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Apolipoprotein E (apo E) plays an important role in receptor mediated clearance of lipoprotein particles from plasma. Common genetic variation in apo E exists with three alleles coding for proteins called E2, E3, and E4. In in vitro receptor binding assays, E2 binds poorly, whereas E3 and E4 function normally. Recently, the apo E phenotype has been shown to have an effect on low density lipoprotein (LDL) cholesterol levels with levels in subjects with E2 lower and E4 higher than E3. We have examined the effect of the apo E polymorphism on dietary fat clearance using the vitamin A-fat loading test, which specifically labels intestinally derived lipoproteins with retinyl palmitate (RP). 27 normal subjects were studied, 10 with E3/3, 9 with E3/2, 7 with E4/3, and 1 with E4/4. After a vitamin A-containing fatty meal, postprandial RP concentrations were measured in chylomicron (Sf greater than 1,000) and nonchylomicron (Sf less than 1,000) fractions for 14 h. Compared with E3/3 subjects, E3/2 subjects had a significantly higher nonchylomicron RP concentration (P less than 0.05) (peak heights and areas below the curves) indicating slower clearance and the E4/3, E4/4 group had a significantly lower nonchylomicron RP concentration (P less than 0.05) indicating faster clearance. The clearance in the latter group was twice that of E3/2 subjects (P less than 0.01). Thus, heterozygosity […]

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Dietary Fat Clearance in Normal Subjects Is Regulated by Genetic Variation in Apolipoprotein E

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Abstract

Apolipoprotein E (apo E) plays an important role in receptor mediated clearance of lipoprotein particles from plasma. Common genetic variation in apo E exists with three alleles coding for proteins called E2, E3, and E4. In vitro receptor binding assays, E2 binds poorly, whereas E3 and E4 function normally. Recently, the apo E phenotype has been shown to have an effect on low density lipoprotein (LDL) cholesterol levels with levels in subjects with E2 lower and E4 higher than E3. We have examined the effect of the apo E polymorphism on dietary fat clearance using the vitamin A-fat loading test, which specifically labels intestinally derived lipoproteins with retinyl palmitate (RP). 27 normal subjects were studied, 10 with E3/3, 9 with E3/2, 7 with E4/3, and 1 with E4/4. After a vitamin A-containing fatty meal, postprandial RP concentrations were measured in chylomicron (Sf > 1,000) and nonchylomicron (Sf < 1,000) fractions for 14 h. Compared with E3/3 subjects, E3/2 subjects had a significantly higher nonchylomicron RP concentration (P < 0.05) (peak heights and areas below the curves) indicating slower clearance and the E4/3, E4/4 group had a significantly lower nonchylomicron RP concentration (P < 0.05) indicating faster clearance. The clearance in the latter group was twice that of E3/2 subjects (P < 0.01). Thus, heterozygosity for the defective form of apo E, E2, delays, and the surprising presence of a functionally normal allele, E4, increases clearance. This apo E effect on exogenous fat clearance may explain the recently described effect of the apo E phenotypes on LDL cholesterol levels.

Introduction

Apolipoprotein (apo) E is a constituent of plasma very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL), high density lipoproteins (HDL), and chylomicron remnants (1–3). It is recognized by LDL receptors and hepatic chylomicron remnant receptors and mediates hepatic uptake of IDL and chylomicron remnants, and in this manner, plays an important role in lipoprotein metabolism (4–8). Different forms of apo E have been recognized in humans due to genetic variation in the apo E gene resulting from three common alleles in the population, e4, e3 and e2, with frequencies of ~ 15, 75, and 10%, respectively. These alleles produce gene products with different isoelectric points, designated from basic to acidic, E4, E3, and E2, respectively. These three alleles result in three homozygous phenotypes, E4/4, E3/3, and E2/2, with approximate frequencies 2, 56, and 1%, respectively, and three heterozygous phenotypes, E4/3, E3/2, and E4/2, with approximate frequencies 23, 15, and 3%, respectively (9–16).

