Inherited Apolipoprotein A-V Deficiency in Severe Hypertriglyceridemia

Claudio Priore Oliva, Livia Pisciotta, Giovanni Li Volti, Maria Paola Sambataro, Alfredo Cantafora, Antonella Belloccchio, Alberico Catapano, Patrizia Tarugi, Stefano Bertolini, Sebastiano Calandra

Objective—Mutations in LPL or APOC2 genes are recognized causes of inherited forms of severe hypertriglyceridemia. However, some hypertriglyceridemic patients do not have mutations in either of these genes. Because inactivation or hyperexpression of APOA5 gene, encoding apolipoprotein A-V (apoA-V), causes a marked increase or decrease of plasma triglycerides in mice, and because some common polymorphisms of this gene affect plasma triglycerides in humans, we have hypothesized that loss of function mutations in APOA5 gene might cause hypertriglyceridemia.

Methods and Results—We sequenced APOA5 gene in 10 hypertriglyceridemic patients in whom mutations in LPL and APOC2 genes had been excluded. One of them was found to be homozygous for a mutation in APOA5 gene (c.433 C>T, Q145X), predicted to generate a truncated apoA-V devoid of key functional domains. The plasma of this patient was found to activate LPL in vitro less efficiently than control plasma, thus suggesting that apoA-V might be an activator of LPL. Ten carriers of Q145X mutation were found in the patient’s family; 5 of them had mild hypertriglyceridemia.

Conclusions—As predicted from animal studies, apoA-V deficiency is associated with severe hypertriglyceridemia in humans. This observation suggests that apoA-V regulates the secretion and/or catabolism of triglyceride-rich lipoproteins. (Arterioscler Thromb Vasc Biol. 2005;25:411-417.)

Key Words: apolipoprotein A-V deficiency ■ hypertriglyceridemia ■ hyperchylomicronemia ■ APOA5 gene ■ nonsense mutation

Hypertriglyceridemia is conventionally defined as severe when the levels of fasting plasma triglycerides are >10 mmol/L.1 It may be primary or secondary to other diseases. Severe hypertriglyceridemias are often referred to as hyperchylomicronemia syndromes, because of plasma accumulation of chylomicrons in the fasting state.1,2

Three inherited disorders have been described in which chylomicrons accumulate in plasma: familial lipoprotein lipase (LPL) deficiency (MIM 238600), familial apolipoprotein C-II deficiency (MIM 608083), and familial inhibitor of LPL (MIM 118830). Familial LPL deficiency is a rare autosomal-recessive disorder caused by a severe deficiency of LPL, the enzyme responsible for the hydrolysis of triglycerides in chylomicrons and very-low-density lipoprotein (VLDL).2 LPL deficiency is usually diagnosed in childhood because of the presence of episodes of abdominal pain, recurrent pancreatitis, eruptive cutaneous xanthomatosis, hepatosplenomegaly, and failure to thrive.2 The diagnosis is based on severely reduced/absent LPL activity in postheparin plasma and on demonstration of mutations in LPL gene in either homozygous or compound heterozygous state.

Familial apolipoprotein C-II (apoC-II) deficiency is an exceedingly rare autosomal recessive disorder caused by a severe defect of apoC-II, the physiological activator of LPL. The few mutations of APOC2 gene reported so far cause a complete absence of apoC-II activity/protein in plasma, resulting in a functional LPL deficiency and in a block of the lipolytic cascade.2 The clinical manifestations of apoC-II deficiency are similar to those of familial LPL deficiency.2

The third inherited disorder of the lipolytic cascade was reported in a single family in which very low levels of postheparin plasma LPL activity were thought to be caused by the presence of a circulating plasma inhibitor of LPL.3 During a systematic analysis of LPL and APOC2 genes in children and adults with severe primary hypertriglyceridemia, we identified 10 patients who had no mutations in either of these 2 genes. These negative findings prompted us to investigate APOA5 gene, another potential candidate gene in the pathogenesis of hypertriglyceridemia.2 This recently discovered gene is located proximal to the well-characterized APOA4-C3-A1 gene cluster on human chromosome 11 (11q23); it encodes the apolipoprotein A-V (apoA-V), a 363-amino acid protein (NP_443200) that bears strong similarity to other apolipoproteins, such as apoA-I and apoA-IV.5,6 Mice with targeted inactivation of apoa5 gene have a
marked elevation (+400%) of plasma triglycerides with respect to controls, caused by an accumulation of VLDL. However, mice overexpressing this gene have reduced plasma levels of triglycerides and VLDL (~70%). Genetic studies in humans have indicated strong association between some common polymorphisms of APOA5 gene and plasma triglyceride concentration.

