A Functional Polymorphism in the Promoter Region of the Microsomal Triglyceride Transfer Protein (MTP −493G/T) Influences Lipoprotein Phenotype in Familial Hypercholesterolemia

Björn Lundahl, Trond P. Leren, Leiv Ose, Anders Hamsten, Fredrik Karpe

Abstract—The microsomal triglyceride transfer protein (MTP) has a key function in intracellular apolipoprotein (apo) B lipidation and secretion of very low density lipoprotein (VLDL). A recently discovered functional polymorphism in the promoter of the MTP gene (−493G/T) affects the plasma concentration of low density lipoprotein (LDL) cholesterol and the VLDL distribution between large and small particle species in healthy men. This phenotype is likely to be explained by an effect on VLDL synthesis. Against this background, we studied the effect of the MTP−493G/T polymorphism in a large cohort (217 men and 211 women) with heterozygous familial hypercholesterolemia (FH). A 40% to 50% lower serum triglyceride level was observed in homozygous carriers of the MTP−493 T allele (T/T, 0.93±0.34; G/T, 1.54±1.40; and G/G, 1.56±1.24 mmol/L; T/T vs G/T P=0.04, T/T vs G/G P=0.02). In contrast to the situation in healthy subjects, the MTP promoter polymorphism did not have a significant effect on the LDL cholesterol levels in FH subjects, although the same trend was observed (T/T, 7.31±1.87; G/T, 7.80±2.12; and G/G, 7.91±2.31 mmol/L, NS). Adjustment for the apo E gene polymorphism by inclusion of subjects homozygous for the apo E3 allele only revealed a reciprocal high density lipoprotein cholesterol–elevating effect (T/T, 1.41±0.73; G/T, 1.18±0.27; and G/G, 1.16±0.29 mmol/L; T/T vs G/G P=0.05, T/T vs G/G P=0.02). In contrast to the situation in healthy subjects, the MTP promoter polymorphism did not have a significant effect on the LDL cholesterol–lowering effect of the rare MTP gene promoter variant (MTP−493T) present in healthy subjects is shifted to a triglyceride-lowering effect in FH. These data suggest that the MTP gene has a role in modulating the clinical phenotype of FH. (Arterioscler Thromb Vasc Biol. 2000;20:1784–1788.)

Key Words: polymorphisms ■ lipoproteins ■ promoter regions ■ microsomes ■ familial hypercholesterolemia

The microsomal triglyceride transfer protein (MTP) is a heterodimeric lipid transfer protein that is composed of a unique 97-kDa subunit and the multifunctional enzyme, protein disulfide isomerase. MTP is present at high concentrations on the luminal side of the endoplasmic reticulum in tissues secreting apo B–containing lipoproteins, ie, the liver, intestine, and, as recently discovered, the heart. In vitro studies have shown that MTP is capable of transferring a variety of lipids, although it has a preference for triglycerides and cholesteryl esters. Absence of a functional MTP causes abetalipoproteinemia, which is a rare, autosomal, recessive disease causing a deficiency in the assembly process and secretion of VLDL and chylomicrons into the plasma. A number of structural mutations leading to abetalipoproteinemia have now been characterized, and in addition, the MTP gene seems polymorphic as such.

Owing to the central role of MTP in VLDL secretion, we recently hypothesized that more subtle changes in the MTP gene structure might influence the plasma lipoprotein phenotype in humans. A common, single-nucleotide polymorphism (a G-to-T substitution at position −493 of the MTP promoter) that affects the promoter activity of the MTP gene was recently discovered in humans. The rarer T variant (allele frequency of 0.2) was associated with elevated transcriptional activity (in vitro in HepG2 cells), and subjects homozygous for the T allele express a phenotype comprising triglyceride-enriched, large VLDL particles; normal whole-plasma triglycerides; and decreased LDL cholesterol concentration.