Type III hyperlipoproteinemia, a disorder characterized by increased cholesterol and triglyceride levels (due to the presence of chylomicron remnants in fasting plasma), premature coronary and peripheral vascular disease, and tuberoeruptive palmar xanthomas is strongly associated with the E2/2 phenotype present in 1% of the population (10, 17, 18). E2 binds poorly to receptors and this is thought to account for the defective chylomicron remnant clearance in this disorder (19, 20). The influence of the other apo E phenotypes on dietary fat clearance has not been studied.

Recently, population based studies have shown that the apo E polymorphism is associated with differences in plasma LDL levels. Phenotypes E4/4 and E4/3 are associated with higher and E3/2 and E2/2 with lower LDL cholesterol levels than E3/3 (12, 13, 21–24). The association of elevated LDL cholesterol levels with coronary heart disease susceptibility is well documented (25, 26) and heightens the importance of understanding the influence of the apo E phenotype on LDL levels. Apo E is not a constituent of LDL and its influence must be indirect.

In the current study, we used the vitamin A-fat loading test, which specifically labels intestinally derived lipoproteins with retinyl palmitate (27–34), to follow the metabolism of exogenous fat to see if the apo E phenotype affects dietary fat clearance. We show that the common apo E phenotypes do affect dietary fat clearance and we then present a model whereby this may explain the effect of the apo E phenotype on LDL cholesterol levels.

Methods

Subjects. 27 normolipidemic, healthy volunteers participated in the study. None of them had diabetes or liver, renal, or thyroid disease. At the time of the vitamin A-fat loading test, 16 subjects were inpatients on the Rockefeller University Hospital Metabolic Ward. They were stabilized for 3 wk on a metabolic diet containing 42% of calories from fat (caloric distribution: fat 42%, protein 15%, carbohydrate 43%, with a polyunsaturated/saturated (P/S) ratio of 0.1 and a cholesterol intake of 175 mg/1,000 cal). The other 11 subjects were admitted to the hospital the morning of the study and remained hospitalized for 24 h. By diet history, these subjects were not on any dietary restrictions. Apo E phenotypes of the 16 inpatient subjects were E3/2 = 5, E3/3 = 7 and Er/3,4/4 = 4. Apo E phenotypes of the 11 outpatient subjects were E3/2 = 3, E3/3 = 4, and E4/3 = 4.

Vitamin A-fat loading test. The vitamin A-fat loading test was performed as recently described (34). After an overnight 12-h fast,
subjects were given a fatty meal plus 60,000 U of aqueous vitamin A/m² body surface. The fatty meal contained 50 g of fat/m² body surface, consisting of 65% of calories as fat, 20% as carbohydrate, and 15% as protein. It contained 600 mg cholesterol/1,000 calories, and the P/S ratio was 0.3. This was given as a milkshake, scrambled eggs, bread and cheese, and was eaten in 10 min. The vitamin A was added to the milkshake. After the meal, subjects stayed fasting for 14 h, but as much drinking water was allowed as desired. To measure levels of retinyl palmitate, blood samples were drawn before the meal and every hour after the meal until 6 h, then every 2 h until 14 h. The subjects tolerated the meal well, and no one had diarrhea or other symptoms of malabsorption.

**Analysis of samples.** Venous blood was drawn from the forearm and transferred to a tube containing sodium EDTA. Samples were immediately centrifuged at 1,500 g for 15 min and 0.5 ml of plasma was stored wrapped in foil at −20°C for retinyl ester assay. Another 0.5 ml was stored at 4°C for triglyceride determinations. An aliquot of 2.5 ml of plasma was transferred into a ½ x 2 in. cellulose nitrate tube and overlayered with 2.5 ml sodium chloride solution (d = 1.006 g/ml). Tubes were subjected to preparative ultracentrifugation for 1.6 x 10⁶ g-min in a rotor (SW-55; Beckman Instruments, Inc., Fullerton, CA) to float chylomicron particles of Sf > 1,000 (35-37). The chylomicon-containing supernatant was removed and brought to a total volume of 2 ml with saline. The infranatant was brought to a volume of 5 ml with saline. 0.5-ml aliquots of supernatant and infranatant were wrapped in foil and assayed for retinyl ester. Additional aliquots were assayed for triglyceride concentration. As discussed elsewhere, the procedure appears to separate a predominantly chylomicon population from a predominantly remnant population (34, 35).

