Dyslipidemia: Genetics, lipoprotein lipase and HindIII polymorphism [version 2; referees: 2 approved]

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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.

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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 world. Cardiovascular disease (CVD) constitutes the greatest cause of morbidity and mortality globally with a high incidence in countries of all economic categories. 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 CVD. In addition, hypertriglyceridemia and mixed dyslipidemias have been associated with the aggregation of metabolic risk factors, like hypertension (HTN) and obesity.

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).

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 growth. The factors are undoubtedly related to high calorie intake described by other Western nations, while lower prevalence has been reported for these pathologies in Canada and South Korea where 45% and 44.1% of their respective populations present evidence of dyslipidemia. The difference of prevalence in these nations is indisputably tied to lifestyle with various publications highlighting diets rich in fiber and low in fats and refined sugars.

In Brazil, de Souza et al., 2003 reported the most frequent dyslipidemias in their 1039 sample population were isolated low HDL-c (18.3%), hypertriglyceridemia (17.1%), and isolated hypercholesterolemia (4.2%). These results differ from those reported in the CARMELA study from Mexico between 2003 and 2005, where the incidence of dyslipidemia in 1722 person sample size reported 16.4% with hypercholesterolemia and 32.5% with hypertriglyceridemia - slightly higher than those reported in Brazil. The differences could be related to the food preferences within Mexico, which include greater amounts of fat, simple sugars, and processed ingredients. It must also be noted that these studies are over 10 years old as no more recent publications in Latin America were found. With the recent rise in dyslipidemias and obesity, these numbers do not necessarily reflect the current reality of these pathologies in the studied populations.

In Venezuela, the CARMELA study evaluated the prevalence of these lipid metabolism disorders in the city of Barquisimeto. The researchers found 59.6% of the 1824 subjects to suffer from dyslipidemia in 2003. A decade later, Linares et al. published a study of 1892 sample size from the city of Maracaibo, Venezuela showing a prevalence of 84.8% - the highest figure reported to date. The difference of prevalence is related both the ten year gap between the studies as well as the regional differences between the sample populations. Even though these two studies occurred in Venezuela, the two sites have different cultures, climate, and completely different nutritional food preferences. The diet of the latter is traditionally high in calories, protein, and carbohydrates with an elevated alcohol intake while only 40% of the former ever ate fast food or other foods outside the home.

In the majority of the studies of prevalences there is a clear tendency to evaluate younger populations, (22–24 years of age) as in the study by Barja et al. between 2009–2011 where 2900 school-age children were evaluated with the average age of 11.42±0.97 years old. Of this sample, 9.4% had isolated hypertriglyceridemia, 7.6% with low HDL-C, 4.9% with isolated hypercholesterolemia, 6.24% with atherogenic dyslipidemia, and 3.9% with mixed dyslipidemia. The existence of hyperlipidemia increases the potential for deposits on the tunica intima and the formation of arterial plaques. A correct early diagnosis of dyslipidemia allows for timely preventive intervention resulting in a reduction cardiovascular disease and facilitates the patient’s clinical treatment.

Dyslipidemia genetics

The association between family history of dyslipidemia and the risk of CVD is supported by a large body of evidence. 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.

Dyslipidemia is one of the most well characterized cardiovascular risk factors. 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 CVD.
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 concentration\textsuperscript{11}. 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\textsuperscript{24,25}. Total deficiency of lecithin cholesterol acyl transferase (LCAT) can be seen after transition of C→T in exon 4 (W147R), G→A in exon 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\textsuperscript{16,27}.

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

- **CEPT:** This mediates the exchange of lipids between lipoproteins. With high levels of CEP T, HDL are transionized into triglycerides (TGs), becoming the substrate for hepatic lipase where TGs are hydrolyzed. Apoproteína (Apo) A-1 is degraded in tubular renal cells and diminishes the amount of HDL-C - increasing the atherogenic potential. The polymorphism rs1801706 (c.*84G>A) of the CEP T gene is associated with CAD\textsuperscript{12}.

