View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Elsevier - Publisher Connector

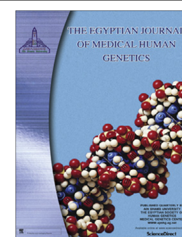
The Egyptian Journal of Medical Human Genetics (2015) 16, 327–332

HOSTED BY

Ain Shams University

The Egyptian Journal of Medical Human Genetics

www.ejmhg.eg.net
www.sciencedirect.com



ORIGINAL ARTICLE

Lipoprotein lipase gene variants: Association with acute myocardial infarction and lipid profiles

Mahyar Bahrami [a], Hamzeh Barati [b], Mohammad Mehdi Jahani [c], Ahmad Fatemi [d], Zohre Sharifi [e], Akram Eydi [b], Sadegh Alipoor [f], Taghi Golmohammadi [g,*]

[a] *Department of Periodontology, School of Dentistry, Shahed University, Tehran, Iran*
[b] *Department of Biology, Sciences & Research Branch, Islamic Azad University, Tehran, Iran*
[c] *Faculty of Veterinary Science, Shahrekord Islamic Azad University, Shahrekord, Iran*
[d] *Department of Hematology, School of Allied Medical Sciences, Iran University of Medical Sciences, Tehran, Iran*
[e] *Blood Transfusion Research Center, High Institute for Research and Education in Transfusion Medicine, Tehran, Iran*
[f] *Department of Nutrition, School of Health, Yasouj University of Medical Sciences, Yasouj, Iran*
[g] *Department of Biochemistry, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran*

Received 17 March 2015; accepted 6 April 2015
Available online 13 May 2015

KEYWORDS

Myocardial infarction;
Lipid metabolism;
Lipoprotein lipase;
rs320;
rs285;
Polymorphism

Abstract *Background:* Studies showed that lipid metabolism disorders are significant risk factors for myocardial infarction and coronary artery disease (CAD). Therefore, genes involved in lipid and lipoprotein metabolism pathways such as lipoprotein lipase (*LPL*), are proper candidates for susceptibility to CAD.

Aim: To investigate the possible association between *LPL* gene variants (HindIII (rs320) and PvuII (rs285)), acute myocardial infarction (AMI) and serum lipid levels.

Subjects and methods: The study population consisted of 211 patients with a diagnosis of premature AMI, and 203 age-matched individuals with normal coronary angiograms as controls. Genotyping of HindIII and PvuII polymorphisms was done by the PCR-RFLP technique.

* Corresponding author at: Department of Biochemistry, School of Medicine, Tehran University of Medical Science, Tehran, Iran. Tel.: +98 2188953004; fax: +98 2164053384.
E-mail address: golmoham@sina.tums.ac.ir (T. Golmohammadi).

Peer review under responsibility of Ain Shams University.

http://dx.doi.org/10.1016/j.ejmhg.2015.04.001
1110-8630 © 2015 The Authors. Production and hosting by Elsevier B.V. on behalf of Ain Shams University.
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Results: Although the H^+ and P^+ alleles were more observed among the patients, there were no significant differences in genotype distributions and allele frequencies of HindIII and PvuII polymorphisms between patient and control subjects ($P > 0.05$). Triglyceride levels were found to be significantly elevated in H^+H^+ and P^+P^+ genotypes compared to others ($P < 0.05$). However, there was no association between HindIII and PvuII genotypes and HDL-C, LDL-C and cholesterol levels.

Conclusion: Our findings indicate that LPL-HindIII and PvuII polymorphisms are not associated with acute myocardial infarction but with triglyceride levels.

© 2015 The Authors. Production and hosting by Elsevier B.V. on behalf of Ain Shams University. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Epidemiological and clinical studies showed that lipid metabolism disorders such as elevated levels of total cholesterol (TC), triglycerides (TGs), low density lipoprotein cholesterol (LDL-C) and low levels of high-density lipoprotein cholesterol (HDL-C) are significant risk factors for myocardial infarction and coronary artery disease [1,2]. Therefore, genes involved in lipid and lipoprotein metabolism pathways including lipoprotein lipase (*LPL*), are proper candidates for susceptibility to CAD [3].