We found that 1 of our patients was homozygous for a single nucleotide substitution in exon 4 of APOA5 gene, which is predicted to cause a premature termination of mRNA translation and the formation of a truncated apoA-V of 144 amino acids. This is the first observation that links apoA-V to a genetic defect of plasma lipoproteins in humans.

Methods

Proband

Proband K.Y. is a 9-year-old boy who was admitted to the hospital at age 5 years for recurrent episodes of abdominal pain and severe hypertriglyceridemia. His healthy parents are first cousins and came from Tunisia. Proband’s brother was apparently healthy.

On physical examination, the proband was found to have planar xanthomas on the right elbow, several eruptive cutaneous xanthomas, and a mild hepatosplenomegaly. His body mass index (kg/m²) was 14.

Routine laboratory tests, with the exception of plasma lipids, were within the reference range. Plasma triglyceride (TG) level was >50 mmol/L (10th to 90th percentiles: 0.48 to 1.30 mmol/L), total cholesterol (TC) was 7.76 mmol/L (10th to 90th percentiles: 3.57 to 5.50 mmol/L), and high-density lipoprotein (HDL) cholesterol was 0.61 mmol/L (10th to 90th percentiles: 1.03 to 1.80 mmol/L). Because he was suspected to have familial hypercholesterolemia secondary to LPL or apoC-II deficiency, he was treated first with medium chain triglyceride (MCT)-containing diet and subsequently with ω-3 fatty acids (EPA + DHA 3.4 g/d), associated with a low-fat diet (<20 g/d).

Informed consent was obtained from all subjects investigated. The study protocol was approved by the institutional human investigation committee of each participating institution.

Plasma Lipids Analysis and LPL Assay

TC, HDL cholesterol, and TG levels were determined by standard methods. The assay of plasma apoC-II and apoC-III was conducted by immunonephelometry using polyclonal antibodies. Lipoprotein and hepatic lipase activities in postheparin plasma were assayed as previously reported. In the first LPL assay, we used postheparin plasma that had been collected during the first clinical examination of the proband and had been stored at −80°C for some weeks. The second LPL assay was performed using freshly isolated postheparin plasma collected from the proband during ω-3 fatty acids treatment. LPL was also assayed in the parents and the brother of the proband. To test the capacity of apoA-V-deficient plasma to activate LPL activity, 10 μL of postheparin plasma from a control subject and proband K.Y. were incubated in the presence of 60 to 150 μL of control or proband’s plasma (used as source of LPL activators).

Analysis of Candidate Genes

Genomic DNA was extracted from peripheral blood leukocytes by standard procedure. All exons and the promoter region of LPL and APOC2 genes were amplified by polymerase chain reaction (PCR) from genomic DNA using appropriate primers.

The coding sequence of APOA5 gene (exons 2 to 4) was amplified using the following primers: 2F (5'-GAG CCC CAA CAG CTC TGT GC-3') and 2R (5'-GGG CCT TGG GCC AGC CAC CA-3') for exon 2; 3F (5'-GGG AGG AGA GCC CAC GCC CT-3') and 3R (5'-GAG GGT GAG GCA GCA GAG GC-3') for exon 3; 4F (5'-GGG CCT GGA TAT CTG TCC CC-3') and 4R (5'-GGG AGT GCC TGG AAA GGC TC-3') for the 5' half of exon 4; and 4eF (5'-GGG GCT CTC CCG GAA GCT CA-3') and 4R (5'-GGT GCT CTC CCG GAA GCT CA-3') for 4R (5'-GGG AGT GCC TGG AAA GGC TC-3') for the 5' half of exon 4. 4eR (5'-GGG GCT CTC CCG GAA GCT CA-3') and 4R (5'-GGG AGT GCC TGG AAA GGC TC-3') for the 5' half of exon 4.

Figure 1. Pedigree of proband K.Y. The proband is indicated by an arrow. All subjects indicated in the Figure (apart from subjects I.1 and I.2) were genotyped for APOA5 gene mutation c.433 C>T (Q145X). Half-shifted symbols indicate heterozygotes for this mutation.

