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BASIC RESEARCH

Impact of lipoprotein lipase gene polymorphisms on ulcerative colitis

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Abstract

AIM: To examine the influence of lipoprotein lipase (LPL) gene polymorphism in ulcerative colitis (UC) patients.

METHODS: Peripheral blood was obtained from 131 patients with UC and 106 healthy controls for DNA extraction. We determined LPL gene polymorphisms affecting the enzyme at Ser447stop, as well as *Hind*Ⅲ and *Pvu* Ⅱ polymorphisms using PCR techniques. PCR products were characterized by PCR-RFLP and direct sequencing. Polymorphisms were examined for association with clinical features in UC patients. Genotype frequencies for LPL polymorphisms were also compared between UC patients and controls.

RESULTS: In patients with onset at age 20 years or younger, C/G and G/G genotypes for Ser447stop polymorphism were more prevalent than C/C genotype (OR = 3.13, 95% CI = 0.95-10.33). Patients with $H^{+/-}$ or $H^{-/-}$ genotype for *Hind*Ⅲ polymorphism also were more numerous than those with $H^{+/+}$ genotype (OR = 2.51, 95% CI = 0.85-7.45). In the group with $H^{+/+}$ genotype for *Hind*Ⅲ polymorphism, more patients had serum triglyceride concentrations over 150 mg/dL than patients with $H^{+/-}$ or $H^{-/-}$ genotype ($P < 0.01$, OR = 6.46, 95% CI = 1.39-30.12). Hypertriglycemia was also more prevalent in patients with $P^{+/+}$ genotypes for *Pvu* Ⅱ polymorphism ($P < 0.05$, OR = 3.0, 95% CI = 1.06-8.50). Genotype frequency for LPL polymorphism did not differ significantly between UC patients and controls.

CONCLUSION: Ser447stop and *Hind*Ⅲ LPL polymorphisms may influence age of onset of UC, while *Hind*Ⅲ and *Pvu* Ⅱ polymorphisms influence serum triglyceride in UC patients.

Key words: Ulcerative colitis; Lipoprotein lipase; Lipid metabolism; Triglyceride

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INTRODUCTION

Inflammatory bowel disease (IBD), characterized by chronic recurrent inflammation of the intestinal tract, includes two common forms: Crohn's disease (CD) and ulcerative colitis (UC). For both forms, the etiology is unclear, but likely to be multifactorial. Factors that may affect IBD include diet, infantile environment and immune defense abnormalities limited to the intestinal tract. Recently, genetic factors have been examined in IBD, but many studies seeking susceptibility genes for IBD have not produced a consensus. We presently investigated possible influence of the lipoprotein lipase (LPL) gene in UC. LPL plays a critical role in lipid metabolism. Dietary triacylglycerol (TAG) exists in the human circulation as macromol-

ecules (TAG-rich lipoprotein) that are too large to pass through the endothelium of most capillaries. LPL catalyses conversion of TAG-rich lipoprotein to triglyceride (TG), very low-density lipoprotein (VLDL), and chylomicrons (CM), all of which circulate and can enter tissues more readily to serve energy source[1,2]. Our interest in LPL in IBD was provoked by identifying high lipid intake as a risk factor for IBD. Shoda *et al*[3] reported associated intake of n-6 polyunsaturated fat and animal fat with development of CD in Japanese patients, while Geering *et al*[4] reported high intake of mono- and polyunsaturated fats to be a risk factor for the UC. Furthermore, the LPL gene has been localized to chromosome 8p22 near N-acetyltransferase2 (NAT2) gene, while Machida *et al*[5] reported an association between NAT2 gene haplotype NAT2*7B and CD. Considering these various findings, we suspected that LPL gene polymorphisms could influence characteristics and incidence of UC. These issues were examined in the present molecular genetic investigation.

