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Microsomal triglyceride transfer protein gene polymorphism strongly influences circulating malondialdehyde-modified low-density lipoprotein

Kenji Okumura[a,*], Akiko Imamura[b], Ryuichiro Murakami[b], Ryotaro Takahashi[b], Xian Wu Cheng[a], Yasushi Numaguchi[c], Toyoaki Murohara[b]

[a]*Cardiovascular Research Medicine, Nagoya University School of Medicine, Nagoya 466-8550, Japan*
[b]*Department of Cardiology, Nagoya University Graduate School of Medicine, Nagoya 466-8550, Japan*
[c]*Medical Science of Proteases, Nagoya University School of Medicine, Nagoya 466-8550, Japan*

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Abstract

Microsomal triglyceride transfer protein (MTP) plays a critical role in the assembly of lipoproteins. Therefore, we studied whether MTP gene polymorphisms are associated with atherosclerosis-promoting parameters, especially metabolic profiles and endothelial function, in healthy young men. One hundred one healthy men (mean age, 30.3 years) were studied. We analyzed the 2 promoter polymorphisms (−493G/T and −400A/T) of the MTP gene. Linkage disequilibrium analysis revealed a significant but incomplete linkage disequilibrium between the 2 polymorphisms (D' = 0.74). The −493T allele carriers (n = 26) showed marked increases in their levels of malondialdehyde-modified low-density lipoprotein (mean value, 135 vs 99 U/L in the G/G carriers; P = .003) and triglycerides (2.15 vs 1.16 mmol/L, P = .014), and reduced low-density lipoprotein particle size (259.2 vs 264.3 nm, P = .023), whereas there was no difference in apolipoproteins, insulin, adiponectin, homocysteine, folate, and endothelial function assessed using ultrasound measurement of brachial artery flow-mediated vasodilation. In contrast, the −400T allele carriers (n = 61) showed a reduced endothelial function (P = .044), accompanied by elevated apolipoprotein B levels in subjects with higher triglyceride levels. These results indicate that both promoter polymorphisms may be associated with the development of atherosclerosis and cardiovascular diseases, but that the mechanism responsible may be different.

1. Introduction

Microsomal triglyceride transfer protein (MTP) is a heterodimeric neutral lipid transfer protein that is expressed at high levels in the lumen of the endoplasmic reticulum of enterocytes and hepatocytes [1]. Microsomal triglyceride transfer protein is capable of transferring all of the lipid classes found in apolipoprotein B–containing lipoproteins, especially triglycerides and cholesterol [2]. This protein plays a critical role in the lipidation of apolipoproteins B-48 and B-100 and hence in the synthesis and secretion of very low-density lipoprotein and chylomicrons from the liver and intestine [3]. A complete lack of functional MTP induces abetalipoproteinemia, which is a rare autosomal recessive disease causing a deficiency in the assembly process and secretion of very low-density lipoprotein and chylomicrons into the plasma [4]. To date, several polymorphisms of the MTP gene have been identified and analyzed in terms of their phenotypes and functional significance [5]. Because functional MTP is an absolute requirement for the assembly of apolipoprotein B–containing lipoproteins, variants of its gene may have an impact on lipoprotein and lipid levels and thus on the development of atherosclerosis.

Low-density lipoprotein (LDL) cholesterol has been widely recognized as a strong predictor of atherosclerosis and cardiovascular events. Low-density lipoprotein is heterogeneous in terms of size, density, and chemical composition [6]. Among LDL-related parameters, the prevalence of small LDL particles and higher plasma oxidized LDL levels have been clinically shown to be more important predictors of developing atherosclerosis than LDL cholesterol itself [7]. Small LDL particles are particularly prone to oxidation, providing a possible mechanism for their atherogenicity [8]. Therefore, small

* Corresponding author. Tel.: +81 52 744 2168; fax: +81 52 744 2177.
E-mail address: kenji@med.nagoya-u.ac.jp (K. Okumura).

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LDL particle size and oxidized LDL have been increasingly recognized as potential clinical markers of increased risk for cardiovascular disease [9,10].

In the present study, we investigated whether 2 common polymorphisms of the MTP gene, −493G/T and −400A/T, are associated with atherosclerosis-promoting parameters, especially metabolic profiles and endothelial function, in healthy young men without atherosclerotic lesions.