- **Familial hypoalphalipoproteinemia and HDL-C deficiency:** Approximately 50% of the HDL-C alterations are explained by polygenic effects in various chromosomal loci that control apolipoprotein expression (A-I, A-II, C-II, C-III y A-IV). Multiple genetic variations such as deletions, inversions, and substitutions of gene coding for apolipoproteins are associated with severe CAD\textsuperscript{13,20}.

- **LCAT:** This liver-synthesized enzyme circulates in plasma forming complexes with HDL and participating in the reverse transport of cholesterol. LCAT deficiencies cause an accumulation of free cholesterol in tissues. One of the most recent described gene alterations is the P-274-S polymorphism that affects biogenesis of HDL-C\textsuperscript{29} and favors development of CVD.

- **ABCA1:** This protein mediates the transport of cholesterol and phospholipids from the cells to LDL. The C-69-T polymorphism of the gene codifies this protein and alterations can result in lower levels of HDL-C with higher levels of TG in obese children\textsuperscript{15}. Additionally, the rs2515602, rs2275542, rs1800976, and rs4149313 polymorphisms are associated with obesity and can negatively affect one’s lipid profile base on one study performed on 535 Chinese patients\textsuperscript{31}.

- **FTO:** This includes a group of 45 genes related to obesity that were grouped together during phylogenetic analysis\textsuperscript{33} and perform an important function in the regulation of food ingestion. FTO mutations are associated with obesity, metabolic syndrome and CAD\textsuperscript{44}. The literature does not specify which lipid metabolism genes affect FTO, but the rs9939609 polymorphism is associated with low HDL-C levels.

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

- **LDLR gene - LDL-C receptor and familial hypercholesterolemia (FH):** 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)\textsuperscript{16}. FH, an autosomal dominant condition caused by mutations on the LDLR gene, is one of the best characterized genetic defects\textsuperscript{17,38}. Mutations on this lipoprotein or one of the proteins involved in its metabolism in duce hypercholesterolemia and elevated LDL-C - both factors predisposing to the premature CAD development.

- **APO B-100 gene – ligand of LDL-C receptor and Familial Apolipoprotein B dysfunction (hypercholesterolemia type B).** ApoB-100 is the principle apolipoprotein in LDL and the ligand of LDLR. The autosomal dominant dislipidemia know as Familial APO B-100 Dysfunction (FDB) and is due to mutations in ApoB-100\textsuperscript{39}. Recently two new mutations on this gene have been described - p.Arg1164Thr and p.Gln4494. These variants have problems with binding to LDLR\textsuperscript{40} where carriers of this mutation bear a greater cardiovascular risk.

- **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 to serve as the ligand for hepatic receptors for the remnants of the aforementioned lipoproteins and regulation of VLDL production. Alterations in this apoprotein cause hyperlipoproteinemia or Type III Hyperlipidemia (HLP III) where the plasma levels of cholesterol and triglycerides are increased\textsuperscript{36}. The polymorphisms in ApoE are associated with variations in plasma cholesterol levels where individuals with this allele mutation exhibit cholesterol levels 10% greater than average\textsuperscript{41}.

- **LPA Gene:** This is formed by a nucleus rich in cholesterol esters, phospholipids, and an ApoB-100 that contains a union site for LDL receptors, but still contains an ApoA molecule. Lp(a) consists of one of the most important cardiovascular risk factors and proves of greater significance when correlated with elevated levels of LDL-C - observed commonly in patients under 60 years old with CVA\textsuperscript{42}. Polymorphisms have been found consisting of variable repetitions of module 4 where the number of repetitions is inversely proportional to the plasma levels of Lp(a)\textsuperscript{43}. Recent work has encountered differences in the distribution of the diverse alleles of ApoA among patients with atherosclerosis and
the isoforms of low weight molecular B, S1, and S2. These are found most frequently in carriers of coronary insufficiency who also show elevated levels of Lp(a). This suggests that the short alleles of ApoA contribute to atherogenesis, increasing the plasma concentration of Lp(a).