Familial hypercholesterolemia (FH) is a common, autosomal, dominant disorder with an estimated prevalence of 1/500 (the heterozygous form) in the general population. In the majority of patients with FH, the disorder is caused by a mutation in the coding region of the gene for the LDL receptor, resulting in excessive elevations of LDL in plasma. Although LDL receptor function is severely affected in FH, the clinical phenotype is highly variable, and this has been

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1784
be augmented on an FH background.14 Of note, the odds ratio lowering of HDL cholesterol levels, and this effect seems to

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The normal LDL cholesterol–modulating effect of apo E in a normal population has generally been difficult to reproduce in

Patients.11 Among common variants in the genes coding for proteins involved in lipoprotein metabolism, variations in the lipoprotein(a) [Lp(a)], lipoprotein lipase, and apo E genes have been investigated on an FH background.12–23 Lp(a) levels are strongly determined by Lp(a) genotype, and Lp(a) levels are significantly higher in individuals with FH. The well-known LDL cholesterol–modulating effect of apo E in a normal population has generally been difficult to reproduce in FH subjects. The normal LDL cholesterol–elevating effect of apo E4 has not been observed at all, whereas a minor lowering effect has been attributed to apo E2 in a few studies. The lipoprotein lipase N291S variant, on the other hand, normally gives rise to elevations of serum triglycerides and lowering of HDL cholesterol levels, and this effect seems to be augmented on an FH background.14 Of note, the odds ratio for cardiovascular disease was elevated almost 4-fold in carriers of the dysfunctional lipoprotein lipase allele.

Against this background, we hypothesized that the MTP–493G/T polymorphism could influence the lipoprotein phenotype in subjects with FH. Furthermore, because the normal effect of the MTP–493 T allele is to lower LDL levels, we wanted to investigate whether this effect was maintained under conditions of failing LDL removal from the plasma.

Methods

Subjects

A total of 428 subjects with FH (217 males and 211 females) were included in this study. They were all unrelated. Seventy-nine percent (339 subjects) had a known mutation in the LDL receptor gene,24 and the remaining 79 subjects were diagnosed on a clinical basis according to the method of Goldstein and Brown.25 The age range was 4 to 87 years (median age, 34 years). All were white of Norwegian descent. None of the subjects possessed the apo B-3500 mutation as determined by the assay of Hansen et al.26

Genotyping for the MTP–493G/T Polymorphism

Genotyping for the MTP–493G/T polymorphism was performed on a nested polymerase chain reaction (PCR) product. Primers for the first PCR were as follows: 5’-CCCTCTTATCTCCTCTTCTAGAA (forward) and 5’-AAGAATCATATTGACCAGCAATC (reverse). This PCR was done with an MgCl2 concentration of 2.0 mmol/L. The PCR protocol used for amplification was as follows: 94°C for 3 minutes followed by 35 cycles at 94°C for 0.5 minute, 55°C for 1 minute, 72°C for 5 minutes, and 72°C for 5 minutes. Primers for the second PCR were as follows: 5’-AGTTTCACACATAAGGACAATCATCTA (forward) and 5’-GGATTTAAATTTAAACTGTTAATTCATATCAC (reverse). One microliter of the product from the first reaction was used for the second. The MgCl2 concentration was elevated to 5.0 mmol/L, and conditions were 94°C for 3 minutes followed by 35 cycles at 94°C for 0.5 minute, 57°C for 1.0 minute, 72°C for 2.0 minutes, and 72°C for 5 minutes. The product of the second PCR was a fragment of 109 bp. This fragment was then incubated overnight with the restriction enzyme HphI, whereby the following genotype-specific fragments were obtained: homozygotes for the T variant, 1 fragment of 109 bp; G/T heterozygotes, 3 fragments of 109, 89, and 20 bp; and homozygotes for the G variant, 2 fragments of 89 and 20 bp. Because of the high risk of contamination when performing a nested PCR, 1 DNA-free control sample was included for every eight sample containing FH DNA.

Genotyping for the Apo E Polymorphism

The method described by Hixson and Vernier27 was used with minor modifications. PCR amplification was made with primers originally designed by van den Maagdenberg et al28 (5’-AGGCCGCGCTCG-GGCCCTT) and (5’-TCCCCACTGTGCGACACCCT). The method described by Hixson and Vernier27 was used with minor modifications. PCR amplification was made with primers originally designed by van den Maagdenberg et al28 (5’-AGGCCGCGCTCG-GGCCCTT) and (5’-TCCCCACTGTGCGACACCCT).

Lipid and Lipoprotein Determinations

Serum cholesterol, HDL cholesterol, and serum triglyceride concentrations were determined by standard enzymatic methods on fasting samples that were drawn before therapy with lipid-lowering drugs was started. The LDL cholesterol concentration was calculated by using the Friedewald formula.29

Statistical Methods

Conventional methods were used for calculation of means and SDs. Coefficients of skewness and kurtosis were calculated to test deviations from a normal distribution. Logarithmic transformation was performed on the individual values of skewed variables, and a normal distribution of transformed values was confirmed before statistical computations and significance testing. Comparisons of clinical and biochemical traits between genotype groups were made by ANOVA with the Scheffe post hoc test and by the χ2 test for sex.