2. Methods

2.1. Study subjects

We studied 101 young, apparently healthy men (mean age, 30.3 ± 4.2 years; range, 25-39 years). All subjects were volunteers, were free of any sign or symptoms of heart disease, and were taking no medication including antidiabetic, antihypertensive, or lipid-lowering drugs. This study was approved by the Ethics Committee of Nagoya University, and written informed consent was obtained from all subjects.

2.2. Biochemical analyses

An overnight fasting venous blood sample was obtained from all subjects. Standard assays were used to measure serum concentrations of total cholesterol, high-density lipoprotein (HDL) cholesterol, LDL cholesterol, and triglycerides, as well as insulin, glucose, hemoglobin A_{1c} (HbA_{1c}), homocysteine, and folate levels. The homeostasis model assessment of insulin resistance (HOMA-IR) was used to estimate insulin sensitivity. The enzyme-linked immunosorbent assay used to measure malondialdehyde-modified (MDA) LDL was based on the method reported by Kotani et al [11]. Plasma total adiponectin and high–molecular weight (HMW) adiponectin concentrations were measured by sandwich enzyme-linked immunosorbent assay (Otsuka Pharmaceutical, Tokyo, Japan, and Fujirebio, Tokyo, Japan, respectively) [12].

2.3. Genotyping of the MTP −493G/T and −400A/T polymorphisms

Genomic DNA was prepared from peripheral blood leukocytes using a QIAamp DNA Blood Mini Kit (Qiagen, Valencia, CA). Genotypes for the −493G/T and −400A/T polymorphisms were determined by polymerase chain reaction–restriction fragment length polymorphism analysis using specific oligonucleotide primers (−493G/T: sense, 5′-AGT TTC ACA CAT AAG GAC AAT CAT CTA-3′, and antisense, 5′-GGA TTT AAA TTT AAA CTG TTA ATT CAT ATC AC-3′; −400A/T: sense, 5′-TAT CTA CTT TAA CAT TAT TTT GAA-3′, and antisense, 5′-AAG AAT CAT ATT GAC CAG CAA TC-3′). Polymerase chain reaction products were digested by *Hph*I and *SSP*I for the −493G/T and −400A/T polymorphisms, respectively [13], and were separated by an 8% polyacrylamide gel and a 2.5% agarose gel.

2.4. LDL particle size

Ethylenediaminetetraacetic acid plasma samples were stored frozen at −70°C until analysis. The LDL particle size was determined by electrophoresis using nondenaturing 4% to 14% polyacrylamide gradient gels under modified methods [14]. In brief, 7.5-μL plasma samples were applied to gels with a final concentration of 20% sucrose and 0.25% bromphenol blue. After electrophoresis, the gels were scanned (CS9300; Shimadzu, Kyoto, Japan); and migration distances from the top of the gel to the most prominent band were measured. The estimated diameter of the major peak in each scan was identified as the LDL particle size.

2.5. Vascular study

The participants were asked to refrain from smoking within 24 hours of measurement. After overnight fasting, brachial artery function was measured following the noninvasive technique described by Celermajer et al [15] on the same day as blood sampling. Using high-resolution ultrasound cardiography (SONOS 5500; Agilent Technologies, Palo Alto, CA), the end-diastolic diameter of the right brachial artery and blood flow by pulse wave Doppler ultrasound were measured. The diameter of the right brachial artery was measured from the anterior to the posterior interface between the media and adventitia, and the mean value of 3 measurements was calculated.

Measurements of flow-mediated dilation (FMD), an endothelium-dependent response, were taken at baseline, then at 1 minute after forearm hyperemia was produced by releasing a forearm cuff inflated to 250 mm Hg for 5 minutes, and finally at rest after the subject had been lying quietly for 10 minutes. After the diameter had recovered to the level of the baseline diameter, glyceryl trinitrate–induced dilation (GTN), an endothelium-independent response, was assessed 3 and 5 minutes after the sublingual application of 300 μg glyceryl trinitrate.

2.6. Statistical analysis

Results were expressed as mean ± SD. Data were analyzed using the Statistical Package for the Social Sciences, version 16.0 (SPSS, Chicago, IL). Continuous variables were tested for normal distribution by the Kolmogorov-Smirnov test. Because the levels of triglycerides, fasting insulin, and HOMA-IR were not normally distributed, they were logarithmically transformed before statistical analysis. Multilocus haplotype frequencies were estimated using the iterative expectation-maximization algorithm [16], and the χ^2 test was used for genetic linkage between the 2 MTP gene polymorphisms. The unpaired Student *t* test was used to calculate the statistical significance between the presence and absence of the −493T allele or −400T allele. Fisher exact test was used to compare the rates

of current smokers between 2 groups of subjects. Analysis of covariance (ANCOVA) was used to compare the mean differences between the 2 groups after adjustment for certain parameters. Bivariate associations for continuous variables were determined by Pearson correlation coefficients (r). A value of P less than .05 was considered statistically significant.

