Screening for a D9N Common Mutation in Exon 2 of the LPL Gene in Thai Normolipidemic and Hyperlipidemic Subjects

NEDNAPIS TIRAWANCHAI, Ph.D.*,
KLAI-UPSORN PONGRAPEEPORN, Ph.D.*,
SOMPONG ONG-AJYOOTH, M.Sc.*
PREYANUJ YAMWONG, M.D.**,
ATIP LIKIDLILID, M.Sc.*,
ANCHALEE AMORNRATTANA, M.Sc**

Abstract

Lipoprotein lipase (LPL) is a multifunctional protein, playing a major role in the hydrolysis of triglyceride-rich lipoproteins. It also affects the maturation of high density lipoprotein (HDL) and low density lipoprotein (LDL). A D9N substitution is a frequent mutation found in exon 2 of the LPL gene. It is due to a G → A transition causing a substitution of Asp by Asn at amino acid residue 9 of the protein. This mutation was screened for in 94 Thai primary dyslipidemic (46 hypercholesterolemic and 48 combined hyperlipidemic) subjects compared to 32 normal healthy subjects using PCR-RFLP. Such a mutation has not, yet, been detected in any of these Thai subjects.

Key word : Lipoprotein Lipase, Exon 2, D9N Mutation

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Dyslipidemia is disturbances in the metabolism of lipoproteins which is responsible for the transport of cholesterol and triglycerides in the plasma. Increased total serum cholesterol, low density lipoprotein-cholesterol (LDL-C) and high density lipoprotein-cholesterol (HDL-C) constitute risk factors for atherosclerosis and coronary heart disease (CHD)[1]. In addition, elevated levels of triglyceride have been shown to increase the risk of atherosclerosis and coronary artery disease (CAD) [2,3].

Lipoprotein lipase (LPL) is a multifunctional glycoprotein with a molecular weight of 61 kDa[4]. It is anchored to the vascular endothelium

* Department of Biochemistry,
** Department of Preventive Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

where it acts as a core enzyme for the clearance of triglyceride-rich lipoprotein from the circulation[1]. In addition, LPL has been found to serve as a ligand for the LDL receptor-related protein (LRP) and, moreover, to affect secretion and uptake of very low density lipoprotein (VLDL) and LDL-C[5].

The human LPL gene has been cloned, sequenced and localized to be on chromosome 8p22[6-8]. It is composed of 10 exons spanning ~30 kilobasepairs (kb). The first exon encodes the 5'-untranslated region, the signal peptide plus the first 2 amino acids of the mature protein. The next 8 exons encode the remaining 446 amino acids and the tenth exon encodes the long 3'-untranslated region of 1,948 nucleotides. Additionally, complementary DNA (cDNA) for the human LPL that encodes a mature protein of 448 amino acids has been cloned and sequenced[4,9].

Many diseases, including obesity, coronary artery disease (CAD), chylomicronemia (pancreatitis) and atherosclerosis, appear to be directly or indirectly related to abnormalities in LPL function[10]. A large number of mutations have been discovered in the human LPL gene[10,11]. They are located at different sites of the gene resulting in a functionally defective catalytic protein which occurs with a frequency of nearly 1 in 500 people. Recently, heterozygosity for mutations in the LPL gene has been found to be associated with partial LPL activity and a milder clinical phenotype[12-15].

Mutations of the gene encoding LPL have been assessed in individuals with dyslipidemic subjects[16], familial LPL deficiency[17-20], familial hypercholesterolemia (FH)[21-24], familial combined hyperlipidemia[25,26], familial noninsulin-dependent diabetes mellitus (NIDDM)[27] and coronary artery disease (CAD)[28]. Among these mutations, frequent ones have been readily described, i.e. D9N in exon 2[16], N291S in exon 6[13, 14,23,29] and S447X in exon 9[30].

The D9N mutation is due to a G → A transition in exon 2 of the LPL gene causing a substitution of Asp by Asn at amino acid residue 9[16]. This mutation has been pronounced in 4-6 per cent of combined hyperlipidemic subjects and has shown to be accompanied by the high-triglyceride-low HDL-C phenotype. The N291S is another common mutation which is due to an A → G transition in exon 6 of the LPL gene, resulting in a substitution of Asn → Ser at amino acid residue 291[13,14, 23,29]. This mutation ranged from 2-5 per cent in different populations and was found to be associated with a partial reduction in LPL activity, a reduced level of HDL-C and an elevated level of triglyceide in some populations[13,14, 31]. Another frequent mutation found at exon 9 of the LPL gene is S447X substitution[30]. This mutation which is due to a C → G transversion creates a premature termination codon at the Ser residue 447 (Ser447-Ter), hence, results in a truncated LPL molecule lacking the C-terminal dipeptide Ser-Gly. Such mutation has been reported in 2-5 per cent of individuals in western populations and is associated with increased triglyceride and reduced HDL-C concentrations.