The human LPL (EC 3.1.1.34) is a 448 amino acid glycoprotein that is synthesized and secreted by many tissues and then transported to the luminal surface of vascular endothelial cells. LPL hydrolyzes triglyceride-rich lipoproteins including chylomicrons and very-low-density lipoprotein (VLDL) and hence plays a central role in lipid metabolism [4,5]. Accordingly, any deficiency in LPL activity could lead to disturbance in lipid metabolism associated with clinical hyperlipidemia and coronary artery diseases [6].

LPL gene spans over 30 Kb on chromosome 8p22 and composed of 10 exons and 9 introns [7]. The association between several polymorphic sites of *LPL* gene including the T-93G (rs1800590), D9N (rs1801177), G188E, N291S (rs268), PvuII (rs285), HindIII (rs320), and S447X (rs328) and CAD risk was investigated in several studies [8–10]. The HindIII polymorphism (rs320) is located in position 495 of *LPL* gene's intron 8th. In this single nucleotide polymorphism (SNP) the ancestral allele (T) is substituted by (G) allele [11]. This nucleotide substitution abolished a restriction site for HindIII. There are supporting evidences which suggest that the common allele (H^+) is significantly associated with high TG and low HDL levels compared to the H^- allele [12,13]. The PvuII polymorphism (rs285) is the result of C into T transition in the LPL gene intron 6th [11]. Previous studies showed that The P^+ allele is associated with high TG and low HDL-C levels [14,15]. However, the association of HindIII and PvuII variants with CAD and serum lipid levels remained to be controversial.

We aimed here to investigate the possible association between LPL gene variants (HindIII (rs320) and PvuII (rs285)), acute myocardial infarction (AMI) and serum lipid levels in an Iranian population through a case-control study.

2. Subjects and methods

2.1. Subjects

The study population consisted of 211 patients with a diagnosis of premature AMI and the age of $\leqslant$50 years who were hospitalized at the Shaheed Rajaei Cardiovascular Center, Tehran, Iran between September 2011 and August 2013. As a control group, 203 age-matched individuals with normal coronary angiograms were recruited from the same demographic area. Two cardiologists confirmed diagnosis of AMI according to the new criteria of the American College of Cardiology and the European Society of Cardiology definition [16]. To obtain clinical information including MI type (STEMI or NSTEMI) and cardiac markers (troponin and creatine kinase-MB) we inspected the medical records. Diabetic patients were excluded from the study. The study adhered to the principles of the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000) and has been approved by Tehran University of medical sciences Ethics Committee and all subjects gave their written informed consent.

2.2. Biochemical analysis

We took blood samples after fasting for 12 h. Serum levels of lipid parameters including TC, TG and HDL-cholesterol were measured enzymatically. We calculated LDL-cholesterol levels by Friedewald equation.

2.3. DNA analysis

We extracted total genomic DNA from EDTA anticoagulated whole blood by Miller's method [17]. Genotyping of HindIII and PvuII polymorphisms was done by the PCR-RFLP technique. For HindIII variant, PCR amplification was performed by following primers: 5′-ACATAAGCACTGAATCGCTCAC-3′ (forward primer) and 5′-CTTCAGCTAGACATTGCTAGTGT-3′ (reverse primer). The cycling condition was as follows: 94 °C for 5 min followed by 30 cycles comprising of 95 °C for 45°s, annealing time at 62 °C for 40 s and extension at 72 °C for 35 s with final extension time of 7 min at 70 °C. For determination of HindIII genotypes, the PCR products (476 bp) were digested by 10 U of HindIII restriction enzyme at 37 °C for 16 h. The resulting fragments separated on a SYBR Green stained 2.5% agarose gel included 476 bp fragment for H^-H^- (GG), 476, 259 and 217 bp fragments for H^+H^- (GT) and 259 and 217 bp fragments for H^+H^+ (TG).