3. Results

3.1. Baseline characteristics of study participants and genotype frequencies of MTP polymorphisms

The clinical characteristics of study participants are shown in Table 1. There were 9 subjects with hypertension (systolic pressure ≥140 mm Hg and/or diastolic pressure ≥90 mm Hg), 8 with hypercholesterolemia (total cholesterol >6.2 mmol/L and/or LDL cholesterol >4.1 mmol/L), and 15 with hypertriglyceridemia (>1.7 mmol/L) among the 101 subjects enrolled in the present study. There was only 1 subject with hyperinsulinemia (>240 mmol/L). Obese subjects (>25 kg/m^2) numbered 16. Two subjects had fasting glucose levels greater than 7.0 mmol/L.

The distributions of the MTP −493G/T and −400A/T polymorphisms are shown in Table 2; their distributions were compatible with the Hardy-Weinberg equilibrium (χ^2 = 0.48, P = .49 and χ^2 = 1.14, P = .29; respectively). Linkage disequilibrium analysis revealed a significant but incomplete linkage disequilibrium between the −493G/T and −400A/T polymorphisms by the expectation-maximization algorithm for haplotype inference (D' = 0.74, Δ^2 = 0.13) and by χ^2 analysis (χ^2 = 15.6, P = .004).

Table 1
Clinical characteristics of the subjects (all healthy men)

Variables	
Age (y)	30.3 ± 4.2
BMI (kg/m^2)	22.9 ± 2.5
Systolic blood pressure (mm Hg)	121 ± 12
Diastolic blood pressure (mm Hg)	71.5 ± 8.9
Total cholesterol (mmol/L)	4.89 ± 0.78
HDL cholesterol (mmol/L)	1.51 ± 0.32
LDL cholesterol (mmol/L)	2.97 ± 0.67
Triglycerides (mmol/L)	1.40 ± 1.60
LDL particle size (nm)	26.6 ± 0.9
MDA-LDL (U/L)	108 ± 55
Apolipoprotein A-I (mg/dL)	138 ± 20
Apolipoprotein B (mg/dL)	83.5 ± 18.8
Fasting glucose (mmol/L)	5.35 ± 0.57
HbA_{1c} (%)	4.69 ± 0.28
Fasting insulin (pmol/L)	64 ± 50
HOMA-IR value	2.68 ± 2.66
Current smokers (n)	30 (30%)
Total adiponectin (μg/mL)	7.34 ± 3.60
HMW adiponectin (μg/mL)	3.86 ± 2.47
Homocysteine (μmol/L)	11.10 ± 6.24
Folic acid (ng/mL)	7.67 ± 3.57
FMD	4.7 ± 2.4
GTN	16.3 ± 5.1
FMD/GTN	0.30 ± 0.14

Values are expressed as means ± SD.

Table 2
Genotype distribution and association of the −493G/T and −400A/T MTP polymorphisms

−400 A/T	−493G/T			
	G/G	G/T	T/T	Total
A/A	37	3	0	40
A/T	27	16	0	43
T/T	11	6	1	18
Total	75	25	1	101

The distributions of the 2 polymorphisms were compatible with the Hardy-Weinberg equilibrium. There was significant linkage disequilibrium between the MTP −493G/T and −400 A/T polymorphisms by the expectation-maximization algorithm for haplotype inference (D' = 0.74, Δ^2 = 0.13) and by χ^2 analysis (χ^2 = 15.6, P = .004).

3.2. Effects of the −493G/T and −400A/T polymorphisms

It was noted that the MTP −493G/T polymorphism was associated with certain plasma lipid levels. Specifically, carriers of the −493T allele showed higher levels of MDA-LDL by 35.6 U/L (P = .003) and triglycerides by 0.99 mmol/L (P = .014), and smaller LDL particle size by 5.1 nm (P = .023) than the other subjects (Table 3). There was no significant difference in apolipoprotein B levels. Even in analysis using the subgroup with higher triglyceride levels (>1.0 mmol/L,

Table 3
Physical and biochemical characteristics in the 2 groups of subjects classified according to the MTP −493G/T polymorphism

