C→T transition that results in a substitution of threonine for isoleucine in codon 123 (T123I) of the protein, resulting in a partial deficiency of *LCAT*^{29,30}.

The following are some genetic alterations associated with hypercholesterolemia and hypertriglyceridemia, including their relationship with increased cardiovascular risk:

1. *LDLR gene – LDL-c receptor and familial hypercholesterolemia*. LDL-c is a macromolecular complex that transports cholesterol and cholesteryl esters from the liver to other peripheral tissues, where cholesterol is introduced to the cells through LDL receptors (LDLR). LDL binds to its receptors before internalization by endocytosis³¹. This transport represents the principal mechanism that regulates cholesterol concentration in plasma. Any defect in this transport results in hypercholesterolemia. Mutations in the *LDLR* gene that codifies the LDL-c receptor is one the best characterized genetic defects causing dyslipidemia. This autosomal dominant condition is called familial hypercholesterolemia^{32,33}. Familial hypercholesterolemia is characterized by elevated levels of cholesterol and LDL-c as a consequence of defects in cholesterol transportation, receptor deficits, or a functional alteration of cellular receptors.
2. *APO B-100 gene – ligand of LDL-c receptor and Familial Apolipoprotein B dysfunction (hypercholesterolemia type B)*. An inadequate cholesterol transport also caused by genetic defects in the ligand of LDLR, the *APO B-100*. This autosomal dominant defect, also known as familial *APO B-100* dysfunction, comes from mutations in *APO B-100* gene, in the short arm of chromosome 2³⁴. The first mutation described is a G→A transition that results in a substitution of Arg3500→Gln on the *APO B-100* receptor of LDL-c^{33,35}. Similarly, there are mutations associated with hypercholesterolemia and elevated TG that correlate with elevated CVD risk. Mutations of the *LDL-r* gene is the cause of familial hypercholesterolemia, which causes elevation of both total and LDL-c cholesterol^{27,28}, and *APO B-100* mutations located in p2 (transition G→A is the best known), resulting in a substitution of Arg3500→Gln in the region of *APO B-100* that binds to LDL-c²⁹, leading to type B hypercholesterolemia³⁵.
3. *APO E gene – Apolipoprotein E and hyperlipoproteinemia or hyperlipidemia type III*. Apolipoprotein E (ApoE) is a principal component of chylomicrons (CMs), very low density lipoprotein (VLDL) and some HDL-c. Its main function is the hepatic clearance of CMs and VLDL, as well as lipolysis by the same lipoprotein lipase (LPL)³⁶. In hyperlipoproteinemia or hyperlipidemia type III, plasma levels of cholesterol and TG increases as a consequence of defective transport of CMs and VLDL, due to a defect in the *ApoE* gene located on the short arm of chromosome 19 (19q13.2)^{37,38}. Polymorphisms in the codifying gene of *ApoE* (alleles ε2, 3 y 4)^{39,40} are associated with variations in plasma levels of cholesterol, where the individuals with ε2 allele have 10% lower cholesterol levels compared to those who express the ε4 allele, leading to cholesterol values 10% above the mean of homozygous individuals for ε3., leads to hyperlipoproteinemia or type III hyperlipidemia with elevated total cholesterol and elevated TG^{41,42}.
4. *Lp(a) gene - lipoprotein (a)– Lp(a)*. Lipoprotein(a) is composed by a common low density lipoprotein (LDL-col) nuclei linked to an apolipoprotein (a) [Apo(a)] by disulfide bonds between a cysteine in the Kringle-IV type 9 (Cys 67) and the cysteine 3734 in Apo B-100⁴³. Structurally, Apo(a) is composed of heavily glycosylated tridimensional structures called “Kringle” because of their similarity with a looped Danish pastry. Each Kringle contains a mean of 80 amino acids stabilized by 3 internal disulfide bonds, which finally surround the LDL molecules⁴³. Apo(a) has high structural similarity with plasminogen, a key proenzyme of the fibrinolytic pathway⁴⁴. Kringle IV domains are classified into 10 distinct subclasses, which compose most of the Apo(a) molecule, plus a linked Kringle V domain that resembles the catalytic region of plasminogen. The Kringle IV type 2 domain gene can be expressed a different number of times, resulting in a variable copy number of this structure (3–40 copies) within the Lp(a) molecule⁴⁴. This determines the basis for the isoform size heterogeneity of Apo(a), whereas, the remaining 9 subtypes of Kringle IV are expressed just in a single copy into the Apo(a) molecule. Lp(a) is one of the most important cardiovascular risk markers^{45,46} and to date, some polymorphisms in the Apo(a) gene, located on chromosome 6 (6q26-q27) have been identified. For example, KIV-2 CNV consists of variable numbers of repeated units of module 4 and the number of repetitions inversely correlates with plasma levels of Lp(a)⁴⁷.
5. *HL gene - hepatic lipase and phenotype of combined familial hyperlipidemia*. Combined familial hyperlipidemia is a genetic lipid disorder that accounts for 10–20% of premature CAD worldwide. Affected individuals' exhibit hypercholesterolemia and/or hypertriglyceridemia and elevated concentrations of *APO B*, with low values of HDL-c. These are collectively called iatrogenic lipoproteinemia phenotype. There have been demonstrations of alterations in common genetic loci between families of both combined familial hyperlipidemia phenotype and iatrogenic lipoproteinemia phenotype. Such loci include genes of superoxide manganese dismutase, transport