Amplification of the PvuII polymorphism carried out by the forward 5′-AAACCTGAGGGAAGGGATGATA-3′ and reverse 5′-TGCTGCTTTAGACTCTTGTCCA-3′ primers. The cycling condition was as follows: 94 °C for 5 min followed by 30 cycles comprising of 95 °C for 45 s, annealing time at 62 °C for 40 s and extension at 72 °C for 40 s with final extension time of 7 min at 70 °C. The PCR product (529 bp) was

digested with 10 units of PvuII restriction enzyme and products separated on a SYBR Green stained 2.5% agarose gel. For the P^-P^- (TT), P^+P^- (TC) and P^+P^+ (CC) genotypes, 529 bp band, 529, 374 and 155 bp bands, and 374 and 155 bp bands were observed, respectively.

2.4. Statistical analysis

Statistical analysis was carried out by Statistical Software Package for the Social Science (SPSS 18.0, Chicago). The quantitative parameters were expressed as mean ± SD and compared by Student's *t*-tests. Genotype distributions and compatibility of which with Hardy–Weinberg equilibrium expectations were checked by chi-square test. Analysis of variance (ANOVA) and Post Hoc tests were performed for the relationship between LDL, HDL, cholesterol and TG levels with LPL genotypes. The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated as a measure of the association of HindIII (rs320) and PvuII (rs285) polymorphisms with acute myocardial infarction. P values less than 0.05, were considered to be significant.

3. Results

A summary of the baseline characteristics of patients and control subjects (211 patients and 203 controls) is presented in Table 1. MI patients showed higher total cholesterol ($P = 0.002$), triglycerides ($P = 0.014$) and LDL-C ($P = 0.001$) compared to the control group. There were no significant differences in BMI and HDL-C level between the two groups ($P > 0.05$). Moreover, the prevalence of hypertension, hyperlipidemia and smoking was significantly higher in patients group than in the control group ($P < 0.05$). The distributions of the LPL genotypes were compatible with Hardy–Weinberg equilibrium ($P > 0.05$). As shown in Table 2, although the H^+ and P^+ alleles were more observed among the patients, there were no significant differences in the genotype distributions and allele frequencies of HindIII and PvuII polymorphisms between patient and control subjects ($P > 0.05$). As well as, we did not find significant differences between rs285 $P^-P^+ + P^+P^+$ versus P^-P^- and rs320 $H^-H^+ + H^+H^+$ versus H^-H^- genotype ratios and AMI ($P > 0.5$). The association between LPL genotypes and lipid levels is summarized in Table 3. As shown in this table, subjects with P^+P^+ genotypes have a high triglyceride level compared to P^-P^- and P^+P^- ($P = 0.05$). For rs320, triglyceride levels were found to be significantly elevated in H^+H^+ genotypes in comparison with others ($P = 0.04$). These results were confirmed by Post-hoc analysis. However, there was no significant association between HindIII and PvuII genotypes and HDL, LDL and cholesterol levels.

Table 1 Demographic and clinical characteristics of the study population.

Parameter	Control group ($n = 203$)	Case group ($n = 211$)	P
Sex (male/female)	90/113	125/86	0.002**
Age (years)	44.7 ± 6.8	46.32 ± 5.2	>0.05
Body Mass Index (kg/m^2)	25.6 ± 4.23	26.5 ± 6.39	0.195
Systolic blood pressure (mmHg)	12.81	13.32	0.055
Diastolic blood pressure (mmHg)	7.86	8.31	0.024*
Smoking (yes/no)	58/145	80/131	0.044*
Hypertension (yes/no)	68/135	97/114	0.010**
Hyperlipidemia (yes/no)	73/130	103/108	0.008**
Family history of CAD (yes/no)	41/162	58/153	0.082
LDL-C (mg/dl)	98.76 ± 22.75	106.55 ± 28.41	0.002**
HDL-C (mg/dl)	41.24 ± 9.1	39.55 ± 9.45	0.066
TG (mg/dl)	156.18 ± 57.38	173.04 ± 79.42	0.014*
TC (mg/dl)	167.17 ± 35.16	179.23 ± 40.76	0.001**

Data are expressed as mean ± standard deviation.
Abbreviations: CAD, coronary artery disease; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; TG, triglycerides; TC, total cholesterol.
* Statistically significant at ⩽0.05.
** Statistically significant at ⩽0.01.