Results

Analysis of Candidate Genes

Proband’s pedigree is shown in Figure 1. Because most members of this large pedigree were living in Tunisia, we were unable to examine them directly. With the exception of the proband (IV.2), his parents (III.6 and III.7), and his brother (IV.1), who have been living in Sicily for several years, all lipid parameters of the other family members (Table 1) were assessed in the country of origin. Table 1 shows that the proband had severe hypertriglyceridemia and hypercholesterolemia; plasma TG levels of his parents were moderately elevated. Maternal grandfather (II.3) had moderate mixed hyperlipidemia; paternal grandfather (II.1) and 2 siblings of proband’s father (III.2 and III.5) had mild hypertriglyceridemia.
The pretreatment level of plasma postheparin LPL activity of the proband (5.08±0.39 μmol free fatty acid [FFA]/mL per hour, mean±SD of triplicate determinations), assayed in vitro in the presence of control plasma, was below the lower limit of our reference range (8 to 15 μmol FFA/mL per hour);16 hepatic lipase activity was 40.4±2.3 μmol FFA/mL per hour (reference range 35 to 55 μmol FFA/mL per hour). A subsequent LPL assay performed with fresh postheparin plasma resulted in a value of 6.10±0.23 μmol FFA/mL per hour (Table 2). LPL activity of a control subject was 113±4.4 μmol FFA/mL per hour (mean±SD of triplicate determinations), assayed in vitro in the presence of control plasma, was below the lower limit of our reference range (35 to 55 μmol FFA/mL per hour). LPL activity in proband’s father and mother (obligate heterozygotes) and proband’s brother were 48.2±2.4, 40.4, and 10.2 mg/dL, respectively (normal range, 7 to 10 mg/dL, respectively). Plasma apoC-III level was 5.7 mmol/L), was 27.4 mg/dL. The plasma level of apoC-III in proband’s father, mother, and brother were 15.2, 16.1, and 11.2 mg/dL, respectively (normal range, 7 to 10 mg/dL).

### Table 1. Plasma Lipid Concentration in Members of the K.Y. Family

<table>
<thead>
<tr>
<th>Subject</th>
<th>ApoA-V Genotype</th>
<th>Age, y</th>
<th>Sex</th>
<th>BMI, kg/m²</th>
<th>TC, mmol/L</th>
<th>TG, mmol/L</th>
<th>Glucose, mmol/L</th>
<th>ApoA-V apoC-III Genotype</th>
<th>ApoA-V apoC-III Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>II.1 QQ</td>
<td>Q145X</td>
<td>76</td>
<td>M</td>
<td>24.7</td>
<td>5.56</td>
<td>3.53</td>
<td>6.10</td>
<td>TT SS</td>
<td>CC ε3ε3</td>
</tr>
<tr>
<td>II.2 QX</td>
<td>Q145X</td>
<td>66</td>
<td>F</td>
<td>25.7</td>
<td>5.82</td>
<td>2.12</td>
<td>6.22</td>
<td>TT SW</td>
<td>CT ε3ε3</td>
</tr>
<tr>
<td>II.3 QX</td>
<td>Q145X</td>
<td>61</td>
<td>M</td>
<td>25.8</td>
<td>8.02</td>
<td>4.45</td>
<td>5.99</td>
<td>TT SW</td>
<td>CT ε3ε3</td>
</tr>
<tr>
<td>II.4 QX</td>
<td>Q145X</td>
<td>55</td>
<td>F</td>
<td>26.3</td>
<td>6.44</td>
<td>1.01</td>
<td>5.88</td>
<td>TT SS</td>
<td>CC ε3ε3</td>
</tr>
<tr>
<td>II.1 QX</td>
<td>Q145X</td>
<td>46</td>
<td>F</td>
<td>29.4</td>
<td>4.42</td>
<td>1.58</td>
<td>5.60</td>
<td>TT SW</td>
<td>CT ε3ε3</td>
</tr>
<tr>
<td>II.2 QX</td>
<td>Q145X</td>
<td>44</td>
<td>M</td>
<td>31.9</td>
<td>5.82</td>
<td>2.50</td>
<td>6.99</td>
<td>TT SW</td>
<td>CT ε3ε3</td>
</tr>
<tr>
<td>II.3 QX</td>
<td>Q145X</td>
<td>40</td>
<td>F</td>
<td>33.5</td>
<td>2.95</td>
<td>0.67</td>
<td>7.10</td>
<td>TT SW</td>
<td>CT ε3ε3</td>
</tr>
<tr>
<td>II.4 QX</td>
<td>Q145X</td>
<td>33</td>
<td>M</td>
<td>27.4</td>
<td>4.34</td>
<td>0.99</td>
<td>6.10</td>
<td>TT SS</td>
<td>CC ε3ε3</td>
</tr>
<tr>
<td>II.5 QX</td>
<td>Q145X</td>
<td>31</td>
<td>F</td>
<td>28.9</td>
<td>5.30</td>
<td>2.70</td>
<td>5.44</td>
<td>TT SS</td>
<td>CC ε3ε3</td>
</tr>
<tr>
<td>II.6 QX</td>
<td>Q145X</td>
<td>36</td>
<td>M</td>
<td>25.2</td>
<td>4.94</td>
<td>4.65</td>
<td>5.27</td>
<td>TT SW</td>
<td>CT ε3ε3</td>
</tr>
<tr>
<td>II.7 QX</td>
<td>Q145X</td>
<td>32</td>
<td>F</td>
<td>26.3</td>
<td>3.75</td>
<td>3.24</td>
<td>5.44</td>
<td>TT SW</td>
<td>CT ε3ε3</td>
</tr>
<tr>
<td>II.8 QX</td>
<td>Q145X</td>
<td>29</td>
<td>F</td>
<td>25.7</td>
<td>4.00</td>
<td>0.52</td>
<td>4.88</td>
<td>TT SW</td>
<td>CT ε3ε3</td>
</tr>
<tr>
<td>II.9 QX</td>
<td>Q145X</td>
<td>17</td>
<td>F</td>
<td>19.0</td>
<td>4.47</td>
<td>0.93</td>
<td>4.88</td>
<td>TT SW</td>
<td>CT ε3ε3</td>
</tr>
<tr>
<td>IV.1 QX</td>
<td>Q145X</td>
<td>10</td>
<td>M</td>
<td>17.8</td>
<td>5.09</td>
<td>0.75</td>
<td>4.16</td>
<td>TT SW</td>
<td>CT ε3ε3</td>
</tr>
<tr>
<td>IV.2 XX</td>
<td>Q145X</td>
<td>5</td>
<td>M</td>
<td>13.5</td>
<td>7.76</td>
<td>50.16</td>
<td>4.60</td>
<td>TT WW</td>
<td>TT ε3ε3</td>
</tr>
</tbody>
</table>