- 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 atherogenic lipoproteinemia phenotype. (ALP). 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.

- ApoCII: Apoprotein CII: This Apo inhibits the activity of LPL. It is a component of the lipoprotein remnants that possess elevated TG levels. The loss of function of this Apo has been associated with low TG levels and a reduction of coronary artery calcification. The polymorphism C3175>G localized in region 3 presents in less than 5% of the population in the UK. Those who present with this polymorphism have elevated TGs and deficient LPL - augmenting the probability of developing CVA. Currently the pharmaceutical companies Isis and Ionis have developed an antisense oligonucleotide the blocks ARNm fora ApoCIII. This is currently in phase 2 of clinical trials and preliminary studies show a significant decline of TGs in patients with ApoCIII mutations.

- 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 hypertriglyceridemia; 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 4)7. The enzymatic activity of LPL is also lowered by mutations of the ApoCII gene, an essential activator of LPL. Specifically, the mutation R72T of the ApoCII gene causes severe hypertriglyceridemia and recurrent pancreatitis.

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.

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.

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 capture. 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 forms. 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.

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 CVD.

**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
Some studies had reported a significant drop in TBP binding affinity in polymorphism carriers, conferring functionality of said SNP. HindIII is one of the most frequent polymorphisms found in various studies, which show that the homozygous genotype T/T (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 Europe66,67 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-)30,31. In addition, those individuals with H+/H+ genotype had a higher concentration of serum levels of TG when compared with homozygous genotype H-1H- with 35.8–36.6% and homozygous G/G (H/H), with 6.93–19%64,65. Similarly, there have been reports of high serum levels of LDL-C61 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 T31.

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 vasoconstriction30–32.

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.36. 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 complications\textsuperscript{77}. Clear associations were found between genotypes of \textit{LPL HindIII} with HTN (H+/H+ with an OR: 2.13; 95% CI: 0.93–4.8)\textsuperscript{72} and smoking\textsuperscript{58}. In a more recent study, it was established that the presence of homzygous genotype for the common allele (H+/H+) of the \textit{LPL} gene is a risk factor for a first episode of myocardial infarction\textsuperscript{80}. Conversely, studies by Imeni et al.\textsuperscript{78} in an Iranian population, showed no statistically significant associations between CAD and genotypic distributions of \textit{HindIII} polymorphism.

Recent studies have shown increased risk of stroke among those with \textit{LPL} gene variations, particularly in the \textit{HindIII} gene\textsuperscript{79}. He et al. reported a lower risk of stroke among patients with \textit{HindIII} polymorphisms with allele G (G vs T; OR=0.78, CI\textsubscript{95%}=0.70–0.87, p<0.001). This pattern was observed in patients with ischemic stroke (G vs T; OR=0.84, CI\textsubscript{95%}=0.74–0.95, p=0.005) and hemorrhagic stroke (G vs T; OR=0.60, CI\textsubscript{95%}=0.48–0.74, p<0.001)\textsuperscript{80}.

In other studies, Imeni et al.\textsuperscript{86} evaluated the relationship between CAD risk and the distribution of \textit{HindIII} polymorphism genotypes and found no statistical significant differences between healthy Irani individuals and those with CAD history.

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

\textbf{Table 1. Lipid disorders according \textit{LPL} gene allele\textsuperscript{79,87,78–80}.}
Ahmadi et al. also showed no significant association between the gene and CAD in the 115 Swiss subjects evaluated. These findings are in contrast to the expected improved cardio-cerebral function expected and leave this line of research open for future investigations.

This polymorphism has not only been associated with HA, rather also with insulin resistance. This is best demonstrated with a study of 110 Asian females with gestational diabetes who were found to have a reduced resistance to insulin than carriers of this rare allele.

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 areas.

These investigations suggest that the presence of the HindIII polymorphism exerts a positive influence in lipid metabolism in patients with normal BMI. Future studies should focus in more detail on the protective function of this genetic factor in the general population.