4. Discussion

LPL plays a critical role in lipid metabolism via chylomicrons and VLDL hydrolysis [4]. Genetic polymorphisms could alter the LPL activity and hence modulate individual's susceptibility to lipid metabolism disorders. It has been shown that LPL variants are associated with clinical hyperlipidemia which contributes to different pathogenic conditions including MI [18].

In the present study, we examined the association of the LPL-HindIII and LPL-PvuII variants with MI in an Iranian population through a case-control study. It should be noted that although all the participants in this study were Iranians, they belonged to different Iranian ethnic groups and therefore, our results should be interpreted carefully.

Although the H^+ and P^+ alleles were more observed among the patients, we could not find a statistically significant difference. Moreover the genotype distribution between the

Table 2 Genotype distribution and relative allele frequencies of HindIII (rs320) and PvuII (rs285) polymorphisms.

Genotypes	Control group ($n = 203$)	Case group ($n = 211$)	P
HindIII (rs320)			
H^-H^-	19 (9.36%)	14 (6.63%)	
H^+H^-	83 (40.89%)	81 (38.39%)	
H^+H^+	101 (49.75%)	116 (54.98%)	0.435
Allele frequency			
H^-	121 (29.8%)	109 (25.83%)	
H^+	285 (70.2%)	313 (74.17%)	0.202
PvuII (rs285)			
P^-P^-	38 (18.72%)	32 (15.17%)	
P^-P^+	93 (45.81%)	101 (47.86%)	
P^+P^+	72 (35.47%)	78 (36.97%)	0.628
Allele frequency			
P^-	169 (41.62%)	165 (39.1%)	
P^+	237 (58.37%)	257 (60.9%)	0.459

Table 3 Association of HindIII (rs320) and PvuII (rs285) polymorphisms with lipid profile.

	TC (mg/dl)	TG (mg/dl)	LDL-C (mg/dl)	HDL-C (mg/dl)
H^-H^-	175.28 ± 34.33	111.85 ± 25.08	94.00 ± 17.78	44.42 ± 7.54
H^-H^+	198.76 ± 39.54	137.93 ± 44.74	102.35 ± 28.74	41.05 ± 9.16
H^+H^+	169.00 ± 41.84	164.63 ± 57.93	85.65 ± 27.90	39.76 ± 10.06
P	0.06	0.04*	0. 15	0.51
P^-P^-	159.54 ± 44.70	107.75 ± 29.17	83.09 ± 32.94	40.09 ± 10.53
P^-P^+	181.76 ± 46.79	144.62 ± 61.5	95.15 ± 29.05	38.79 ± 8.68
P^+P^+	198.94 ± 39.13	170.13 ± 60.78	102.36 ± 27.14	43.36 ± 9.80
P	0.07	0.05*	0.22	0.22
P^-P^+/P^+P^+	187.39 ± 44.82	153.31 ± 61.77	97.51 ± 28.41	40.29 ± 9.23
P^-P^-	159.54 ± 44.70	107.75 ± 29.17	83.09 ± 32.94	40.09 ± 10.53
P	0.06	0.04*	0.13	0.94

Data are expressed as mean ± standard deviation.
Abbreviations: TC, total cholesterol; TG, triglycerides; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol.
* Statistically significant at ⩽0.05.

two groups was not significant. The association of PvuII and CAD/MI has been studied in a number of studies. Researchers failed to detect significant association of PvuII with CAD/MI in Saudi Arabian [19], Turkish [20], French [21], Welsh [22], Japanese [23] and Tunisian [9], however, Duman et al. showed the association with MI in Turkish population [10]. LPL-HindIII has been shown to be associated with CAD/MI in Japanese [23], Toulouse [21], South Indian [13] and Tunisian [9], however some other studies failed to show significant association in the studied populations [9,19,24,25].