proteins of cholesteryl esters/lecithin, cholesterol acyl transferase and *AI-CIII-AIV*, as well as a great variety of studies relating polymorphisms in the promoter region of the *LH* gene (C-480T and C-514T polymorphisms) with lowering on plasma levels of HDL-c^{48,49}.

6. *LPL* gene - lipoprotein lipase, *Apo CII* and familial dyslipidemia type *O* or familial chylomicronemia. Any mutations on the *LPL* gene, which results in a partial deficiency of the enzyme, will cause an increase in TG concentration. This is the basis of familial chylomicronemia, familial dyslipidemia type I or familial hypertriglyceridemia⁵⁰. These are monogenic diseases with autosomal recessive inheritance, consisting with pure hypertriglyceridemia, TG values of 300 to 800 mg/dl, cholesterol <240 mg/dl, increases in VLDL and CMs, and lowering of LDL-c and HDL-c. To date, some *LPL* variants have been characterized because of amino acids substitutions in different positions (D9N, N291S, substitutions of glycine for glutamine on codon 188 and serine for a termination signal on codon 447)⁵¹. The enzymatic activity of *LPL* is also lowered by mutations on the *ApoC2* gene, located on chromosome 19q and codifies an essential activator of *LPL*⁵².

This information justifies the use of genetic markers for early diagnosis and cardiovascular risk assessment, especially in children and adolescents, in order to adopt early nutritional or pharmacologic interventions with the aim to mitigate atherosclerotic artery disease.

Lipoprotein lipase

The *LPL* gene is located on the short arm of chromosome 8, on the region 21.3 (8p21.3). It is formed of 10 exons and 9 introns (Figure 1), and the gene codifies a protein of 475 amino acids^{53,54}.

LPL is a multifunctional glycoprotein enzyme that plays an important role on lipid metabolism. After being secreted, it adheres to the luminal surface of endothelial cells where it hydrolyzes TG in circulating lipoproteins. This constitutes the limiting step on lipoprotein elimination, such as CMs from exogenous sources, and those endogenous sources, like VLDL, in circulation^{55,56}.

In this way, *LPL* affects serum levels of TG, generating lipoprotein remnants that are processed by hepatic lipase. Recently, it

has been demonstrated that *LPL* serves as a ligand for the protein related to the LDLR and influences hepatic secretion and VLDL and LDL-c capture⁵⁷. Additionally, *LPL* has been linked to the retention of LDL-c by the sub-endothelial matrix and arterial wall, increasing LDL and VLDL conversion into more atherogenic forms⁵⁸. Genetic modifications can affect *LPL* activity, which results in changes in lipid metabolism. Examples are slow hydrolysis of CMs and VLDL-c, longer LDL-c half-life, and decreased production of HDL^{59,60}.