Our report presented here is the preliminary screening of one of the most frequent mutations in the LPL gene, i.e. the D9N mutation in exon 2, using Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) in Thai hypercholesterolemic and combined hyperlipidemic subjects compared to normolipidemic subjects.

MATERIAL AND METHOD

Subjects

One-hundred and twenty-six experimental subjects were divided into 32 normolipidemic and 94 primary hyperlipidemic subjects. Normal controls were obtained from healthy unrelated individuals who visited The Health Screening Clinic, Department of Preventive Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University. They consisted of 10 males (age 34-64 years, mean age 43.8 ± 14.2 years) and 22 females (age 23-58 years, mean age 41.3 ± 10.1 years). Their cholesterol and triglyceride levels were ≤200 mg/dL and ≤200 mg/dL, respectively.

Primary hyperlipidemias were recruited from 94 subjects who attended the Lipid Clinic, Department of Preventive Medicine, Faculty of Medicine Siriraj Hospital. They were divided into 46 hypercholesterolemic and 48 combined hyperlipidemic subjects. Hypercholesterolemic subjects consisted of 11 males (age 40-74 years, mean age 54.8 ± 10.7 years) and 35 females (age 27-72 years, mean age 53.8 ± 11 years). Their cholesterol and triglyceride levels were 200 mg/dL and ≤200 mg/dL, respectively. Combined hyperlipidemic subjects were selected from 25 males (age 35-81 years, mean age 51.8 ± 11.6 years) and 23 females (age 44-75 years, mean age 59.3 ± 9.8 years).

Their cholesterol and triglyceride levels were both 200 mg/dL. All subjects gave informed consent for participation in the study.

Collection of blood, lipid analyses and DNA isolation

Fasting venous blood samples (10 mL) were collected into tubes containing EDTA. Plasma was collected from each subject for determination of the levels of total cholesterol, triglyceride and HDL-C which were examined by the Department of Clinical Chemistry, Faculty of Medical Technology, Mahidol University using enzymatic methods (the kits used were from Boeringer Mannheim and Hoffman La Roche for determination of total cholesterol and triglyceride & HDL-C, respectively). The automated analyzer (Hitachi 917) was used to determine all lipid concentrations. The level of LDL-C was calculated using the method described by Friedewald *et al*[32]. Leukocyte DNA was extracted by guanidine-HCl method[33]. The DNA was then redissolved in Tris-EDTA buffer (10 mM Tris, 1 mM EDTA, pH 7.6) and stored at –20°C until used.

Oligonucleotide primers

DNA primer sequences for the study of the D9N mutation in exon 2 of the LPL gene were synthesized by BioService Unit, BIOTEC Center, NSTDA. They were Tq1 ; 5'-CTCCAGTTAACCT CATATCC-3' and Tq2 ; 5'-CACCACCCCAATCC ACTC-3'[16].

Amplification of exon 2 of the LPL gene

Amplification was performed in a Perkin Elmer 2400 thermal cycler. The 20 µL PCR reaction mixture contained 0.2-0.5 µg gDNA, 10 mM Tris-HCl pH 9.0, 50 mM KCl, 1.5 mM $MgCl_2$, 200 µM each of dATP, dCTP, dGTP, dTTP (Pharmacia), 0.3 µM of each primer and 2.5 units of *Taq* DNA polymerase (Pharmacia). Blanks containing no added DNA were run with each set of amplification. The PCR cycles were slightly modified from that described by Mailly *et al*[16]. They were 5 min denaturation at 97°C, followed by 30 cycles of 1 min at 98°C, 2 min at 53°C and 1.5 min at 72°C, followed by 7 min extension at 72°C.

Restriction endonuclease digestion and agarose gel electrophoresis

Following amplification, the PCR-amplified DNA was used directly for digestion with a restriction enzyme *Taq* I (New England BioLabs). The final volume of 20 µL reaction contained 10 µL of the amplified DNA, 10 units of the enzymes and an incubation buffer recommended by the manufacturer's instruction. The reaction mixture was incubated overnight at 65°C. The digested products were analyzed by electrophoresis on a 3.5 per cent agarose gel (Sigma) in TBE buffer (89 mM Tris-borate, 2 mM EDTA, pH 8.3) at 100 volts for 1-1.5 h. DNA was visualized on a UV-transilluminator after staining with ethidium bromide. The 100 bp ladder (Pharmacia) was used as a reference molecular weight marker.