In spite of controversies on the association of LPL variants with CAD, a growing body of evidence revealed that LPL-HindIII and PvuII are associated with TG levels [9,12,25–27]. Our results showed that individuals with H^+ or P^+ allele have higher TG level than H^- or P^-. Since both LPL-HindIII and PvuII are intronic variants, their possible contribution to modulating TG levels might be interpreted in the context of haplotypes harboring them. However rs285 did not reside in an extended haplotype, rs320 resided in 54 kb haplotype in EUR population. rs320 is in strong linkage disequilibrium with a number of other variants including rs330 (r^2 = 0.98, D' = 1). rs330 is a conserved SNP (confirmed by SiPy algorithm) and located in active chromatin as resided in DNase sensitive domain [28]. Genomic functional studies indicated that rs285 is located in the canonical sequences which formed motifs for Ascl2 and NHLH1 transcription factor binding sites (Fig 1) [29]. Phenotypic consequences would be expected by allelic substitutions in rs285 position.

Selection pressures shaped the human genome and phenotypic consequences would be expected from loci under positive selection. There are studies that suggest that genes involved in nutrient metabolism are under positive selections [30]. The rationale for this assumption is based on the fact that nutrient consumption habits of humans have changed through time as humans accommodate to new environment. In this regard, the LPL variants could be analyzed to measure the extent of the positive selection. Taking advantage of db PSHP [31] we analyzed rs320 and rs285 in 14 different populations from 1000 genomes project to determine positive section pressure on them. We found rs320 does not subject to positive selection (−2 ⩽ iHS score ⩽ 2) but rs285 does (2 ⩽ iHS score) in YRI population (Fig 1). Such evidences could partially explain the phenotypic differences among human populations. Since

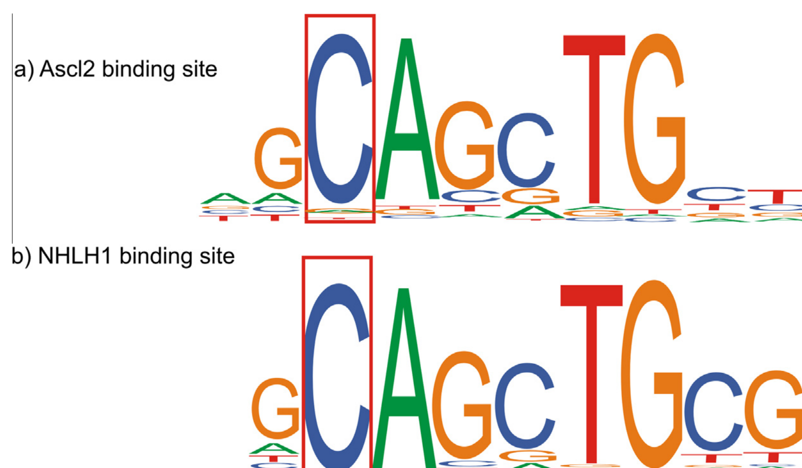


Figure 1 Position weight matrix for Ascl2 and NHLH1 transcription factor binding site. (a) Canonical motif for Ascl2 binding. (b) Canonical motif for NHLH1 binding. The red rectangular in the sequence logo represents rs285 position in the relevant motif.