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 lipid disorders with the aim to has a better understanding of the cardiovascular risk factors in Latin America.

Data availability
All data underlying the results are available as part of the article and no additional source data are required.

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References

1. Heikin A, Stein JJ, Lin S, et al.: Dyslipidemia Part 1—Review of Lipid Metabolism and Vascular Cell Physiology. Vasc Endovascular Surg. 2016; 50(2): 107–18.
2. Murray CJ, Lopez AD: Mortality by cause for eight regions of the world: Global Burden of Disease Study. Lancet. 1997; 349(9061): 1269–76.
3. Gordon DJ, Probstfield JL, Garrison RJ, et al.: High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Circulation. 1989; 79(1): 8–15.
4. Isomaa B, Almgren P, Tuomi T, et al.: Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care. 2001; 24(4): 683–9.
5. Carr MC, Brunzell JD: Abdominal obesity and dyslipidemia in the metabolic syndrome: importance of type 2 diabetes and familial combined hyperlipidemia in coronary artery disease risk. J Clin Endocrinol Metab. 2004; 89(6): 2601–7.
6. Onat A, Hergenç G, Sarı I, et al.: Dyslipidemic hypertension: distinctive features and cardiovascular risk in a prospective population-based study. Am J Hypertens. 2005; 18(3): 409–16.
7. Brown CD, Higgins M, Donato KA, et al.: Body mass index and the prevalence of hypertension and dyslipidemia. Obes Res. 2000; 8(9): 605–19.
8. Joffres M, Shields M, Tremblay MS, et al.: Dyslipidemia prevalence, treatment, control, and awareness in the Canadian Health Measures Survey. Can J Public Health. 2013; 104(3): e252–257.
9. İltan Ç, Beytullah Y, Şemsettin Ş, et al.: Serum lipid and lipoprotein levels, dyslipidemia prevalence, and the factors that influence these parameters in a Turkish population living in the province of Tokat. Turk J Med Sci. 2010; 40(5): 771–82.
10. Tóth PP, Potter D, Ming EE: Prevalence of lipid abnormalities in the United States: the National Health and Nutrition Examination Survey 2003–2006. J Clin Lipidol. 2012; 6(4): 325–30.
11. Lee MH, Kim HC, Ahn SV, et al.: Prevalence of Dyslipidemia among Korean Adults: Korea National Health and Nutrition Survey 1998–2005. Diabetes Metab J. 2012; 36(1): 43–55.
12. de Souza LF, Souza TF, de Souza TF, et al.: Prevalence of dyslipidemia and risk factors in Campos dos Goytacazes, in the Brazilian state of Rio de Janeiro. Arq Bras Cardiol. 2003; 81(3): 249–64.
13. Aguilar-Salinas CA, Gómez-Pérez FJ, Rull J, et al.: Prevalence of dyslipidemias in the Mexican National Health and Nutrition Survey 2006. Salud Publica Mex. 2010; 52 Suppl 1: 54–53.
14. Chiqui RA, Bermúdez V, Añez R, et al.: Prevalencia de dislipidemia y factores asociados en la ciudad de Cuenca, Ecuador. Síndrome Cardiometálico 2014; (4(2)): 31–41. Reference Source

15. Vinueza R, Boisson CP, Acedo M, et al.: Dislipidemia en seven Latin American cities: CARMELA study. Prev Med 2010; 50(3): 106–11. Published Abstract | Publisher Full Text

16. Linares S, Bermúdez V, Rojas J, et al.: Prevalence of dislipidemias and factores psicobiológicos asociados en individuos adultos del municipio Maracaibo, Venezuela. Síndrome Cardiometálico. [Internet]. 2015; 3(3): 63–75. Reference Source

17. Bermúdez V, Salazar J, Rojas J, et al.: Prevalence, Lipid Abnormalities and Risk Factors Associated with Low HDL-C Levels in Maracaibo City, Venezuela. J J Commun Med. 2015; 1(2): 9. Reference Source