Around 100 mutations have been described on the *LPL* gene. The most frequent are Asp9sn, Gly188Glu and Asn291Ser. The mutations in the homozygous form are associated with hyperlipoproteinemia type I (familial chylomicronemia). Heterozygous mutations have a significant incidence in the general population (3–7%) and leads to up to a 50% decreased activity of *LPL*, causing an increase in TG and a decrease in HDL-c. All these lipid profile patterns increase the risk of CVD⁶¹.

LPL gene polymorphisms

Genetic studies have revealed around 100 mutations and polymorphisms in simple nucleotides on the *LPL* gene, some are protective, which others are deleterious:

1. *Ser447x (rs328) polymorphism* is located in exon 9, where cytosine is substituted by guanine on position 1959. This polymorphism leads to the suppression of both final amino acids, serine and glycine on position 447 of the protein that codifies a *LPL* protein prematurely truncated, which has increased lipolytic activity and increased levels of post-heparin *LPL* activity in X447 carriers. This is associated with the variant Ser447X, with low levels of TG, small increases of HDL-c levels, and a moderate CVD risk reduction⁶².
2. *PvuII (rs285) polymorphism*, located on intron 6, is located 1.57 kb from the Splicing Acceptor (SA) site. This polymorphism is the product of a change of cytosine for thymine. The region that contains the *PvuII* site is similar to the site of splicing, which interferes with the correct splicing of mRNA. However, the physiological role of this polymorphism is not completely clear yet, since it does not alter the serum concentration of lipids, nor the amino acid sequence, and a previous meta-analysis suggests that cardiovascular risk is not influenced by this polymorphism⁶³.

Figure 1. Chromosomal origin of the *LPL* gene. The authors confirm that this is an original image and has not been re-used or adapted from another source.

3. *HindIII* (rs320) polymorphism is one of the most common polymorphisms of *LPL* gene (see below).

HindIII (rs320) polymorphism

HindIII is a transition of intronic bases of thymine (T) to guanine (G) on position 495 of intron 8 of the *LPL* gene, which eliminates the restriction site for the *HindIII* enzyme (Figure 2 and Figure 3).

HindIII is one of the most frequent polymorphisms found in various studies, which show that the homozygous genotype T/T

Figure 2. Recognition sequence of *HindIII* enzyme. The authors confirm that this is an original image and has not been re-used or adapted from another source.

(H⁺/H⁺) represents from 45.1 to 56.4% of Iranian and south Indian populations, respectively most frequent, followed by the heterozygous T/G with 35.8–36.6% and homozygous G/G (H⁻/H⁻), with 6.93–19%^{64,65}. Similar results have been reported in Europe^{66,67} and Brazil⁶⁸.

The allele H⁺ (presence of thymine “T” or restriction site of *HindIII* enzyme) results in a cut on the base pair sequence in two bands of 217pb and 139pb. This is associated with a decrease in the activity of *LPL* in comparison with the allele H⁻ (presence of “G” or absence of the enzymatic restriction site or presence of *HindIII* polymorphism). With 137pb, in which there is no cut in the *LPL* gene intron 8 sequence, maintaining a unique sequence of 356pb (Figure 4)⁶⁹, leading to both alterations in lipidic metabolism and cardiovascular risk profile modifications in these populations.