MATERIALS AND METHODS

Subjects

We studied 131 patients with UC (75 males and 56 females) and 106 healthy controls (53 males and 53 females). Diagnosis of UC was based on conventional clinical, radiologic, endoscopic, and pathologic criteria. Characteristics of UC patients are shown in Table 1. We investigated the effect of LPL polymorphism on clinical features as shown in this table. To examine LPL polymorphisms in terms of influence on UC incidence, we compared LPL genotype frequencies in UC patients with those in controls.

Table 1 Characteristics of patients with ulcerative colitis

Characteristic	UC (n = 131)
Age of onset (yr)	36.8 ± 15.3
Colitis duration (yr)	8.8 ± 7.7
Extension	
Proctitis	22 (16.8%)
Left-sided	59 (45.0%)
Pancolitis	50 (38.2%)
Type of clinical course	
First episode	14 (10.7%)
Chronic relapse	79 (60.3%)
Chronic persistent	38 (29.0%)
Severity	
Mild	40 (30.5%)
Moderate	61 (46.6%)
Severe	30 (22.9%)

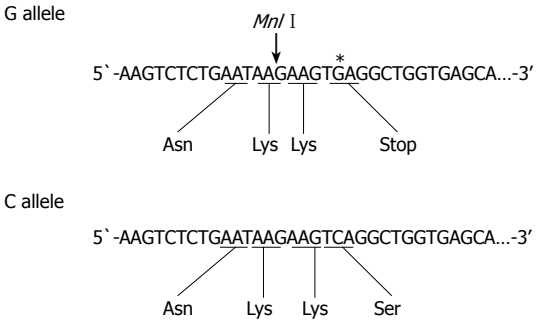

Figure 1 Strategy for detection of the C/G allele (Ser/stop) in exon 9 of the lipoprotein lipase by PCR-RFLP analysis. Introduction of G (*) is in place of C creates a new *Mnl* Ⅰ site.

DNA extraction

Blood samples were obtained from patients and controls after they had given informed consent to sampling and analyses. This study was approved by the Fujita Health University Ethics Committee. DNA was extracted from blood samples using a PUREGENE DNA isolation kit (Gentra Systems, Inc, Minneapolis, USA).

Genotype

LPL polymorphisms were typed using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) methods to detect Ser447stop, *Hin*dⅢ and *Pvu*Ⅱ polymorphisms[6]. The primer sets were as follows: for Ser447stop, 5′-GATGTGGCCTGAGTGTGACAG-3′ (forward) and 5′-TCCCTTAGGGTGCAAGCTCAG-3′ (reverse); for *Hin*dⅢ, 5′-GATGTCTACCTGGATAATCAAAG-3′(forward) and 5′-CTTCAGCTAGACATTGCTAGTGT-3′ (reverse); and for *Pvu*Ⅱ, 5′-GAGACACAGATCTCTCTTAAGAC-3′ (forward) and 5’-ATCAGGCAATGCGTATGAGGTAA-3’ (reverse). PCR was carried out in a 30-μL aliquot containing 50 ng of genomic DNA, 12 pmol of each primer, 3.0 μL of 10 × buffer solution, 20 nmol/μL of dNTP, and 1U of Taq polymerase. PCR conditions for Ser447stop included initial denaturation at 95℃ for 5 min, followed by 35 amplification cycles, each cycle containing denaturation at 95℃ for 30 s, primer annealing at 62℃ for 30 s, and extension at 72℃ for 30 s. PCR conditions for *Hin*dⅢ and *Pvu*Ⅱ included initial denaturation at 95℃ for 5min, followed by 35 amplification cycles, each cycle containing denaturation at 95℃ for 30 s, primer annealing at 61℃ for 30 s, and extension at 72℃ for 30 s. PCR products subjected to overnight digestion with *Mnl*Ⅰ, *Hin*dⅢ, and *Pvu*Ⅱ were examined by electrophoresis on 20 g/L agarose gels. The strategy for the detection of the G allele (Ser447stop) is shown in Figure 1. A 315-bp segment of exon 9 of the lipoprotein lipase gene was amplified by the PCR. In the presence of the G allele, the amplified DNA contains a new site for *Mnl*Ⅰ, but does not contain a site in the presence of the C allele. However, there is a restriction site for *Mnl*Ⅰ in the forward primer sequence regardless of G/C mutation. After digestion, the PCR product yielded 248- and 67-bp fragments. The PCR product containing a *Hin*dⅢ restriction site yielded 210- and 140-bp fragments, while the product containing a *Pvu*Ⅱ restriction site yielded 222- and 209-bp fragments. Some products after digestion were examined on polyacrylamide gels (GeneGel Excel 12.5/24 kit from GE Healthcare Bio-sciences, Tokyo) and stained with DNA silver staining kit (GE Healthcare Bio-sciences,