MTP G−493T	G/G (n = 75)	G/T or T/T (n = 26)	P value
Age (y)	31.0 ± 4.4	28.4 ± 6.0	.06
BMI (kg/m^2)	23.0 ± 2.7	22.6 ± 4.7	.55
Systolic blood pressure (mm Hg)	121.7 ± 12.8	119.2 ± 9.4	.35
Diastolic blood pressure (mm Hg)	71.6 ± 9.1	71.5 ± 8.7	.96
Total cholesterol (mmol/L)	4.87 ± 0.76	4.91 ± 0.82	.85
HDL cholesterol (mmol/L)	1.54 ± 0.34	1.42 ± 0.26	.11
LDL cholesterol (mmol/L)	2.94 ± 0.65	3.03 ± 0.75	.55
Triglycerides (mmol/L)	1.16 ± 0.72	2.15 ± 2.80	.014
LDL particle size (nm)	264.3 ± 9.6	259.2 ± 9.9	.023
MDA-LDL (U/L)	99.3 ± 42.9	134.9 ± 68.4	.003
Apolipoprotein A-I (mg/dL)	138.7 ± 21.8	135.8 ± 13.7	.52
Apolipoprotein B (mg/dL)	83.4 ± 18.1	86.0 ± 20.7	.40
Fasting glucose (mmol/L)	5.35 ± 0.57	5.35 ± 0.59	.94
HbA_{1c} (%)	4.66 ± 0.27	4.79 ± 0.30	.039
Fasting insulin (pmol/L)	62.7 ± 41.9	67.7 ± 69.6	.96
HOMA-IR value	2.58 ± 2.06	2.91 ± 3.93	.95
Current smokers (n)	25 (33%)	5 (19%)	.22
Total adiponectin (μg/mL)	7.0 ± 3.6	8.2 ± 3.5	.17
HMW adiponectin (μg/mL)	3.7 ± 2.5	4.2 ± 2.6	.38
Homocysteine (μmol/L)	11.7 ± 7.0	9.4 ± 2.4	.11
Folate (ng/mL)	7.78 ± 3.85	7.34 ± 2.58	.59
FMD	4.66 ± 2.41	4.60 ± 2.26	.91
GTN	15.91 ± 5.12	17.30 ± 5.20	.24
FMD/GTN	0.30 ± 0.15	0.29 ± 0.13	.73

Values are expressed as means ± SD. Triglycerides, fasting insulin, and HOMA-IR were logarithmically transformed before statistical analysis.

n = 51) or that with higher body mass index (BMI) (>22.5 kg/m^2, n = 51), the results remained unchanged.

In contrast, carriers of the −400T allele showed a modest but significant decrease in the FMD/GTN ratio representing endothelial function (P = .044, Table 4). There were no statistically significant differences in triglyceride (P = .077) or apolipoprotein B (P = .25) levels; however, within the higher triglyceride subgroup, carriers of the −400T allele showed higher levels of apolipoprotein B (94.6 ± 20.0 vs 79.7 ± 18.4 mg/dL, P = .009) and LDL cholesterol (5.18 ± 0.75 vs 4.82 ± 0.80 mmol/L, P = .049). In the higher BMI subgroup, there were no significant differences in apolipoprotein or lipid levels, whereas carriers of the −400T allele showed a modest but significant decrease in the FMD/GTN ratio compared with the other subjects (0.27 vs 0.33, P = .020).

The statistical difference in MDA-LDL was also tested by ANCOVA; and the results are shown in Table 5 after adjusting for variables with a value of P less than .2 in univariate analysis, including LDL particle size. The difference in MDA-LDL between the groups according to the −493G/T genotype remained statistically significant after adjustment for differences in triglycerides, LDL particle size, HDL cholesterol, age, adiponectin, and homocysteine. However, the significant difference in MDA-LDL between the genotypes disappeared after adjustment for all of these factors (Table 5).

Table 4
Physical and biochemical characteristics in the 2 groups of subjects classified according to [Float1]the MTP −400A/T polymorphism