**Retinyl ester assay.** The assays were carried out in subdued light with HPLC grade solvents. Retinyl acetate was added to the samples as an internal standard. The samples were then mixed with ethanol 4 ml, hexane 5 ml, and water 4 ml with vortexing between each addition. Two phases were formed and 4 ml of the upper (hexane) phase was removed and evaporated under nitrogen (38). The residue was dissolved in a small volume of benzene, and an aliquot was injected into an HPLC 5 µm ODS-18 radial compression column. 100% methanol was used as the mobile phase at a flow rate of 2 ml/min. The effluent was monitored at 340 nm, and the peak of retinyl palmitate (RP) was identified by comparison to the retention time of purified standard (Sigma Chemical Co., St. Louis, MO). In agreement with previous reports (31, 33), it was found that 75–80% of total plasma retinyl esters were accounted for by retinyl palmitate. In addition, the distribution of retinyl esters remained constant throughout the study. The amounts of RP in plasma and lipoprotein fractions were quantitated by the area ratio method (39) using retinyl acetate as a reference (34).

**Lipid and lipoprotein determination.** Cholesterol and triglycerides were measured enzymatically using the reagents cholesterol 236691 and triglyceride 126012 (Boehringer Mannheim, Inc., Indianapolis, IN). Total and HDL cholesterol measurements were standardized by the Lipid Standardization Program of the Center for Disease Control, Atlanta, Georgia. HDL cholesterol was determined after precipitation of whole plasma with dextran sulfate-magnesium (40). HDL plus LDL cholesterol was measured on the infranatant after a 2-h spin in the Beckman airfuge to float the VLDL. Appropriate corrections were made for dilution factors, and VLDL, LDL, and HDL cholesterol levels were calculated.

**Apolipoprotein E phenotyping.** 5 ml of plasma was added to each of two quick-seal ultracentrifuge tubes, ½ x 2½ in. The tubes were filled to the top with saline, sealed, and spun at 39,000 rpm for 20 h at 4°C using a 40.3 Beckman rotor. The floating VLDL layer was removed with a syringe and transferred to a glass tube for delipidation with ethanol/acetone 1:1 at a temperature of −20°C. The tubes were vortexed, kept at −20°C for 1 h, spun, and the supernatant discarded. The pellet was washed twice with cold ether, and dissolved in 0.2 to 0.3 ml of a buffer containing 6 M urea, 0.01 M Tris HCl, 0.01 M dithiothreitol, pH 8.6. Protein concentration was determined by a Bio-Rad assay using bovine serum albumin as a reference. A one-dimensional isoelectric focusing gel was prepared in a 6-M urea buffer containing 7.5% acrylamide, 0.2% N,N'-methylene-bis-acrylamide (BIS) and 2% amorpholines of pH 4–6.5. The gel was prefocused for 1 h at 4°C at 110 V, and then 50 µg of VLDL protein was applied to each gel lane. Focusing was carried out for 17 h at 4°C at 250 V. After focusing, the gels were fixed in trichloroacetic acid-sulfosalicylic acid, stained with Coomassie Blue (0.1%) in methanol, water, acetic (4.5/4.5/1:0), and destained. Specimens from individuals with known apo E phenotypes were run along with new samples to aid in the interpretation of the results.