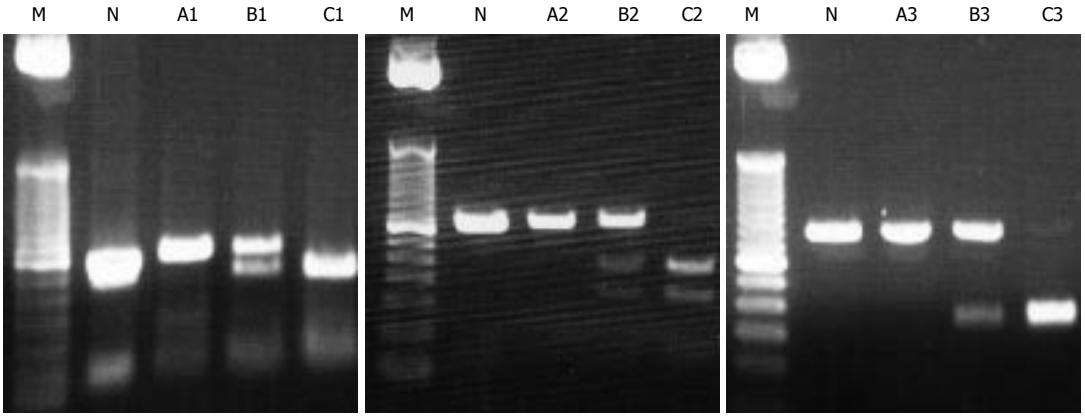

Figure 2 Electrophoresed pattern of LPL polymorphism. M: Marker, N: No digestion. In Ser447stop, A1: C/C genotype (315 bp); B1: C/G genotype; C1: G/G genotype. In *Hind*Ⅲ, A2: $H^{+/+}$genotype; B2: $H^{+/-}$genotype (350 bp); C2: $H^{-/-}$genotype. In *Pvu*Ⅱ, A3: $P^{+/+}$ genotype (431 bp); B3: $P^{+/-}$genotype; C3: $P^{-/-}$genotype.

Table 2 Allele frequency and genotype distribution of LPL polymorphism in UC patients and controls

	Allele frequency		Genotype (%)		OR (95% CI)
Ser447stop	C	G	CC	CG+GG	
UC (n = 131)	0.92	0.08	111 (84.7)	19 + 1 (15.3)	1.49
Control (n = 104)	0.88	0.12	82 (78.8)	19 + 3 (21.2)	(0.76-2.91)
*Hind*Ⅲ	H^+	H^-	$H^{+/+}$	$H^{+/-}$ + $H^{-/-}$	
UC (n = 130)	0.80	0.20	86 (66.1)	37 + 7 (33.9)	1.28
Control (n = 106)	0.74	0.26	64 (60.4)	28 + 14 (39.6)	(0.75-2.18)
*Pvu*Ⅱ	P^+	P^-	$P^{+/+}$	$P^{+/-}$ + $P^{-/-}$	
UC (n = 131)	0.70	0.30	65 (49.6)	53 + 13 (50.4)	1.44
Control (n = 106)	0.64	0.36	43 (40.6)	50 + 13 (59.4)	(0.86-2.42)