MTP A−400T	A/A (n = 40)	A/T or T/T (n = 61)	P value
Age (y)	30.1 ± 4.5	30.5 ± 4.0	.65
BMI (kg/m^2)	23.1 ± 2.5	22.8 ± 2.6	.64
Systolic blood pressure (mm Hg)	121.2 ± 12.7	121.0 ± 11.7	.95
Diastolic blood pressure (mm Hg)	72.4 ± 9.6	71.0 ± 8.5	.43
Total cholesterol (mmol/L)	4.86 ± 0.79	189.5 ± 29.5	.79
HDL cholesterol (mmol/L)	1.55 ± 0.32	57.6 ± 12.7	.39
LDL cholesterol (mmol/L)	2.90 ± 0.72	2.99 ± 0.65	.49
Triglycerides (mmol/L)	1.25 ± 0.82	1.52 ± 1.94	.77
LDL particle size (nm)	264.1 ± 9.4	262.2 ± 10.2	.37
MDA-LDL (U/L)	100.5 ± 46.6	114.0 ± 56.0	.20
Apolipoprotein A-I (mg/dL)	138.7 ± 19.9	137.5 ± 20.1	.78
Apolipoprotein B (mg/dL)	80.7 ± 18.0	85.1 ± 19.2	.25
Fasting glucose (mmol/L)	5.31 ± 0.63	5.38 ± 0.53	.52
HbA_{1c} (%)	4.68 ± 0.30	4.70 ± 0.28	.76
Fasting insulin (pmol/L)	62.0 ± 39.7	65.2 ± 56.3	.78
HOMA-IR value	2.57 ± 2.18	2.73 ± 2.94	.90
Current smokers (n)	14 (35%)	16 (26%)	.38
Total adiponectin (μg/mL)	7.2 ± 3.4	7.5 ± 3.8	.68
HMW adiponectin (μg/mL)	3.9 ± 2.3	3.8 ± 2.6	.95
Homocysteine (μmol/L)	12.2 ± 8.5	10.4 ± 4.1	.15
Folate (ng/mL)	7.29 ± 3.35	7.92 ± 3.71	.38
FMD	5.19 ± 2.54	4.29 ± 2.18	.060
GTN	15.91 ± 5.02	16.50 ± 5.26	.57
FMD/GTN	0.34 ± 0.14	0.28 ± 0.14	.044

Values are expressed as means ± SD. Triglycerides, fasting insulin, and HOMA-IR were logarithmically transformed before statistical analysis.

Table 5
Differences in MDA-LDL between the groups according to the MTP −493G/T polymorphism after adjustment for certain parameters

MTP G−493T	G/G (n = 75)	G/T or T/T (n = 26)	P value
MDA-LDL (U/L)	99.3 ± 42.9	134.9 ± 68.4	.0026
After adjusting for			
Triglycerides (Ln)			.008
LDL particle size			.011
HDL cholesterol			.006
Age			.008
Total adiponectin			.009
Homocysteine			.005
Triglycerides (Ln)			.024
LDL particle size			
HDL cholesterol			
Triglycerides (Ln)			.121
LDL particle size			
HDL cholesterol, age,			
total adiponectin			

Values are expressed as means ± SD. P value was calculated by ANCOVA. Ln indicates natural logarithm.

Neither MDA-LDL nor LDL particle size was correlated with the FMD/GTN ratio (r = 0.045, P = .66 and r = −0.108, P = .29, respectively), suggesting that oxidized LDL levels are not associated with endothelial function in healthy young subjects. When the subjects were divided on the basis of smoking status, no statistical differences were found in clinical characteristics.

4. Discussion

Because MTP is an absolute requirement for the assembly and cellular secretion of apolipoprotein B–containing lipoproteins [4], any variant of its gene may have an impact on plasma lipid levels and therefore on the development of atherosclerosis. However, there have been conflicting reports concerning lipoprotein and lipid levels [13,17-19], although the −493G/T polymorphism has been shown to be associated with a prevalence of coronary artery disease [20] and peripheral artery disease [21] in cohort and case-control studies, respectively. In the present study, we demonstrate for the first time that the −493T allele elevates plasma MDA-LDL levels in healthy young men without overt cardiovascular disease. We specifically recruited such subjects to eliminate environmental factors and genetic factors that emerge with aging, such as dyslipidemia and hypertension.

We selected only 2 polymorphisms in the promoter region of the MTP gene because previous reports have demonstrated that these polymorphisms may be associated with plasma lipoprotein and lipid levels such as levels of apolipoprotein B and LDL cholesterol [18-20]. We found no deviation from the Hardy-Weinberg equilibrium in the distribution of the 2 polymorphisms in study subjects. However, polymorphisms of the MTP gene have been reported to be in linkage disequilibrium [5]; and the present

analysis revealed a significant but incomplete linkage disequilibrium (D' = 0.74). We observed that only the −493G/T polymorphism was significantly associated with plasma lipid factors such as MDA-LDL and triglyceride levels and variance of LDL particle size, but not with apolipoproteins, adiponectins, or endothelial function.