Table 2. Frequencies of Apo E Genotypes in the FH Subjects

<table>
<thead>
<tr>
<th>Apo E Genotype</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>E2/2</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>E2/3</td>
<td>27</td>
<td>6.4</td>
</tr>
<tr>
<td>E2/4</td>
<td>11</td>
<td>2.6</td>
</tr>
<tr>
<td>E3/3</td>
<td>265</td>
<td>63.1</td>
</tr>
<tr>
<td>E3/4</td>
<td>104</td>
<td>24.7</td>
</tr>
<tr>
<td>E4/4</td>
<td>13</td>
<td>3.1</td>
</tr>
</tbody>
</table>

Table 1. Serum Concentrations of Lipids and Major Lipoproteins in FH Subjects Grouped According to the MTP–493G/T Genotype

<table>
<thead>
<tr>
<th></th>
<th>−493GG (n = 229)</th>
<th>−493GT (n = 173)</th>
<th>−493TT (n = 22)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum cholesterol, mmol/L</td>
<td>9.83±2.48</td>
<td>9.65±2.12</td>
<td>9.08±1.97</td>
<td>NS</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>7.91±2.31</td>
<td>7.80±2.12</td>
<td>7.31±1.87</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.18±0.33</td>
<td>1.20±0.30</td>
<td>1.35±0.58</td>
<td>NS</td>
</tr>
<tr>
<td>Serum triglycerides, mmol/L</td>
<td>1.56±1.24</td>
<td>1.54±1.40</td>
<td>0.93±0.34*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Age, y</td>
<td>33.8±15.1</td>
<td>34.3±15.6</td>
<td>30.6±10.4</td>
<td>NS</td>
</tr>
<tr>
<td>Sex, M/F, n/n</td>
<td>114/115</td>
<td>95/78</td>
<td>9/13</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean±SD. Differences between genotype groups were assessed by ANOVA with the Scheffe post hoc test for continuous variables and by the χ2 test for sex.

*P=0.02 compared with G/G and P=0.04 compared with G/T.
TABLE 3. Serum Concentrations of Lipids and Major Lipoproteins in FH Subjects Grouped According to Apo E Genotype

<table>
<thead>
<tr>
<th></th>
<th>E2+ (n=27)</th>
<th>E3/3 (n=263)</th>
<th>E4+ (n=116)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum cholesterol, mmol/L</td>
<td>10.01±2.60</td>
<td>9.84±2.43</td>
<td>9.44±1.99</td>
<td>NS</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>8.06±2.54</td>
<td>7.95±2.23</td>
<td>7.59±2.10</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.29±0.28</td>
<td>1.18±0.32</td>
<td>1.23±0.38</td>
<td>NS</td>
</tr>
<tr>
<td>Serum triglycerides, mmol/L</td>
<td>1.53±0.90</td>
<td>1.43±1.22</td>
<td>1.57±1.26</td>
<td>NS</td>
</tr>
<tr>
<td>Age, y</td>
<td>36.6±11.9</td>
<td>33.2±16.2</td>
<td>34.2±13.1</td>
<td>NS</td>
</tr>
<tr>
<td>Sex, M/F, n/n</td>
<td>14/13</td>
<td>134/129</td>
<td>64/52</td>
<td>NS</td>
</tr>
</tbody>
</table>

E2+ indicates apo E2/3 carriers; E4+, apo E3/4 and apo E4/4 carriers. Values are mean±SD. Differences between genotype groups were assessed by ANOVA with the Scheffé post hoc test for continuous variables and by the χ² test for sex.

Results

The frequency of the MTP−493T allele was 25.5%, which is similar to that in a healthy Scandinavian population. Serum concentrations of lipids and major lipoproteins in FH subjects grouped according to MTP−493G/T genotype are shown in Table 1. Subjects homozygous for the rare MTP−493 T variant had a 40% lower serum triglyceride concentration compared with subjects carrying 1 or 2 copies of the common G allele (T/T, 0.93±0.34; G/T, 1.54±1.40; and G/G, 1.56±1.24 mmol/L; T/T versus G/T P=0.04, T/T versus G/G P=0.02). Whole-serum cholesterol concentrations were unaffected by the MTP promoter polymorphism. LDL cholesterol was not significantly affected, although levels were slightly lower in homozygotes for the T allele (T/T, 7.31±1.87; G/T, 7.80±2.12; and G/G, 7.91±2.31 mmol/L, NS). There was a tendency to higher HDL cholesterol levels among homozygotes for the T variant (P=0.08), and this effect was statistically significant in women but not in men (in women T/T, 1.49±0.70; G/T, 1.31±0.30; and G/G, 1.25±0.35 mmol/L; in men T/T, 1.16±0.27; G/T, 1.12±0.26; and G/G, 1.11±0.29 mmol/L).