Apo indicates apolipoprotein; BMI, body mass index; F, female; M, male; TC, total cholesterol; TG, triglyceride.

### Plasma Lipids and ApoC-III Levels

Mean plasma TG level (unadjusted and adjusted values for age and sex) was higher in Q145X carriers (adjusted TG value: 2.27±1.13 mmol/L) than in noncarrier family members (adjusted TG value: 1.74±1.26 mmol/L); however, this difference did not reach the level of significance. Mean plasma TC level (unadjusted and adjusted values for age and sex) was similar in the 2 groups (adjusted TC values: 5.05±0.93 versus 5.09±1.25 mmol/L).

The plasma level of apoC-III in the proband, measured during treatment with ω-3 fatty acids (when his plasma TG level was 5.7 mmol/L), was 27.4 mg/dL. The plasma level of apoC-III in proband’s father, mother, and brother were 15.2, 16.1, and 11.2 mg/dL, respectively (normal range, 7 to 10 mg/dL).

### Activation of LPL Activity by ApoA-V–Deficient Plasma

To test the capacity of proband’s plasma (apoA-V–deficient plasma) to activate LPL activity, we performed the assays illustrated in Table 2. LPL activity of a control subject was...
found to be reduced by \( \approx 40\% \) when the assay was performed in the presence of apoA-V–deficient plasma as enzyme activator. Similar results were obtained when the proband’s LPL activity was assayed in the presence of apoA-V–deficient plasma. LPL activity of both control and proband’s plasma decreased as the concentration of apoA-V–deficient plasma increased (from 60 to 150 \( \mu \)L) in the incubation medium. A similar decrease, although less pronounced, was observed when control plasma was used as LPL activator (Table 2).