**Postheparin plasma lipolytic activities.** Lipolytic activities were determined 1 wk before the vitamin A-fat loading test. Lipoprotein lipase (LPL) and hepatic triglyceride lipase (HTGL) were released into the circulation by intravenous heparin injection at a dose of 60 U/kg body wt. After 15 min blood was drawn into tubes containing 4 ml EDTA. The plasma was immediately separated at 4°C by centrifugation at 2,700 rpm for 12 min and promptly frozen at −70°C. The assay itself is a modification of the method of Krauss (41) as recently described (34). In short, 20 µl of postheparin plasma is added to freshly sonified substrate, containing radiolabeled and unlabeled triolein and triton in a Tris HCl buffer pH 8.6, mixed, and incubated for 20 min at 37°C. The reaction is stopped by a mixture of chloroform, methanol, and heptane, and a base in the form of K₂CO₃ is added. After mixing and centrifugation, an aliquot of the aqueous phase is counted and the total lipolytic activity is given as micromoles FFA liberated/milliliter plasma/hour. Another aliquot of 20 µl of postheparin plasma is incubated for 1 h at 4°C with 25 µl of rabbit anti-human LPL antiserum before the lipase assay described above. The antiserum was prepared in our laboratory by injecting rabbits with LPL purified from fresh human breast milk. This antiserum completely inhibited the activity of purified human breast milk lipoprotein lipase, but had no effect on human hepatic lipase purified by heparin Sepharose chromatography from postheparin plasma. LPL activity is the difference between total and antiserum-inhibited activity. The latter is taken to be the HTGL activity.

**Statistical analysis.** The differences between groups of subjects were analyzed for significance mainly using unpaired Student t tests. Differences in dietary fat clearance between the apo E phenotype groups were also sought using analysis of variance, and Duncan’s multiple comparison tests. Calculations were performed on The Rockefeller University Hospital CLINFO system.

**Results**

**Subject characteristics.** The clinical features, lipid levels, and plasma postheparin lipolytic activities for groups of subjects are presented in Table 1. When males and females are compared, males had lower HDL cholesterol levels (P = 0.003) and a trend towards lower LPL and higher HTGL activities, P = 0.11 and P = 0.054, respectively. The subjects were also grouped by age as older (40–72 yr) and younger (19–28 yr). Older subjects had lower LPL (P = 0.019) and higher HTGL (P = 0.032) activities when compared with younger subjects. Apo E phenotype analysis revealed 9 subjects with E3/2, 10 with E3/3, 7 with E4/3, and 1 with E4/4. There were no subjects with E4/2 or E2/2. For purposes of analysis, the results from the person with E4/4 were combined with those for the E4/3 group. This did not substantially affect any of the results. E3/2 individuals had lower LDL cholesterol levels than E3/3 subjects (P = 0.003), whereas those in the E4/3, E4/4 grouping showed a trend to higher LDL cholesterol levels than E3/3 individuals, but this was not significant (P = 0.116). The apo E

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1. Abbreviations used in this paper: HTGL, hepatic triglyceride lipase; LPL, lipoprotein lipase; RP, retinyl palmitate.
Table I. Clinical and Laboratory Data for Subjects Undergoing the Vitamin A-Fat Loading Test*