The age distribution did not differ between FH patients grouped according to MTP−493G/T genotype (T/T, 33.3±8.8; G/T, 35.1±15.4; and G/G, 34.4±12.2 years, NS). ANCOVA with age as a covariate increased the genotype-specific differences in LDL cholesterol concentration (interaction of MTP genotype×age, P=0.015), whereas the serum levels of other lipids and lipoproteins, including triglycerides, were unaffected.

The frequencies of the apo E genotypes are shown in Table 2. The overall allele frequencies of E2, E3, and E4 were 0.044, 0.618, and 0.344, respectively. Subjects were divided into 3 main apo E genotype groups to investigate the effect on serum lipid and lipoprotein levels of the apo E gene: E2+ (n=27, consisting of apo E2/3 carriers), E3/3 (n=265, consisting of apo E3/3 carriers), and E4+ (n=117, consisting of apo E3/4 plus apo E4/4 carriers). Carriers with the apo E2/4 genotype (n=11) were not included in this analysis. There were no significant effects of apo E genotype alone on serum lipids or lipoprotein levels (Table 3). Although apo E genotype did not significantly influence serum concentrations of lipids and major lipoproteins in the present FH cohort, we wanted to study the effect of the MTP−493G/T genotypic variation on a homogeneous apo E background. The lipid and lipoprotein phenotype was therefore studied in the E3/3 group. The triglyceride-lowering effect of the MTP−493 T allele remained significant, and in addition, a significant reciprocal elevation of HDL cholesterol emerged (T/T, 1.41±0.73; G/T, 1.18±0.27; and G/G, 1.16±0.29 mmol/L; T/T versus G/T P=0.06, T/T versus G/G P=0.04). ANCOVA with age as a covariate did not affect any of the lipid and lipoprotein results in regard to the apo E polymorphism.

The present FH group is unique because 35% of the patients (n=151) are carriers of the same mutation at position +1 (G→A) of intron 3 (Elverum). This feature enabled the study of MTP−493G/T and apo E genotypic variations on a homogeneous FH background. The magnitude of serum triglyceride change depending on the MTP−493 T allele was essentially maintained with the homogeneous FH-Elverum background but was no longer statistically significant (Table 4). The apo E genotype showed a borderline statistically significant effect on HDL on the Elverum background (E2+, 1.35±0.30; E3/3, 1.35±0.30; E4+, 1.30±0.23 mmol/L).

TABLE 4. Serum Concentrations of Lipids and Major Lipoproteins in FH-Elverum Subjects Grouped According to the MTP−493G/T Genotype

<table>
<thead>
<tr>
<th></th>
<th>−493GG (n=81)</th>
<th>−493GT (n=62)</th>
<th>−493TT (n=6)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum cholesterol, mmol/L</td>
<td>10.39±2.70</td>
<td>9.70±1.88</td>
<td>9.13±1.62</td>
<td>NS</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>8.43±2.29</td>
<td>7.95±1.82</td>
<td>7.46±1.59</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.15±0.31</td>
<td>1.16±0.27</td>
<td>1.30±0.23</td>
<td>NS</td>
</tr>
<tr>
<td>Serum triglycerides, mmol/L</td>
<td>1.50±1.25</td>
<td>1.32±1.05</td>
<td>0.83±0.32</td>
<td>NS</td>
</tr>
<tr>
<td>Age, y</td>
<td>32.5±12.3</td>
<td>27.7±12.7</td>
<td>31.2±7.4</td>
<td>NS</td>
</tr>
<tr>
<td>Sex, M/F, n/n</td>
<td>43/38</td>
<td>38/24</td>
<td>3/3</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean±SD. Differences between genotype groups were assessed by ANOVA with the Scheffé post hoc test for continuous variables and by the χ² test for sex.
Large number of receptors might be involved. It cannot be LDL, because lipolysis has to occur, and after that step, a situation. Furthermore, removal of VLDL from the plasma is subject to much more complex regulation than is removal of defective LDL removal from the plasma, it is less likely that the production rate of apo B-containing particles is a limitations notwithstanding, our findings are in line with our previous observations, they are internally consistent, and underlying metabolic mechanisms can be envisaged, as discussed above.