### Treatment of Hypertriglyceridemia

As an initial treatment trial, the patient was given a low-fat diet supplemented with medium chain TGs. Because no beneficial response was observed after a 2-month period, we decided to treat the patient with \( \omega-3 \) fatty acids (3.4 g/d), because chronic \( \omega-3 \) fatty acid supplementation significantly lowers postprandial TG concentration, regardless of the type of fat in the test meal, and has been successfully used in some cases of severe primary hyperchylomicronemia. In view of the substantial reduction in serum TG (\( \approx 90\% \)) and TC (\( \approx 60\% \)) observed after 2 months, this treatment was continued for 4 months, monitoring the lipid profile on a monthly basis. During this period, plasma TG remained <8 mmol/L and the patient had no episodes of abdominal pain. At the end of 8 months of treatment, eruptive cutaneous xantomas had completely disappeared. Treatment with low-fat diet and \( \omega-3 \) fatty acids was continued over the next 36 months. During this period, plasma TG showed large fluctuations ranging from 1.96 to 9.12 mmol/L, with a mean value of 5.74 mmol/L. We attributed these fluctuations to the poor compliance to treatment and to a less stringent follow-up schedule.

### Discussion

In the present report, we described a patient who presented the classical features of the familial chylomicronemia syndrome (severe hypertriglyceridemia, recurrent episodes of abdominal pain, and eruptive xanthomatosis) and who was found to be homozygous for a pathogenic mutation in the recently discovered \( APOA5 \) gene. This mutation is predicted to result in a truncated apoA-V of 144 amino acids \( \approx 40\% \) the size of the wild-type protein. This truncated protein, if synthesized and secreted, is presumably devoid of any function, because it lacks the region between residues 171 and 245, which contains 3 very hydrophobic, strongly amphipathic \( \alpha \)-helices, predicted to have high surface activity for interaction with lipids. Because the analysis of amino acid variability among human, rat, and mouse apoA-V sequences has revealed that several domains of the carboxy-terminal...
Figure 2. Upper panel, Localization of 2 common polymorphisms (−1131T/C and c.47C/G) and the pathogenic mutation (c.433C>T, Q145X) identified in apoA-V gene of proband K.Y. Lower panel, The result of the screening for the c.433C>T mutation based on PCR amplification and enzyme digestion with PstI. Lane 1 shows proband; lane 2, proband’s father; lane 3, unaffected family member; MW, molecular size marker.

half of the protein are highly conserved, it is likely that these domains (all missing in the truncated protein) have a key functional role.

By extending the genetic analysis to all family members available for study, we discovered 10 carriers of the pathogenic mutation. Only 5 of them had plasma TG levels >1.70 mmol/L. This result suggests that other genetic/environmental factors contribute to the elevation of plasma TG in heterozygotes for apoA-V deficiency as it occurs in heterozygotes for LPL deficiency in whom the level of fasting plasma TG may be in the normal range or slightly elevated, the latter in the case of subjects older than 50 or with some degree of adiposity. In our kindred apoA-V carriers, plasma TG levels (Table 1). However, postheparin LPL activity measured in proband’s parents who had mild hypertriglyceridemia (subjects III.6 and III.7 in Table 1) was within the normal range, as was that found in proband’s brother (subject IV.1 in Table 1) who had normal plasma TG.

To the best of our knowledge, this is the first pathogenic mutation of apoA-V found in humans. The plasma lipid phenotype observed in our proband resembles the one found in apos5 knockout mice, which have a marked elevation of serum TG and VLDL. The mechanism whereby apoA-V affects plasma TG and VLDL/cholesterol levels is a matter of intensive investigation. The apoA-V might act in the plasma by affecting the lipolytic cascade, in the hepatocytes/enterocytes by modulating the assembly/secrection of TG-rich lipoproteins, or in both these compartments. In human, rat, and mouse plasma, apoA-V is found mostly in HDL; its concentration is very low (eg, 100 μg/dL in rat and 5 to 50 μg/dL in human plasma) as compared with that of the other major HDL apolipoproteins (apoA-I and apoA-IV) and the LPL activator apoC-II. Fruchart-Najib et al found that in mice overexpressing human apoA5 gene, VLDL TG secretion by the liver was similar to that found in control mice, whereas plasma VLDL TG turnover was much faster and strongly correlated with increased LPL activity in postheparin plasma. They also showed that recombinant apoA-V interacted with LPL protein in vitro and increased its activity.\(^\text{30}\) Schaap et al\(^\text{31}\) using adenovirus-mediated transfer of murine apoA5 gene into mice found that in vivo hyperexpression of apoA-V stimulated LPL-dependent clearance of TG-rich lipoproteins and in vitro stimulated LPL activity up to 2.3-fold only in the presence of apoC-II. These combined observations\(^\text{30, 31}\) strongly suggest that apoA-V acts as a stimulatory modifier of apoC-II induced LPL-mediated TG hydrolysis. Whether the minute amounts of apoA-V present in human plasma under physiological conditions are sufficient to promote this LPL activation remains to be firmly established. In this context, we tried to assess the capacity of proband’s plasma (apoA-V–deficient plasma) to act as activator of LPL in vitro. We found that when apoA-V–deficient plasma was used as activator, LPL activities of a control subject and the proband were reduced as compared with those observed when control plasma was used as LPL activator. The finding that increasing the concentration of apoA-V–deficient plasma in the incubation mixture was associated to a further decrease of LPL activity strongly suggests that our apoA-V–deficient plasma contains an LPL inhibitor. Because the concentration of apoC-III in apoA-V–deficient plasma was 2.7-fold that of the control plasma used in the vitro assay (Table 2), it is conceivable to assume that the reduced LPL activation capacity of apoA-V–deficient plasma is the result of a combined effect of the absence of an activator (apoA-V) and the presence of an inhibitor (apoC-III).\(^\text{31, 33}\)