<table>
<thead>
<tr>
<th>Subject category</th>
<th>Males</th>
<th>Females</th>
<th>Age (yr)</th>
<th>Body mass index (kg/m²)</th>
<th>E Phenotype</th>
<th>Lipoprotein lipase (μmol FFA/ml/h)</th>
<th>Hepatic triglyceride lipase (mg/dl)</th>
<th>Plasma lipids (mg/dl)</th>
<th>Cholesterol (mg/dl)</th>
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<tbody>
<tr>
<td>Males (n = 14)</td>
<td>14</td>
<td>—</td>
<td>31±15</td>
<td>23.8±2.1</td>
<td>E3/2</td>
<td>3</td>
<td>7</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>E3/3</td>
<td>6</td>
<td>3</td>
<td>4</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>E4/3</td>
<td>7</td>
<td>3</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>E4/4</td>
<td>7</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Females (n = 13)</td>
<td>—</td>
<td>13</td>
<td>34±18</td>
<td>23.5±2.5</td>
<td>E3/2</td>
<td>7.4±1.9&lt;sup&gt;2&lt;/sup&gt;</td>
<td>13.7±4.5</td>
<td>172±33</td>
<td>72±24</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>E3/3</td>
<td>7.6±1.9&lt;sup&gt;2&lt;/sup&gt;</td>
<td>14.4±5.9&lt;sup&gt;2&lt;/sup&gt;</td>
<td>164±30</td>
<td>71±22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>E4/3</td>
<td>5.0±2.4&lt;sup&gt;2&lt;/sup&gt;</td>
<td>19.5±4.5&lt;sup&gt;2&lt;/sup&gt;</td>
<td>184±28</td>
<td>85±19</td>
</tr>
<tr>
<td>Age group 19–28&lt;sup&gt;a&lt;/sup&gt; (n = 16)</td>
<td>9</td>
<td>7</td>
<td>21±3</td>
<td>23.6±1.8</td>
<td>E3/2</td>
<td>6.8±2.7</td>
<td>15.0±4.5&lt;sup&gt;2&lt;/sup&gt;</td>
<td>160±22</td>
<td>71±11</td>
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<tr>
<td>Age group 40–72&lt;sup&gt;b&lt;/sup&gt; (n = 10)</td>
<td>5</td>
<td>5</td>
<td>50±13</td>
<td>24.6±4.6</td>
<td>E3/2</td>
<td>6.1±2.8</td>
<td>16.6±6.7&lt;sup&gt;2&lt;/sup&gt;</td>
<td>177±23</td>
<td>89±26</td>
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<tr>
<td>Phenotype E3/2 (n = 9)</td>
<td>3</td>
<td>6</td>
<td>33±13</td>
<td>22.8±2.1</td>
<td>E3/3</td>
<td>9</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Phenotype E3/3 (n = 10)</td>
<td>8</td>
<td>2</td>
<td>30±16</td>
<td>24.8±2.4</td>
<td>E4/3</td>
<td>—</td>
<td>10</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Phenotype E4/3, E4/4 (n = 8)</td>
<td>4</td>
<td>4</td>
<td>35±19</td>
<td>23.3±5.6</td>
<td>E4/4</td>
<td>6.8±2.9</td>
<td>17.2±6.5&lt;sup&gt;2&lt;/sup&gt;</td>
<td>193±12</td>
<td>73±13</td>
</tr>
</tbody>
</table>

* Values are means±SD.  <sup>a</sup> Significantly different (P < 0.01) males vs. females.  <sup>b</sup> Significantly different (P < 0.05) younger vs. older.  <sup>c</sup> Significantly different from E3/3 phenotype (P < 0.05) and from E4/3, E4/4 phenotypes (P < 0.01).  <sup>d</sup> One of the subjects was between the two age groups and not included in either one.

\[ \text{RP}_{\text{cholesterol}} \text{ and \ cholesterol response} \]

Effects of age and sex on lipid responses. Plasma cholesterol and triglyceride response were also shown in Figure 1. Table II shows the and peak RP responses for the different groups during the vitamin A-fat loading test for the concentrations of cholesterol and triglyceride. Plasma cholesterol and triglyceride response were significantly higher in older subjects than in younger ones. The peak RP was delayed in older subjects and the cholesterol response was also delayed. Phospholipid and triglyceride response were higher in males than in females. The peak RP response and area below the curve were also shown in Figure 1. Table II shows the and peak RP responses for the different groups during the vitamin A-fat loading test for the concentrations of cholesterol and triglyceride. Plasma cholesterol and triglyceride response were also shown in Figure 1. Table II shows the and peak RP responses for the different groups during the vitamin A-fat loading test for the concentrations of cholesterol and triglyceride.
Figure 1. Effect of sex, age, and apolipoprotein E polymorphism on chyomicron and nonchylomicron RP concentration curves (in micrograms per liter) in normal subjects. The upper panel shows RP responses of males (-----) (n = 14) and females (---) (n = 13). The middle panel compares older (-----) (n = 10) to younger (----) (n = 16) subjects. The lower panel shows RP responses of subjects with apo E3/2 (-----) (n = 9), apo E3/3 (----) (n = 10), and apo E4/3, E4/4 (-----) (n = 8) phenotypes. For each group, the levels at each time point were averaged.
Subjects homozygous for the defective form of apo E, with the E2/2 phenotype, can develop an overt fasting hyperlipidemia, called type III hyperlipoproteinemia. This is characterized by the presence of chylomicron remnants in fasting plasma (10, 17, 18). This is not surprising since chylomicron remnants depend on apo E for recognition and clearance by the liver chylomicron remnant receptor. Although the E2/2 phenotype is present in 1% of the population, < 5% of people with E2/2 have overt type III hyperlipoproteinemia and disease expression is related to age, diet, adiposity, hormonal status, and probably the presence of other hyperlipidemia genes (46, 47). Even in normolipidemic E2/2 subjects, elevated levels of chylomicron remnants have been described implying decreased clearance (22, 33, 48).