RESULTS

Lipid analysis

Plasma levels of total cholesterol, triglyceride, LDL-C and HDL-C of the normolipidemic, hypercholesterolemic and combined hyperlipidemic subjects were summarized in Table 1. Mean ages were 42.13 ± 11.42, 54.04 ± 10.81 and 55.4 ± 11.32 years for the normolipidemic, hypercholesterolemic and combined hyperlipidemic subjects, respectively.

Table 1. Mean ages and lipid profiles of Thai normolipidemic, hypercholesterolemic (HC) and combined hyperlipidemic (CHL) subjects

	Normolipidemic subjects* (n =32)	HC subjects* (n =46)	CHL subjects (n = 48)
Age (years)	42.13 ± 11.42	54.04 ± 10.81	55.40 ± 11.32
Cholesterol (mg/dL)	180.38 ± 22.60	286.91 ± 40.37	276.17 ± 55.19
Triglyceride (mg/dL)	87.56 ± 37.16	127.61 ± 39.41	378.17 ± 270.29
LDL-C (mg/dL)	102.49 ± 30.91	198.56 ± 54.35	167.27 ± 60.60
HDL-C (mg/dL)	60.38 ± 17.42	58.46 ± 34.52	41.35 ± 11.45

* Mean ± S.D.

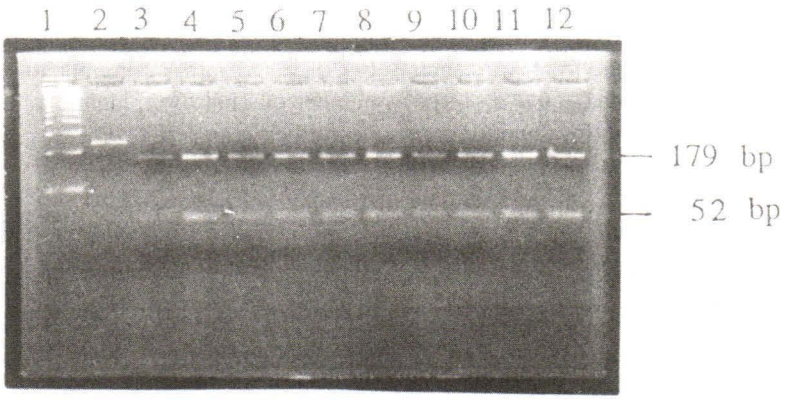

Fig. 1. 3.5% agarose gel electrophoretic pattern of the *Taq* I-digested exon 2 of the LPL gene. Lane 1 was 100 bp DNA molecular weight marker. Lane 2 was the undigested PCR-amplified DNA. Lanes 3-12 were *Taq* I digested PCR-amplified DNA.

DNA analysis and agarose gel electrophoresis

Screening of exon 2 of the LPL gene was undertaken using PCR-RFLP in 94 hyperlipidemic compared to 32 normolipidemic subjects. After amplification, a band of 237 basepairs (bp) was seen on an agarose gel (Fig. 1). Upon *Taq* I digestion, the amplified DNA was fragmented into 179 and 52 bp (G-*Taq* I cutting-Asp9). If a G → A transition occurs, the Asn will, then, be substituted for Asp at amino acid residue 9. Hence, this mutation will abolish the *Taq* I site and both 179 and 58 bp (A-*Taq* I not cutting-Asn9) will be observed upon digestion with the enzyme. Using PCR-RFLP, this mutation was not detected in any of the Thai normolipidemic or hyperlipidemic subjects (Fig. 1).

DISCUSSION

The D9N mutation of the LPL gene has been shown to be frequent in patients with combined hyperlipidemia[16]. It has been reported to be present in between 1.6-4.4 per cent of the healthy population from Sweden, The Netherlands and United Kingdom. However, in combined hyperlipidemic subjects, it has been reported to be roughly twice as high (4-9.8%). This mutation has also been shown to be significantly associated with hypertriglyceridemia and a partial function of the LPL activity when expressed *in vitro*. In addition, this Asn9 LPL variant was observed to confer the P-P-/H+H+ (homozygotes for *Pvu* II noncutting and *Hin*d III cutting characteristics) haplotypes of the LPL gene.

The D9N mutation of the LPL gene was shown to be 4.8 per cent in Dutch patients with coronary atherosclerosis[34]. Heterozygous carriers of this Asp9Asn mutation had a positive family history of coronary vascular disease significantly more often than noncarriers. They also exhibited lower level of HDL-C but higher levels of LDL-C and triglyceride. In addition, this mutation was observed to have an impact on the occurrence of premature CAD and the progression of coronary atherosclerosis in these patients.