Shaap et al\(^\text{31}\) also observed that apos5 hyperexpression in mice diminished VLDL TG production rate without affecting VLDL particle production, suggesting that apoA-V impaired lipadation of apoB. The hypothesis that apoA-V might act intracellularly by reducing VLDL TG secretion had been first proposed by Weinberg et al,\(^\text{24}\) who, on the basis of the structural analysis and interfacial properties of apoA-V, suggested that this apolipoprotein might retard the assembly of TG-rich lipoproteins. They demonstrated that apoA-V transfected in COS-1 cells was poorly secreted, remained associated with the endoplasmic reticulum, and did not traffic to the Golgi.\(^\text{24}\)

With regard to the treatment of hypertriglyceridemia in our patient, we first conducted a 2-month trial with a low-fat MCT-containing diet, which is one therapeutic option in hyperchylomicronemia syndrome, because MCTs are absorbed directly into the portal circulation and do not appear to contribute to the generation of chylomicron TG. The treatment with ω-3 fatty acids was found to have beneficial effects in terms of reduction of hypertriglyceridemia, episodes of abdominal pain, and eruptive cutaneous xanthomas.
Omega-3 fatty acids have not been frequently used in the treatment of genetic disorders of plasma lipolytic cascade (LPL and apoC-II deficiency), because in this group of patients the main defect is the inability to hydrolyze circulating plasma TG in VLDL and chylomicrons. Some cases, however, have been reported in which ω-3 treatment in combination with MCT-containing diet was found to have beneficial effects in these patients.

The plasma TG-lowering effect of ω-3 fatty acids may be caused by several mechanisms. It has been known for a long time that ω-3 fatty acids inhibit the synthesis/secretion of VLDL TG by the liver. Recent in vivo and in vitro studies have demonstrated that this reduced VLDL secretion is related to an increased intracellular degradation of apoB-100 through a novel pathway designated postendoplasmic reticulum presecretory proteolysis. This pathway is activated by the increased lipid peroxidation and oxidative stress related to the high hepatic content of ω-3 polyunsaturated fatty acids. There is also recent evidence in normolipidemic humans that ω-3 fatty acids reduce postprandial TG and apoB-48 levels, chylomicron TG half-life, and chylomicron size, and that they increase preheparin LPL activity during the fed state. These data indicate that ω-3 fatty acid supplementation accelerates TG clearance by increasing LPL activity, thus providing a rationale for this treatment in genetic disorders of the lipolytic cascade.

In conclusion, we identified a pathogenic mutation in APOA5 gene, predicted to cause apoA-V deficiency, in a patient with severe hypertriglyceridemia. Heterozygotes for this mutation had normal or moderately elevated plasma TGs. Supplementation of a low-fat diet with MCT had no effect on this mutation had normal or moderately elevated plasma TGs. Although it is possible that a combination of MCT-containing diet was found to have beneficial effects in these patients, the beneficial effects of ω-3 fatty acids was beneficial.

Acknowledgments
This work was supported by grants from University of Modena and Reggio Emilia (S.C.) and University of Genova (S.B.).

References


Inherited Apolipoprotein A-V Deficiency in Severe Hypertriglyceridemia
Claudio Priore Oliva, Livia Pisciotta, Giovanni Li Volti, Maria Paola Sambataro, Alfredo Cantafora, Antonella Bellocchio, Alberico Catapano, Patrizia Tarugi, Stefano Bertolini and Sebastiano Calandra

Arterioscler Thromb Vasc Biol. 2005;25:411-417; originally published online December 9, 2004;
doi: 10.1161/01.ATV.0000153087.36428.dd
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/25/2/411

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/