In summary, we have found that a common, functional variant of the MTP gene promoter, which normally has a marked LDL cholesterol–lowering effect, presents with reduced serum triglycerides in FH. This new genetic variant is therefore a modulator of the lipoprotein phenotype in FH and might also reduce the cardiovascular risk of subjects with FH.

Acknowledgments

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References

5. Wetterau JR, Aggerbeck LP, Bouma ME, Eisenberg C, Munck A, Hermier M, Schmutz J, Gay G, Rader DJ, Gregg RE. Absence of deficiency of lipoprotein lipase, which should be an LDL receptor–independent mechanism, seems to produce an augmented hypertriglyceridemic effect on an FH background compared with the normal situation. An elevated Lp(a) level is a risk factor for coronary heart disease in patients with FH. The Lp(a) level is strongly determined by the Lp(a) genotype, and the concentrations of Lp(a) are increased in FH. Modulation of the lipoprotein phenotype in FH by the MTP−493G/T polymorphism is of potential clinical relevance because combined hyperlipidemia confers a considerable increase in risk of coronary artery disease compared with isolated hypercholesterolemia. A tendency to hypertriglyceridemia has also been specifically linked to atherosclerotic lesion progression in FH.

When interpreting the present data, it should be emphasized that a type I error cannot be excluded owing to the number of variables examined and the multiple comparisons performed on a fairly limited patient group. However, these restrictions notwithstanding, our findings are in line with our previous observations, they are internally consistent, and underlying metabolic mechanisms can be envisaged, as discussed above.

In summary, we have found that a common, functional variant of the MTP gene promoter, which normally has a marked LDL cholesterol–lowering effect, presents with reduced serum triglycerides in FH. This new genetic variant is therefore a modulator of the lipoprotein phenotype in FH and might also reduce the cardiovascular risk of subjects with FH.

Discussion

The present study shows that a common, single-nucleotide polymorphism in the MTP gene promoter (−493G/T) affects the lipoprotein phenotype in subjects with FH. FH subjects homozygous for the rare MTP−493 T variant exhibited a significantly lower serum triglyceride level, whereas the effect on LDL levels seen in healthy individuals was not as clear in the FH population. The mechanism behind this alteration in lipoprotein phenotype expression is unknown and cannot be determined from an association study like this, but it is likely to be related to the regulation of VLDL secretion, which is particular for the FH situation. It is known from previous studies that the total apo B secretion rate is decreased in patients with FH compared with normal individuals and particularly so in comparison with hypertriglyceridemic subjects. Under normal circumstances, the major proportion of apo B is secreted as large, triglyceride-rich VLDL particles, whereas in FH, almost 40% of apo B is secreted as smaller and denser IDL and LDL particles. It is therefore perhaps not very surprising that an elevated MTP activity (presumed to be present in MTP−493 T carriers) might result in a different phenotype in FH compared with the normal situation. In addition, because it is well established that the elevated LDL levels in FH are a direct consequence of defective LDL removal from the plasma, it is less likely that the production rate of apo B–containing particles is a major determinant of the plasma LDL level in the FH situation. Furthermore, removal of VLDL from the plasma is subject to much more complex regulation than is removal of LDL, because lipolysis has to occur, and after that step, a large number of receptors might be involved. It cannot be ruled out that alternative removal pathways for VLDL are upregulated in the FH situation and that certain subpopulations of VLDL are more affected than others by these processes.

Previous studies of common genetic variants of enzymes or proteins involved in lipoprotein metabolism, likely to modify the clinical presentation of FH, are limited to the apo E and lipoprotein lipase genes and to Lp(a). The apo E polymorphism seems to modulate LDL concentrations less in FH than in normal subjects, which is in line with the present findings. On the other hand, the effect of a heterozygous

<table>
<thead>
<tr>
<th>Table 5: Serum Concentrations of Lipids and Major Lipoproteins in FH-Elverum Subjects Grouped According Major Apo E Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>E2+ (n=15)</strong></td>
</tr>
<tr>
<td>Serum cholesterol, mmol/L</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
</tr>
<tr>
<td>Serum triglycerides, mmol/L</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Sex, M/F, n/n</td>
</tr>
</tbody>
</table>

*P=0.04 compared with E3/3 and P=0.07 compared with E4+.


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