Table 3 Age of onset of UC patients and LPL polymorphisms

Age of onset (yr)	Genotype		OR (95% CI)
Ser447stop	C/G+G/G	C/C	
< 20 (n = 15)	5	10	3.13
⩾ 20 (n = 116)	16	100	(0.94-10.33)
*Hind*Ⅲ	$H^{+/-}$ + $H^{-/-}$	$H^{+/+}$	
< 20 (n = 15)	8	7	2.31
⩾ 20 (n = 115)	36	79	(0.84-7.45)
*Pvu*Ⅱ	$P^{+/-}$ + $P^{-/-}$	$P^{+/+}$	
< 20 (n = 15)	9	6	1.55
⩾ 20 (n = 116)	57	59	(0.52-4.64)

Tokyo), e.g. *Pvu*Ⅱ digestion-cases. Electrophoresed patterns of LPL polymorphisms are shown in Figure 2.

Results of PCR-RFLP were confirmed by direct sequencing. DNA was extracted from agarose gels using an extraction kit (QIAGEN, Hilden, Germany). Then genotype was confirmed by sequence analysis using an auto sequencer (data not shown).

Statistical analysis

All data were analyzed by Excel 2000 and STASTISCA software. Clinical features of UC, allele frequency, and genotype distribution were evaluated by using χ^2 test. A P value less than 0.05 was considered statistically significant.

Allelelic and genotype frequencies were determined from observed genotype counts, and the extensions of Hardy-Weinberg equilibrium were evaluated by using χ^2 test.

RESULTS

LPL polymorphisms and risk of UC

The allele frequency of LPL polymorphism and the genotype distribution are shown in Table 2. The observed genotype data were consistent with Hardy-Weinberg equilibrium (Ser447stop: $\chi^2 = 0.48$, $P = 0.49$; *Hind*Ⅲ: $\chi^2 = 1.73$, $P = 0.19$; *Pvu*Ⅱ: $\chi^2 = 0.88$, $P = 0.35$). In the patient group, one patient was not able to identify with genotype of *Hind*Ⅲ polymorphism. In the control group, two patients were not able to identify with genotype of Ser447stop polymorphism. The allele frequency of Ser447stop polymorphism showed no difference between UC patients and controls. Frequencies of C/C, C/G and G/G genotypes of Ser447stop polymorphism in the control group were 78.8%, 18.3% and 2.9%, respectively, while these were not significantly different in patients. In the control group, frequencies of $H^{+/+}$, $H^{+/-}$ and $H^{-/-}$ genotypes for *Hind*Ⅲ polymorphism were 60.4%, 26.4% and 13.2%, respectively, while frequencies of $P^{+/+}$, $P^{+/-}$ and $P^{-/-}$ genotype for *Pvu*Ⅱ polymorphism were 40.6%, 47.1% and 12.3%, respectively. In UC patients, neither *Hind*Ⅲ nor *Pvu*Ⅱ polymorphisms differed significantly from genotype and allele frequencies in controls.

LPL polymorphism and characteristics of UC patients

We sought to identify associations between characteristics of UC patients (age at onset, gender, nature of the clinical course, extent of lesions, severity of colitis) and LPL polymorphisms. The relationship between age of onset of UC patients and their LPL polymorphisms are summarized in Table 3. In patients with onset at age 20 years or younger, more patients had either C/G or G/G genotype for Ser447stop than a C/C genotype (OR = 3.13, 95% CI = 0.95-10.33). In this early-onset group, more patients had either an $H^{+/-}$ or $H^{-/-}$ genotype for *Hind*Ⅲ polymorphism than an $H^{+/+}$ genotype (OR = 2.51, 95% CI = 0.85-7.45). Other characteristics (gender, nature of