In contrast, the −400A/T polymorphism was found to be related to endothelial function; but the significance was not marked (P = .044), suggesting that a difference in phenotype may emerge in obese subjects, as previously reported [18]. In addition, plasma triglycerides tended to be associated with this polymorphism (P = .077). The effect of this polymorphism on endothelial function suggests a gene-dose effect (data not shown). Interestingly, considering that apolipoprotein B levels are reported to be affected by the −400A/T polymorphism only in the presence of visceral adipose tissue accumulation [18], the present results revealed that carriers of the −400T allele showed significantly higher apolipoprotein B levels in the subgroup with higher triglycerides levels, but not in the subgroup with higher BMI. Similar correlations with lipid levels are consistent with previous reports [5,21].

It should be noted that the present study demonstrates that the strongest atherogenic lipid MDA-LDL was affected the most strongly and almost independently by the −493G/T polymorphism. Oxidized LDL is a biochemical marker of oxidative damage and shows atherogenic action in the vascular wall, including the stimulation of foam cell formation and the activation of inflammation [22]. Malondialdehyde-modified LDL is recognized to be a surrogate marker of oxidized LDL, and it has been suggested that circulating MDA-LDL levels could be a useful indicator in identifying patients with coronary artery disease [23] and are considered a key factor in the etiology of atherosclerosis through oxidized LDL toxicity [24].

To the best of our knowledge, no significant associations of the −493G/T polymorphism with LDL cholesterol, triglycerides, or apolipoprotein have been previously reported [17,20,25]. Ledmyr et al [20] found no significant relationship between plasma lipids and lipoproteins, despite their finding that the −493G/T polymorphism conferred an increased risk of coronary heart disease. These discrepancies between studies can be explained by differences in study subjects. Most studies recruited subjects with already expressed atherosclerotic disease or with several risk factors at older than 40 years, whereas in the present study, we analyzed only healthy young men without overt cardiovascular disease. With respect to the −493T allele, Ledmyr et al [5] observed a small but significant increase in plasma total cholesterol without changes in triglycerides in healthy 50-year–old men; and more recently, Zák et al [25] observed markedly increased triglyceride levels with no change in LDL cholesterol in metabolic syndrome. The subjects recruited in the present study were much younger and therefore much less affected by environmental factors such as lifestyle. Although no precise mechanism can be explained at present, the present results indicate that the −493T allele plays a role in increasing levels of MDA-LDL and triglycerides and decreasing LDL particle size, suggesting the promotion and development of atherosclerosis and cardiovascular disease.

With respect to the −400A/T polymorphism, Karpe et al [19] found no association with lipids or apolipoproteins, whereas another study found that carriers of the −400T/T genotype showed decreased plasma LDL apolipoprotein B levels [5]. In the present study, however, we demonstrated that, in the subgroup with higher triglyceride levels, carriers of the −400T allele showed only higher levels of apolipoprotein B and LDL cholesterol. Our results are consistent with those described by Berthier et al [18], who found that the −400T allele elevated LDL apolipoprotein B levels only in viscerally obese subjects.

Although the 2 polymorphisms are involved in the promoter region, the phenotype and functional differences cannot be explained by the degree of transcription of the MTP gene. One possible explanation for this proposes linkage disequilibrium between polymorphisms. To date, several polymorphisms of the MTP gene have been found. Interestingly, the −493G/T and I/T 128 polymorphisms were in almost complete linkage disequilibrium with a D' value of 0.97 [5], implying that the presence of the −493T allele results in a single amino acid residue replacement, changing the function and activity of the produced MTP. The −493T allele has also been reported to enhance the expression of the MTP gene in vitro [19]. In addition, a presently unidentified polymorphism may also contribute strongly to lipid and lipoprotein levels.

A previous study reports that MTP polymorphisms are associated with increased insulin levels in subjects with metabolic syndrome [25]. Insulin is known to inhibit the promoter area and decrease expression of the MTP gene [26]; but, as reported in the present study, the association between MTP polymorphisms and insulin is not yet definite. Endothelial function was not found to be associated with MDA-LDL in the healthy young men recruited for this study.

In conclusion, both of the tested promoter polymorphisms may be associated with the development of atherosclerosis; but the mechanism responsible for this effect may be different. Because the −493G/T and 128I/T polymorphisms are in near-complete linkage disequilibrium, both the quantity and quality of MTP appear to be associated with differences in the phenotype effects of these polymorphisms.

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