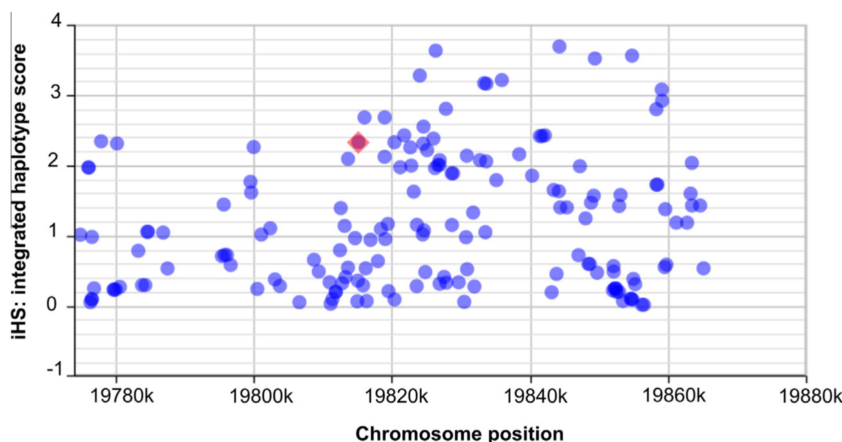


Figure 2 Positive selection extent on rs285. The figure represents flanking variants (blue circle) of rs285 (shaded in red) on the iHS score scale. Cut of positive selection is iHS score equal or more than 2. *Y* axis represents iHS score and *x* axis shows the chromosomal coordinates of SNPs.

iHS score is positive in this case, haplotypes harboring ancestral allele (T), are more favored and consequently alternate allele (C) would be selected against. TT individuals have lower level of TG and T substitutions for C looks a deleterious variation (see Fig. 2).

In conclusion, our findings indicate that LPL-HindIII and PvuII polymorphisms are not associated with MI but with TG levels. The association might be explained by haplotype structures and selection pressure on the human genome. Studies with large sample size or meta-analysis should be carried out to shed light on the possible association of LPL and MI and TG levels.

Acknowledgements

The authors extend their appreciation to the study participants and also technical assistance of staff members of the Blood Transfusion Research Center. This study was supported by grants from the Tehran University of Medical Sciences.

References

[1] Pankow JS, Folsom AR, Cushman M, Borecki IB, Hopkins PN, Eckfeldt JH, et al. Familial and genetic determinants of systemic markers of inflammation: the NHLBI family heart study. Atherosclerosis 2001;154(3):681–9.

[2] Gordon DJ, Probstfield JL, Garrison RJ, Neaton JD, Castelli WP, Knoke JD, et al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Circulation 1989;79(1):8–15.

[3] Vassallo RR, Stearns FM. Lipemic plasma: a renaissance. Transfusion 2011;51(6):1136–9.

[4] Kersten S. Physiological regulation of lipoprotein lipase. Biochim Biophys Acta 2014;1841(7):919–33.

[5] Stein Y, Stein O. Lipoprotein lipase and atherosclerosis. Atherosclerosis 2003;170(1):1–9.

[6] Mead JR, Irvine SA, Ramji DP. Lipoprotein lipase: structure, function, regulation, and role in disease. J Mol Med 2002;80(12):753–69.

[7] Sparkes RS, Zollman S, Klisak I, Kirchgessner TG, Komaromy MC, Mohandas T, et al. Human genes involved in lipolysis of plasma lipoproteins: mapping of loci for lipoprotein lipase to 8p22 and hepatic lipase to 15q21. Genomics 1987;1(2):138–44.

[8] Sagoo GS, Tatt I, Salanti G, Butterworth AS, Sarwar N, van Maarle M, et al. Seven lipoprotein lipase gene polymorphisms, lipid fractions, and coronary disease: a HuGE association review and meta-analysis. Am J Epidemiol 2008;168(11):1233–46.

[9] Rebhi L, Kchok K, Omezzine A, Kacem S, Rejeb J, HadjMbarek IB, et al. Six lipoprotein lipase gene polymorphisms, lipid profile and coronary stenosis in a Tunisian population. Mol Biol Rep 2012;39(11):9893–901.

[10] Duman BS, Türkoğlu Ç, Akpinar 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.

[11] Gotoda T, Yamada N, Murase T, Shimano H, Shimada M, Harada K, et al. Detection of three separate DNA polymorphisms in the human lipoprotein lipase gene by gene amplification and restriction endonuclease digestion. J Lipid Res 1992;33(7):1067–72.

[12] Munshi A, Babu MS, Kaul S, Rajeshwar K, Balakrishna N, Jyothy A. Association of LPL gene variant and LDL, HDL, VLDL cholesterol and triglyceride levels with ischemic stroke and its subtypes. J Neurol Sci 2012;318(1):51–4.

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

[14] Chamberlain J, Thorn J, Oka K, Galton D, Stocks J. DNA polymorphisms at the lipoprotein lipase gene: associations in normal and hypertriglyceridemic subjects. Atherosclerosis 1989;79(1):85–91.