Table 4 Triglyceride levels of UC patients and LPL polymorphisms

Triglycerides (mg/dL)	Genotype		OR (95%CI)
Ser447stop	C/C	C/G + G/G	
⩾ 150 (n = 20)	19	1	4.93 (0.61-40.03)
< 150 (n = 68)	54	14	
*Hind*Ⅲ	$H^{+/+}$	$H^{+/-} + H^{-/-}$	
⩾ 150 (n = 20)	18[b]	2	6.46 (1.39-30.12)
< 150 (n = 67)	39	28	
*Pvu*Ⅱ	$P^{+/+}$	$P^{+/-} + P^{-/-}$	
⩾ 150 (n = 20)	13[a]	7	3.0 (1.06-8.50)
< 150 (n = 68)	26	42	

[a]$P < 0.05$ *vs* $P^{+/-} + P^{-/-}$ group; [b]$P < 0.01$ *vs* $H^{+/-} + H^{-/-}$ group.

the clinical course, extent of lesions, severity of colitis) showed no significant differences between polymorphism-defined groups. Details of treatment among UC patients contained 5-aminosalicylic acid agents only (35 cases), steroid therapy (65 cases), operation (20 cases), other therapy (plasma exchange in 31 cases, immunosuppressant in 4 cases). We classified UC patients into a steroid-effective group (remission with a conventional steroid dose) and a steroid-resistant group (lack of such a remission, requiring surgery or other therapy, such as plasma exchange). We did not find an effect of LPL polymorphism on steroid effectiveness of UC patients.

We also investigated serum total cholesterol in terms of LPL polymorphism in UC patients. First, 108 UC patients were classified into groups with total cholesterol below or above 220 mg/dL. LPL polymorphisms did not differ between these groups. Next, triglyceride concentration in 88 UC patients was divided into those below or above 150 mg/dL (Table 4). Patients with an $H^{+/+}$ genotype for *Hind*Ⅲ polymorphism were more likely to have triglyceride concentrations over 150 mg/dL than those with an $H^{+/-}$ or $H^{-/-}$ genotype ($P < 0.01$, OR = 6.46, 95% CI = 1.39-30.12). This was also true for patients with a $P^{+/+}$ genotype for *Pvu*Ⅱ polymorphism compared with those with $P^{+/-}$ or $P^{-/-}$ genotype ($P < 0.05$, OR = 3.0, 95% CI = 1.06-8.50).

DISCUSSION

The LPL gene, located on chromosome 8p22[7], consists of 10 exons. As for the LPL polymorphisms investigated in this study, the Ser447stop polymorphism is within exon 9[8], involving substitution of G for C at nucleotide 1595. The *Hind*Ⅲ polymorphism is located in intron 8[9,10], and *Pvu*Ⅱ in intron 6[9,11]. Abnormalities in LPL function have been associated with various diseases, those linked with LPL polymorphisms are cardiovascular disease[12], cerebrovascular disease[13], chylomycronemia[14], insulin resistance[15], Alzheimer´s disease[16] and various infections[17]. Life styles and habits also can influence many diseases, possibly including UC. We presently sought out the relationship between UC and the LPL gene.