Some studies have demonstrated that the common allele (T or H⁺) is associated with lower levels of HDL-c in contrast with the uncommon allele (G or H⁻)^{70,71}. In addition, those individuals

INTRON 8	GTAATTAAAT	GTATTTTTCT	----- (≈ 330bp) -----	CGAGATGCTA
	CCTGGATAAT	CAAAGATTCA	AACCAACCTC	TTCCAGAAGG
	AAGATAATCT	CAACCTGTCT	CCGCAGCCCC	ACCCATGTGT
	TGAATTACAC	AGAGATCGCT	ATAGGATTTA	AAGC ^T TTTAT
	CTGGGATTTT	GCAAACTATA	GTGTGCTGTT	ATTGTTAATT
				TAAAAAACT

Figure 3. Intron 8, restriction site of *HindIII* (AAGCTT > AAGCGT). The authors confirm that this is an original image and has not been re-used or adapted from another source.

Figure 4. Enzymatic restriction sites in *HindIII*⁶⁹. The authors confirm that this is an original image and has not been re-used or adapted from another source.

with H+/H+ genotype had a higher concentration of serum levels of TG when compared with homozygous genotype H-/H-^{66,67,70,72}. Similarly, there have been reports of high serum levels of LDL-c⁷¹ and a higher global cardiovascular risk in patients who carry the common allele (T or H+), see [Table 1](#). Some studies had reported a significant drop in the *LPL* activity among carriers of the uncommon G allele when compared with the more common allele T⁵⁷.

LPL expressed by macrophages and other cells contained in the vascular walls is involved in the early atherogenic process and is associated with increased atherosclerosis. Overexpression of *LPL* is also associated with insulin resistance and HTN by increased sodium retention, inflammation, vascular remodeling, sympathetic nervous system activation, oxidative stress and vasoconstriction^{73–75}.

On the other hand, HTN (mostly systolic) has been shown to be associated with the polymorphism *HindIII* in the Mexican population in studies by Muñoz-Barrios *et al.*⁷⁶. Similarly, the homozygous genotype for the common allele (H+) was associated with a higher risk of myocardial infarction in patients older than 90 years old in contrast with carriers of the uncommon allele (H-), associated with a lower prevalence of cardiovascular complications⁷⁷. Clear associations were found between genotypes of *LPL HindIII* with HTN (H+/H+ with an OR: 2.13; 95% CI: 0.93-4.8)⁷² and smoking⁵⁸. In a more recent study, it was established that the presence of homozygous genotype for the common allele (H+/H+) of the *LPL* gene is a risk factor for a first episode of myocardial infarction⁶⁵. Conversely, studies by Imeni *et al.*⁷⁸ in an Iranian population, showed no statistically significant associations between CAD and genotypic distributions of *HindIII* polymorphism.

Recent studies have shown increased risk of stroke among those with *LPL* gene variations, particularly in the *HindIII* gene⁷⁹. He *et al.* reported a lower risk of stroke among patients with *HindIII* polymorphisms with allele G (G vs T; OR=0.78, CI95%=0.70-0.87, p<0.001). This pattern was observed in patients with ischemic stroke (G vs T. OR=0.84, CI95%=0.74-0.95, p=0.005) and hemorrhagic stroke (G vs. T; OR=0.60, CI95%=0.48-0.74, p<0.001)⁸⁰.

Table 1. Lipid disorders according *LPL* gene allele^{66,67,70–72}.

Serum lipid levels	Triglycerides	LDL	HDL
Common allele (H+)	High	High	Low
Uncommon allele (H-)	Low	Low	High

From a neurologic point of view, there is scant data associating homozygous common genotype (H+/H+) with the development of Alzheimer's disease of late appearance. This is founded on the *LPL* function in regulation cognitive function, mediated by cholesterol and Vitamin E transport to neuronal cells on the hippocampus and other brain areas⁶⁴. These investigations appear to indicate that the *HindIII* polymorphism might exert a positive influence in human metabolism, which translates into improved cardiac and cerebrovascular function.

Conclusions

Dyslipidemias are independent risk factors for atherosclerotic artery disease. High TC, TAG and LDL-C, as well as decreased serum HDL-C, are frequently associated with low physical activity and poor eating habits, but there is a large number of mutations and single nucleotide polymorphism related to a specific protein dysfunction within major lipoprotein metabolism pathways like CETP, ApoA, LCAT, LDL receptor, Apo B-100 and *LPL*.