The D9N substitution of the LPL gene has readily been recognised in FH patients[24]. This mutation is present in 4.5 per cent of Dutch FH heterozygotes. Patients carrying this common mutation not only were at higher risk for coronary vascular disease but also showed a reduced level of HDL-C and an elevated level of triglyceride.

Additionally, the D9N mutation is found to be associated with the T → G transition at position –93 of the proximal promoter region of the LPL gene[35,36]. This combined –93 T → G/Asn9 haplotype of the LPL gene was found, in a gender-related manner, to be significantly associated with elevated levels of LDL-C, VLDL-C and VLDL-triglyceride in Dutch males suffering from familial combined hyperlipidemia[35]. Furthermore, Dutch males with angiographically-diagnosed CAD who were carriers of this combined –93 T→G/Asn9 variant of the LPL have been observed to be predisposed to decreased HDL-C levels and a higher increasing risk of CAD[36].

The D9N mutation in exon 2 of the LPL gene was not in evidence in our report of Thai subjects. It is speculated that the failure to identify such a mutation might reflect the inadequacy of the number of samples. Association of this mutation and hyperlipidemia in Thai subjects is as yet inconclusive, and remains to be elucidated. This mutation has been shown to have some effect on lipid and lipoprotein abnormalities which would predict a relatively increased risk of premature CAD in dyslipidemic subjects. Screening for this mutation, together with other common mutations in a larger number of Thai dyslipidemic subjects should, thus, be further assessed.

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การศึกษาการกลายพันธุ์ของยีนที่สร้างเอนไซม์ไลโปโปรตีนไลเปสที่บริเวณ exon 2 ในคนไทยที่มีภาวะไขมันสูงปฐมภูมิ

เนตรนภิส ธีระวัลย์ชัย, ปร.ด., ปรียานุช แย้มวงษ์, พ.บ.**,*
คล้ายอัปสร พงศ์รพีพร, ปร.ด., อธิป ลิขิตลิลิต, วท.ม.*,*
สมพงษ์ องอาจยุทธ, วท.ม., อัญชลี อมรรัตน์, วท.ม.***

ไลโปโปรตีนไลเปสเป็นเอนไซม์สำคัญที่ทำหน้าที่กำจัดไตรกลีเซอร์ไรด์จากกระแสเลือด นอกจากนี้ยังช่วยในการสร้าง HDL และ LDL ถ้ายีนที่สร้างเอนไซม์นี้มีความผิดปกติ ก็จะทำให้เกิดภาวะไขมันสูงตามมา การกลายพันธุ์ของยีนที่สร้างเอนไซม์ไลโปโปรตีนไลเปส จะพบได้บ่อยที่บริเวณ exon 2 ของยีน ซึ่งเกิดการแทนที่ของเบส จาก G เป็น A ทำให้กรดอะมิโนตำแหน่งที่ 9 ซึ่งเดิมเป็น Asp เปลี่ยนไปเป็น Asn ในที่นี้จะศึกษาการกลายพันธุ์ของยีนที่สร้างเอนไซม์นี้ที่ตำแหน่งดังกล่าว ในผู้ที่มีภาวะไขมันสูงปฐมภูมิของไทยจำนวน 94 ราย ซึ่งแบ่งเป็น ผู้ที่มีโคเลสเตอรอลสูงเพียงอย่างเดียว จำนวน 46 ราย และผู้ที่มีโคเลสเตอรอลกับ ไตรกลีเซอร์ไรด์สูง จำนวน 48 ราย เปรียบเทียบกับผู้ที่มีภาวะไขมันปกติจำนวน 32 ราย โดยใช้วิธี PCR-RFLP รายงานนี้ยังไม่พบการกลายพันธุ์ของยีนที่สร้างเอนไซม์ไลโปโปรตีนไลเปสที่ exon 2 ในคนไทยตัวอย่างที่เลือกมาทำการศึกษา

คำสำคัญ : ไลโปโปรตีนไลเปส, การกลายพันธุ์ของยีน

เนตรนภิส ธีระวัลย์ชัย, ปรียานุช แย้มวงษ์, คล้ายอัปสร พงศ์รพีพร, อธิป ลิขิตลิลิต, สมพงษ์ องอาจยุทธ, อัญชลี อมรรัตน์
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* ภาควิชาชีวเคมี,
** ภาควิชาเวชศาสตร์ป้องกันและสังคม, คณะแพทยศาสตร์ศิริราชพยาบาล, มหาวิทยาลัยมหิดล, กรุงเทพ ฯ 10700