This study is probably the first to report an association between characteristic of UC and LPL polymorphism, representing two important findings. The first finding was that *Hind*Ⅲ and *Pvu*Ⅱ polymorphisms affected serum triglyceride concentrations in UC patients. Some studies reported that Ser447stop polymorphism activated LPL, decreasing triglycerides and increasing HDL cholesterol. As opposited to Ser447stop, *Hind*Ⅲ polymorphism lowered LPL activity, and elevated triglycerides, and decreased HDL cholesterol. *Pvu*Ⅱ polymorphism has similar function[12,18]. Using a cutoff triglyceride value of 150 mg/dL, the above relationship for *Hind*Ⅲ and *Pvu*Ⅱ polymorphisms held true in our UC patients. Patients homozygous for *Hind*Ⅲ polymorphism were even more likely to have triglyceride above 150 mg/dL than those homozygous for *Pvu*Ⅱ polymorphism. *Hind*Ⅲ polymorphism, therefore, would appear to suppress LPL activity more strongly than *Pvu*Ⅱ polymorphism. Among studies of associations between triglyceride in healthy individuals and LPL polymorphism, Ann *et al*[19] reported that *Hind*Ⅲ polymorphism elevated triglycerides, while Chamberlain *et al*[18] pointed out some subjects with *Hind*Ⅲ polymorphism showed normal concentrations. Since associations between elevated triglyceride in healthy individuals and *Hind*Ⅲ polymorphism thus are a matter of some disagreement, our finding that UC patients with $H^{+/+}$ genotype for LPL polymorphism were particularly likely to have elevated triglycerides, some part of the difference seen in our UC patients might be specific to UC.

Previous studies have reported that serum triglyceride concentrations did not differ between UC patients and controls[20,21]. In this study, however, patients with $H^{+/+}$ genotype had serum triglyceride concentrations over 150 mg/dL compared to patients with $H^{+/-}$ or $H^{-/-}$, thereby suggesting that *Hind*Ⅲ polymorphism may contribute to elevate triglyceride levels directly or may influence other gene-elevated triglyceride concentrations. Although few studies have examined associations between UC and LPL, lipid intake has been reported to influence risk of IBD. Many studies have reported relationship between lipid metabolism and inflammation. During various human inflammatory states, serum triglyceride concentrations increase because some cytokines responsible for inflammatory responses, including tumor necrosis factor (TNF)-α, interferon (IFN)-γ, inhibit LPL activity[22]. Other studies reported that lipopolysaccarides derived from Gram-negative bacteria reduced LPL activity in macrophages[23]. LPL also directly induces the expression of the TNF-α gene[24], which synergizes with IFN-γ in stimulating nitric oxide synthetase expression in macrophages[25]. Since LPL is strongly associated with cytokines, it may contribute to development of inflammation. In addition, De Sanctis *et al*[26] reported an association between natural killer (NK) cells and LPL polymorphism. Some studies have suggested that UC is associated with changes in humoral immunity[27,28] and cellular immunity[29], while UC may be associated with loss of immune tolerance in the intestine. Association between LPL and characteristic of UC may shed some light on mechanisms of onset of UC.

The second finding was that Ser447stop polymorphism

and *Hin*dⅢ polymorphism might be associated with age of onset of UC patients. In patients with onset at 20 years or younger, more patients had either C/G or G/G genotype at Ser447stop than a C/C genotype, while more patients had either $H^{+/-}$ or $H^{-/-}$ genotype for *Hin*dⅢ polymorphism than $H^{+/+}$ genotype. As for the significance of relatively early onset, the LPL gene might influence onset of disease directly or by acting upon another gene or factor. In addition to genotype, age may affect LPL activity, while lipid metabolism might influence onset of IBD. Hamilton *et al*[30] reported that older individuals had inefficient triglyceride metabolism and elevated serum triglycerides because of reduction of LPL activity in postural skeletal muscle during aging. Among UC patients in our study, 10% (2/20) of those aged 20 to 29 years and 15% (4/26) of those aged 30 to 39 years showed triglycerides over 150 mg/dL, while Arai *et al*[31] reported that, in a Japanese population sample, the mean triglyceride concentration was 83 mg/dL in the third, and 118 mg/dL in the fourth decade of life. Our finding that younger UC patients appeared more likely to have high triglyceride concentration requires further investigation.

In conclusion, our study indicates that LPL polymorphism influences lipid metabolism in UC patients and age of onset of UC, and might contribute to onset and biologic behavior of UC.

Many studies have considered gene polymorphisms in UC, but few have suggested an influence of polymorphism on metabolism in UC patients. Further study on LPL and other gene polymorphisms in UC remains an important line of investigation.

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