We have previously shown that the vitamin A-fat loading test, as applied in our laboratory, is an adequate tool to follow the metabolism of large and small postprandial fat particles, which we believe correspond principally to chylomicron and chylomicron remnants, respectively. The large particles (Sf > 1,000) called the chylomicron fraction in normal people are cleared in proportion to HDL levels and postheparin lipoprotein lipase activity. In addition, their clearance is delayed in type IV patients with improvement documented after gemfibrozil therapy. The small particles (Sf < 1,000) called the nonchylomicron fraction in normal people are cleared in proportion to postheparin hepatic triglyceride lipase levels and show delayed clearance in type III hyperlipoproteinemic patients (34). In the current study, we show that individuals with the E3/2 phenotype have delayed postprandial clearance of the small particles, the nonchylomicron fraction that behaves like chylomicron remnants. This is similar, but in a milder form, to what is seen in E2/2 individuals and documents a metabolic defect in postprandial fat metabolism in carriers of the defective allele, E2, who comprise ~ 15% of the general population.

A very surprising result of the current study was that individuals with the E4/3 phenotype, who comprise ~ 23% of the general population, actually had accelerated postprandial clearance of the nonchylomicron fraction. This suggests that they clear chylomicron remnants into the liver more rapidly than E3/3 individuals and strikingly twice as fast as E3/2 individuals. E4 behaves normally in receptor binding assays (19) compatible with its amino acid substitution being outside of the receptor binding region. Therefore, another explanation is required to explain its anomalous behavior compared to E3. One hypothesis is the following (Fig. 3): In the fasting state it has been observed that most plasma apo E resides in HDL and after fat ingestion apo E shifts from HDL to postprandial particles (49–51). Since E4 contains no cysteine, where E3 contains one residue of cysteine, it can be conjectured that E4 in HDL cannot form disulfide bonds with other proteins and shifts more rapidly than E3 to chylomicron remnants. Disulfide bonding of apo E to apo A-II in HDL has been demonstrated (52). In this manner individuals with E4 might more efficiently and rapidly deliver dietary fat to the liver. A recent study injecting radiolabeled E4 and E3 showed that E4 was cleared more rapidly than E3 from plasma and that E3 preferentially associated with HDL (53). These observations are compatible with the hypothesis.

Very recently, it has become apparent that the common apo E phenotypes profoundly affect LDL cholesterol levels in the general population. In comparison to E3/3 individuals (56% of population), E3/2 individuals have lower and E4/3 individuals have higher LDL cholesterol levels (12, 13, 21–24). The LDL levels in the current study show the same trend and the difference seen between the phenotypes in the metabolic behavior of postprandial particles suggest a mechanism for the LDL observations (Fig. 3). The liver is the main site of removal of plasma LDL. It is a dynamic organ with several constantly active, regulated mechanisms affecting its cholesterol and fatty acid pools. Therefore, the rate of exogenous fat removal by the liver could influence the liver’s rate of removal of endogenous fat containing particles. One mechanism could be by LDL receptor regulation. Thus, the slower hepatic clearance of dietary fat in E3/2 subjects could result in up regulation of LDL receptors, and a decrease in plasma LDL levels. The faster hepatic clearance of dietary fat in E4/3 subjects could cause the opposite, down regulation of LDL receptors, and an increase in plasma LDL levels. A recent analysis estimated that 16% of the genetic variation in LDL cholesterol levels in the general population could be accounted for by the three structural alleles at the apo E gene locus (54). The data presented in the current report could explain the mechanism of this relationship.

Acknowledgments

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