[15] Chung HJ, Yoon YM, Han TH, Park H, Song J, Kim JQ. Polymorphisms at the lipoprotein lipase gene: possible associations with coronary artery disease and blood lipid levels in Koreans. Korean J Clin Pathol 1999;19(6):617–23.

[16] Antman E, Bassand J-P, Klein W, Ohman M, Sendon JLL, Rydén L, et al. Myocardial infarction redefined—a consensus document of the Joint European Society of Cardiology/American College of Cardiology committee for the redefinition of myocardial infarction: the Joint European Society of Cardiology/American College of Cardiology Committee. J Am Coll Cardiol 2000;36(3):959–69.

[17] Miller S, Dykes D, Polesky H. A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Res 1988;16(3):1215.

[18] Pirim D, Wang X, Radwan ZH, Niemsiri V, Hokanson JE, Hamman RF, et al. Lipoprotein lipase gene sequencing and plasma lipid profile. J Lipid Res 2014;55(1):85–93.

[19] Abu-Amero KK, Wyngaard CA, Al-Boudari OM, Kambouris M, Dzimiri N. Lack of association of lipoprotein lipase gene polymorphisms with coronary artery disease in the Saudi Arab population. Arch Pathol Lab Med 2003;127(5):597–600.
[20] Isbir T, Yilmaz H, Agachan B, Karaali Z. Cholesterol ester transfer protein, apolipoprotein E and lipoprotein lipase genotypes in patients with coronary artery disease in the Turkish population. Clin Genet 2003;64(3):228–34.
[21] Jemaa R, Fumeron F, Poirier O, Lecerf L, Evans A, Arveiler D, et al. Lipoprotein lipase gene polymorphisms: associations with myocardial infarction and lipoprotein levels, the ECTIM study. Etude Cas Témoin sur l'Infarctus du Myocarde. J Lipid Res 1995;36(10):2141–6.
[22] Mattu RK, Needham E, Morgan R, Rees A, Hackshaw AK, Stocks J, 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 Vasc Biol 1994;14(7):1090–7.
[23] Shimo-Nakanishi Y, Urabe T, Hattori N, Watanabe Y, Nagao T, Yokochi M, et al. Polymorphism of the lipoprotein lipase gene and risk of atherothrombotic cerebral infarction in the Japanese. Stroke 2001;32(7):1481–6.
[24] Araújo L, Cendoroglo M, Gigek C, Chen E, Smith Mde A. Association of lipase lipoprotein polymorphisms with high-density lipoprotein and triglycerides in elderly men. Genet Mol Res 2010;9(1):86–96.
[25] 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):573–82.
[26] Razzaghi H, Aston C, Hamman R, Kamboh M. Genetic screening of the lipoprotein lipase gene for mutations associated with high triglyceride/low HDL-cholesterol levels. Hum Genet 2000;107(3):257–67.
[27] Shin E, Park N-Y, Jang Y, Oh H, Jeong J, Lim Y, et al. The association of lipoprotein lipase PvuII polymorphism and niacin intake in the prevalence of metabolic syndrome: a KMSRI-Seoul study. Genes Nutr 2012;7(2):331–41.
[28] Ward LD, Kellis M. HaploReg: a resource for exploring chromatin states, conservation, and regulatory motif alterations within sets of genetically linked variants. Nucleic Acids Res 2012;40(D1):D930–4.
[29] Boyle AP, Hong EL, Hariharan M, Cheng Y, Schaub MA, Kasowski M, et al. Annotation of functional variation in personal genomes using RegulomeDB. Genome Res 2012;22(9):1790–7.
[30] Akey JM. Constructing genomic maps of positive selection in humans: where do we go from here? Genome Res 2009;19(5):711–22.
[31] Li MJ, Wang LY, Xia Z, Wong MP, Sham PC, Wang J. DbPSHP: a database of recent positive selection across human populations. Nucleic Acids Res 2013. http://dx.doi.org/10.1093/nar/gkt1052.