18. Miller M: Dyslipidemia and cardiovascular risk: the importance of early prevention. QJM. 2009; 102(9): 657–667. Published Abstract | Publisher Full Text | Full Free Text

19. Gus J, Rotter J, Sparks R, et al.: Molecular Genetics of Coronary Artery Disease: Candidate Genes and Processes in Atherosclerosis. Monograph Hum Genet. Karger, 1992; 14: I–XVII. Publisher Full Text

20. Genest JJ Jr, Macnair M, O'Brien J, et al.: Familial lipoprotein disorders in patients with premature coronary artery disease. Circulation. 1992; 85(6): 2025–2033. Published Abstract | Publisher Full Text

21. Aulchenko YS, Ripatti S, Lindqvist I, et al.: Low Lp(a) level is strongly associated with long-term coronary heart disease risk in European population cohorts. Nat Genet. 2009; 41(1): 47–55. Published Abstract | Publisher Full Text | Free Full Text

22. Nordestgaard BG, Chapman MJ, Humphries SE, et al.: Apolipoprotein E polymorphism and cardiovascular disease: a HuGE review. Am J Epidemiol. 2002; 156(5): 487–495. Published Abstract | Publisher Full Text

23. Schmidt K, Noureen A, Kronenberg F, et al.: Structure, function, and genetics of lipoprotein (a). J Lipid Res. 2016; 57(8): 1339–1359. Published Abstract | Publisher Full Text | Free Full Text

24. Bucci M, Tava C, Giambertino MA, et al.: Lp(a) and cardiovascular risk: Investigating the hidden side of the moon. Nutr Metab Cardiovasc Dis. 2016; 26(11): 980–986. Published Abstract | Publisher Full Text

25. Bermúdez V, Arraiz N, Cano C, et al.: Lipoprotein (a): molecular and epidemiologic basis about its role in cardiovascular diseases. Revista Latinoamericana de Hipertension. 2008; 3(4): 113–122. Reference Source

26. Bermúdez V, Arraiz N, Rojas E, et al.: Abnormally high lipoprotein (a) levels in aboriginal american communities from venezuela faced to other african-descending populations: Are ethnic origins related? Revista Latinoamericana de Hipertension. 2008; 3(3): 66–72. Reference Source

27. Parson W, Kraft HG, Niederstrasser H, et al.: A common nonsense mutation in the repetitive kringle iv-2 domain of human apolipoprotein a (a) results in a truncated protein and low plasma Lp (a). Hum Mutat. 2004; 24(6): 474–480. Published Abstract | Publisher Full Text

28. Verma P, Verma DK, Sethi R, et al.: The rs2070895 (-250G/A) Single Nucleotide Polymorphism in Hepatic Lipase (HL) Gene and the Risk of Coronary Artery Disease in North Indian Population: A Case-Control Study. J Clin Diagn Res. 2015; 19(1): GC01–GC06. Published Abstract | Publisher Full Text | Free Full Text

29. Eicher JE, Dunn ST, Perveen G, et al.: Apolipoprotein E polymorphism and cardiovascular disease: a HuGE review. Am J Epidemiol. 2002; 156(5): 487–495. Published Abstract | Publisher Full Text

30. Stroes ES, Moulin P, Parhofer KG, et al.: Diagnostic algorithm for familial chylomicronemia syndrome. Atheroscler Suppl. 2017; 23(Supplement C): I–7. Published Abstract | Publisher Full Text

31. Clees SM, Loubser OJ, Collins J, et al.: The LPL S447X SNP is associated with decreased blood pressure and plasma triglycerides, and reduced risk of coronary artery disease. Clin Genet. 2001; 60(4): 293–300. Published Abstract | Publisher Full Text

32. Baggs G, Manzato E, Gabelli C, et al.: Apolipoprotein C-II deficiency syndrome. Clinical features, lipoprotein characterization, lipase activity, and correction of hypertriglyceridemia after apolipoprotein C-II administration in two affected patients. J Clin Invest. 1996; 97(2): 525–527. Published Abstract | Publisher Full Text | Free Full Text