In this regard, the *LPL* gene *HindIII* polymorphism (rare allele H-) poses a protective function through its role in producing an improved lipid profile (low TG and LDL-c and high HDL-c). On the other hand, the presence of common allele (T or H+) is associated with pro-atherogenic dyslipidemias and raised cardiovascular risk. The uncommon allele (G or H-) with an absence of restriction *HindIII* enzyme exhibits a lower prevalence of at least 20% according to the current available literature.

There are no studies in Venezuela that allows us to know the true prevalence of the *HindIII* polymorphism, nor to corroborate the association with changes in the lipid profile or an increased risk for cardiovascular diseases, so we suggest performing a national populational genetic study in search for this lipidic disorders with the aim to has a better understanding of the cardiovascular risk factors in Latin America.

Competing interests

No competing interests were disclosed.

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Carlos Aguilar-Salinas

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Authors of the paper "Dyslipidemia: Genetics, lipoprotein lipase and HindIII polymorphism" summarizes several papers published by Latin American researchers about lipid disorders. The document highlight the need for more studies about genetics of dyslipidemia in this region.

The main limitations of the study are:

- The paper covers a large number of topics. As a result, information is presented without a critical analyses. Since the HindIII polymorphism is the main issue under review, a large proportion of the review could be summarized and the HindIII polymorphism data extended. For example, the genes involved in familial hypoalphalipoproteinemia are enlisted partially (i.e. ABCA1 was not mentioned). It is not clear the reason to devote several paragraphs for FH genes when they are not related with the main topic of this review.
- Reasons for the large differences in the prevalence of the lipid disorders between Latin-American surveys could be critically discussed.
- The style of the manuscript could be upgraded. The flow of the information should be improved.
- It is kindly suggested to consider a redesign of the structure of the document.

Is the topic of the review discussed comprehensively in the context of the current literature?

Partly

Are all factual statements correct and adequately supported by citations?

Partly

Is the review written in accessible language?

Partly

Are the conclusions drawn appropriate in the context of the current research literature?

Partly

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 19 January 2018

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David J. Galton

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This review deals with the following genes involved in lipid metabolism: CETP, LCAT, LDL receptor, apoE, Lp(a), hepatic lipase and lipoprotein lipase. However it misses out details of the apoC3 gene which is the only one in which a specific therapy (volanesorsen) has been developed. A review of this can be found in Galton (2017)¹.

The authors then go on to deal with the Hind 111 polymorphism of Lipoprotein lipase. A common *HindIII* polymorphism in intron 8 (T/G) of the LPL gene has been found to be associated with altered plasma TG and HDL-cholesterol, and CAD risk in several studies, but they do not comment on its functional significance.

It is known that certain intronic sequence contain regulatory elements that are important for transcription and translational regulation of a gene. A recent study (Chen et al. (2008)²) showed that this Hind 111 polymorphism affects the binding site of a transcription factor that regulates the transcription of LPL gene. Electrophoretic mobility shift assays revealed that the *HindIII* site binds to a transcription factor and that the mutant allele has lower binding affinity than the wild type allele. Transcription assays containing the entire intron 8 sequence along with full-length human LPL promoter were carried out in COS-1 and human vascular smooth muscle cells. The mutant allele was associated with significantly decreased luciferase expression level compared to the wild type allele in both the muscle (3.394 ± 0.022 vs. 4.184 ± 0.028 ; $P=4.7 \times 10^{-6}$) and COS-1 (11.603 ± 0.409 vs. 14.373 ± 1.096 ; $P<0.0001$) cells. This study demonstrates for the first time that the polymorphic *HindIII* site in the LPL gene is functional because it affects the binding of a transcription factor and it also has an impact on LPL expression.

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Is the topic of the review discussed comprehensively in the context of the current literature?

Partly

Are all factual statements correct and adequately supported by citations?

Yes

Is the review written in accessible language?

Yes

Are the conclusions drawn appropriate in the context of the current research literature?

Yes

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