33. Oka K, Tkacovic GT, Nakano T, et al.: Structure and phosphomorph of human lipoprotein lipase gene. Biochim Biophys Acta. 1990; 1049(1): 21–6. Published Abstract | Publisher Full Text | Free Full Text

34. Deeb SS, Peng RL, Song T, et al.: Structure of the human lipoprotein lipase gene. Biochemistry. 1989; 28(10): 4313–5. Published Abstract | Publisher Full Text

35. Eckel RH: Lipoprotein lipase. A multifunctional enzyme relevant to common metabolic diseases. N Engl J Med. 1989; 320(16): 1060–8. Published Abstract | Publisher Full Text

36. Baggio G, Manzato E, Gabelli C, et al.: Apolipoprotein C-II deficiency syndrome. Clinical features, lipoprotein characterization, lipase activity, and correction of hypertriglyceridemia after apolipoprotein C-II administration in two affected patients. J Clin Invest. 1996; 97(2): 525–527. Published Abstract | Publisher Full Text | Free Full Text

37. Eckel RH: Lipoprotein lipase. A multifunctional enzyme relevant to common metabolic diseases. N Engl J Med. 1989; 320(16): 1060–8. Published Abstract | Publisher Full Text

38. Wang H, Eckel RH: Lipoprotein lipase: from gene to obesity. Am J Physiol Endocrinol Metab. 2009; 297(2): E271–288. Published Abstract | Publisher Full Text

39. Fernández-Borja M, Belloso D, Viella E, et al.: 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. Published Abstract

40. Daoud MS, Ataya FS, Fouda D, et al.: Associations of three lipoprotein lipase

Page 9 of 13
gene polymorphisms, lipid profiles and coronary artery disease. Biomed Rep. 2013;1(4): 573–82. PubMed Abstract | Publisher Full Text | Free Full Text

59. Gerdes C, Gerdes LU, Hansen PS, et al.: 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. PubMed Abstract | Publisher Full Text

60. Heizmann C, Kirchgessner T, Kwiterovich PO, et al.: DNA polymorphism haplotypes of the human lipoprotein lipase gene: possible association with high density lipoprotein levels. Hum Genet. 1991; 86(6): 578–84. PubMed Abstract | Publisher Full Text

61. Petrescu-Dănilă E, Voicu PM, Ionescu CR: [Mutagenic aspects of the lipoprotein lipase gene]. Rev Med Chir Soc Med Nat Iasi. 2003; 107(3): 257–87. PubMed Abstract | Publisher Full Text

62. Groenemeijer BE, Hallman MD, Reymer PW, et al.: Lipoprotein lipase gene polymorphism and risk of myocardial infarction in South Indian population. J Stroke Cerebrovasc Dis. 2004; 13(6): 313–20. PubMed Abstract | Publisher Full Text

63. Cagatay P, Susleyici-Duman B, Ciftci C: Polymorphism serum lipids and risk for coronary artery disease: meta-analysis. Dis Markers. 2007; 23(3): 161–6. PubMed Abstract | Publisher Full Text | Free Full Text

64. Sayad A, Noruzinia M, Zarnami M, et al.: Lipoprotein Lipase HindIII Intronic Polymorphism in a Subset of Iranian Patients with Late-Onset Alzheimer’s Disease. Cell J. 2012; 14(1): 67–72. PubMed Abstract | Publisher Full Text | Free Full Text

65. Tanguturi PR, Pullareddy B, Krishna BR, et al.: Lipoprotein lipase gene HindIII polymorphism and risk of myocardial infarction in South Indian population. Indian Heart J. 2013; 65(6): 603–607. PubMed Abstract | Publisher Full Text | Free Full Text

66. Georges JL, Régis-Bailly A, Salah D, et al.: Family study of lipoprotein lipase gene polymorphisms and plasma triglyceride levels. Genet Epidemiol. 1996; 13(2): 179–92. PubMed Abstract | Publisher Full Text | Free Full Text

67. Mathi RK, Needham EW, Morgan R, et al.: DNA variants at the LPL gene locus associate with angiographically defined severity of atherosclerosis and serum lipoprotein levels in a Welsh population. Arterioscler Thromb. 1994; 14(7): 1090–7. PubMed Abstract | Publisher Full Text

68. Rios DL, Vargas AF, Ewald GM, et al.: Common variants in the lipoprotein lipase gene in Brazil: association with lipids and angiographically assessed coronary atherosclerosis. Clin Chem Lab Med. 2003; 41(10): 1351–6. PubMed Abstract | Publisher Full Text

69. Larson I, Hoffmann MM, Or dovas JM, et al.: The lipoprotein lipase HindIII polymorphism: association with total cholesterol and LDL-cholesterol, but not with HDL and triglycerides in 342 females. Clin Chim. 1999; 48(7): 963–8. PubMed Abstract

70. Razzaghi H, Aton CE, Hanman RF, et al.: Genetic screening of the lipoprotein lipase gene for mutations associated with high triglyceride/low HDL-cholesterol levels. Hum Genet. 2000; 107(3): 257–87. PubMed Abstract | Publisher Full Text

71. Holmer SR, Hengstenberg C, Mayer B, et al.: Lipoprotein lipase gene polymorphisms, cholesterol subfractions and myocardial infarction in large samples of the general population. Cardiovasc Res. 2000; 47(4): 806–12. PubMed Abstract | Publisher Full Text

72. Hemimi N, Salam ME, Abdi-Elewa M: The Lipoprotein Lipase HindIII Polymorphism And The Susceptibility To Hypertension. Egypt J Biochem Mol Biol. 2005; 27(1). PubMed Full Text

73. Goodarzi MO, Guo X, Taylor KD, et al.: Lipoprotein lipase is a gene for insulin resistance in Mexican Americans. Diabetes. 2004; 53(1): 214–20. PubMed Abstract | Publisher Full Text

74. Mead JR, Cryer A, Ramji DP: Lipoprotein lipase, a key role in atherosclerosis? FEBS Lett. 1999; 462(1–2): 1–6. PubMed Abstract | Publisher Full Text

75. McFarlane SI, Banerji M, Sowers JR: Insulin resistance and cardiovascular disease. J Clin Endocrinol Metab. 2001; 86(2): 713–8. PubMed Abstract | Publisher Full Text

76. Muñoz-Barrios S, Guzmán-Guzmán IP, Muñoz-Valle JF, et al.: 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. PubMed Abstract | Publisher Full Text | Free Full Text

77. Malgina NA, Memet’ev AS, Kostomarov IV, et al.: [Connection of HindIII-polymorphism in the lipoprotein lipase gene with myocardial infarct and life span in elderly ischemic heart disease patients]. Mol Biol (Mosk). 2001; 35(5): 787–91. PubMed Abstract

78. Imeni M, Hasanzad M, Noji T, 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. Publisher Full Text

79. Shimo-Nakanishi Y, Urabe T, Hattori N, et al.: Association between Lipoprotein Lipase Polymorphism and the Risk of Stroke: A Meta-analysis. J Stroke Cerebrovasc Dis. 2017; 26(11): 2570–2578. PubMed Abstract | Publisher Full Text
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Version 2

Referee Report 01 October 2018
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No additional comments.

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Referee Report 05 March 2018
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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 paragrapjs 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 have read this submission. I 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.

Referee Report 19 January 2018

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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 × 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.

References
1. Galton DJ: Clarifying complex inheritance: apolipoprotein C3 and atherosclerosis. *Curr Opin Lipidol*. 2017; 28 (4): 308-312 PubMed Abstract I Publisher Full Text
2. Chen Q, Razzaghi H, Demirci FY, Kamboh MI: Functional significance of lipoprotein lipase HindIII polymorphism associated with the risk of coronary artery disease. *Atherosclerosis*. 2008; 200 (1): 102-8 PubMed Abstract I Publisher Full Text

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

**Competing Interests:** No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.