A Nonsense Mutation in the Apolipoprotein A-I Gene Is Associated With High-Density Lipoprotein Deficiency and Periorbital Xanthelasmas


Abstract  Conflicting data from epidemiological trials, genetic family studies, transgenic animal models, and in vitro experiments have created controversy regarding the importance of HDL and apolipoprotein (apo) A-I for reverse cholesterol transport and protection from atherosclerosis. In this study we identified a homozygous nonsense mutation in codon 32 (Q32X) of the apoA-I gene as the molecular basis of apoA-I deficiency in a 31-year-old woman who did not present with clinical signs of atherosclerosis. Despite half-normal plasma concentrations of HDL cholesterol and apoA-I in subjects heterozygous for this mutation, the history of the patient's large family did not indicate any increased prevalence of myocardial infarction. (Arterioscler Thromb. 1994;14:1915-1922.)

Key Words  • atherosclerosis  • genetics  • reverse cholesterol transport  • polymerase chain reaction amplification  • direct sequencing

Human apolipoprotein (apo) A-I is synthesized in the liver and small intestine as a 267-amino-acid-long preproapolipoprotein of known sequence. After cotranslational cleavage of the 18-amino-acid-residue-long presegment, proapoA-I is secreted into the plasma and the lymph where it is processed to the 243 amino acid residues encompassing mature apoA-I. As the major protein constituent of HDL, apoA-I solubilizes lipids in the aqueous plasma environment. Moreover, it activates the cholesterol esterifying enzyme lecithin:cholesterol acyltransferase (LCAT). In vitro HDL as well as apoA-I-containing proteoliposomes bind to plasma membranes of various cells and thereby promote cholesterol efflux (reviewed in Reference 5). On the basis of these properties, apoA-I is regarded as a key protein for the flux of cholesterol from peripheral cells to the liver, a process termed reverse cholesterol transport. Genetically or environmentally determined impairments of this process are thought to provide the basis for the inverse correlation of HDL cholesterol and apoA-I serum concentrations with the risk of atherosclerotic vessel diseases.

To date, several defects in the genes of apoA-I, LCAT, and lipoprotein lipase (LPL) have been identified as the molecular basis of familial HDL deficiency. Although patients homozygous for these defects have severely reduced or even no measurable HDL, and heterozygous individuals frequently have low HDL cholesterol levels, there is no obvious association with increased risk for myocardial infarction in several affected families. By contrast, some other homozygous null allele carriers were shown to suffer from myocardial infarction at a young age. In this report we describe a novel nonsense mutation in the apoA-I gene underlying HDL deficiency in an Italian woman who does not suffer from clinical symptoms of coronary heart disease (CHD) and whose family does not show an increased prevalence of this disease.

Methods

Subjects

The patient is an apparently healthy 31-year-old woman of Italian origin. During her first pregnancy at age 22, she developed bilateral periorbital xanthelasmas, which did not progress after delivery. She has smoked 10 to 12 cigarettes per day since the age of 18. The patient did not suffer from clinical signs of coronary artery disease and had normal resting and stress ECGs. The history of the large Sicilian family did not indicate any increased prevalence of myocardial infarctions. Among 8 siblings of the proband patient's heterozygous parents, 7 persons aged 57 to 73 years were alive and had no symptoms of atherosclerotic disease. The parents of the homozygous proband patient are first cousins. The studies were performed with the subjects' informed consent.

Quantification of Lipids and Apolipoproteins

Serum concentrations of cholesterol and triglycerides were determined using an autoanalyzer (Hitachi/Boehringer Mannheim). Concentrations of phosphatidylcholine and sphingomyelin were determined as described previously. HDL cholesterol was analyzed after precipitation of apoB-containing lipoproteins with phosphotungstic acid/MgCl₂ (Boehringer Mannheim). LDL cholesterol was determined by the method of Friedewald. ApoA-I, apoA-II, and apoB were quantified...
by immunoturbidimetry as described previously. Lipoproteins containing apoA-I but not apoA-II (LpA-I) were quantified with a commercially available test (Sebia).

**Isolation of Lipoproteins and Apolipoproteins**

Lipoproteins were isolated from plasma by sequential isopycnic ultracentrifugation. Apolipoproteins were precipitated from lipoproteins by incubation with ethanolic 3:1 (vol/vol). For isolating apoA-I from the homozygous patient's plasma, delipidated HDL apolipoproteins were separated by gel filtration with low-molecular-weight standards provided by Pharmacia. The fractions eluted with the retention time of normal apoA-I were then separated by reversed-phase high-performance liquid chromatography (HPLC) using the running conditions described previously. The protein assumed to be apoA-I was analyzed by ultraviolet-laser desorption ionization mass spectrometry (UV-LDI MS) and automated gas-phase sequencing.

**Electrophoretic Procedures**

Agarose gel electrophoresis of plasma was performed on 10 µL plasma in self-casted gels (0.75% agarose) using a 50 mmol/L merbital buffer (pH 8.7) (Serva). For isoelectric focusing (IEF) of apoA-I, 2 to 5 µL plasma or apolipoproteins isolated from lipoproteins of 20 µL of plasma were incubated with 50 µL of a buffer containing 0.01 mol/L Tris HC1 (pH 8.2), 1% decylsulfate (wt/vol), 2.5% carrier ampholytes (wt/vol), and 200 mmol/L dithiothreitol. Samples were separated by IEF as described by Menzel et al or by two-dimensional (2D) SDS-PAGE following the SDS-PAGE protocol of Neville. After electroblotting to nitrocellulose, a mixture of monoclonal anti-human apoA-I antibodies (provided by Dr J.C. Fruchart, Dr L.K. Curtiss, and Dr A. Catapano) was bound to the immobilized antigen. Biotinylated anti-mouse IgG and streptavidin-conjugated peroxidase were used for visualization.

**Direct Sequencing of PCR-Amplified DNA**

Genomic DNA was isolated from 500 µL EDTA-blood samples obtained from the homozygous proband, her relatives, and normal control subjects as described previously. Three fragments of the apoA-I gene were amplified from genomic DNA by polymerase chain reaction (PCR). PCR was performed for 30 cycles with 1-minute denaturation at 96°C, 1 minute of annealing at 60°C, and 1 minute of extension at 72°C following the buffer conditions recommended by the supplier of the Taq polymerase (Ampli Taq, Perkin Elmer/Cetus). In separate reactions, three pairs of primers (Table 1) were used in a ratio of 0.1 µmol/L:0.01 µmol/L to achieve the amplification of single-strand DNA along with double-stranded DNA. PCR products were separated by electrophoresis in a 3% NuSieveGTG agarose (FMC) gel. After electrophoretion into a microconcentrator (Centricon 100, AMICON), the DNA sequence was desalted and concentrated by ultrafiltration. Sequencing was carried out on single-stranded templates, using the T7 sequencing kit of Pharmacia, following the protocol of the supplier. Electrophoresis was carried out in a 6% polyacrylamide gel containing 7 mol/L urea. In addition to sequencing, the presence of the apoA-I gene mutation was also analyzed by a Mae I restriction fragment length polymorphism (RFLP). For this analysis a fragment of the apoA-I gene was amplified by the use of primers 3 and 4. Digestion was performed as recommended by the supplier of the restriction endonuclease (Boehringer Mannheim). Reaction product lengths were determined by electrophoresis in a 4% NuSieveGTG agarose gel.

**Results**

HDL cholesterol levels in the 31-year-old proband patient were very low (Table 2). Serum concentrations of apoA-I and LpA-I were below the lower detection limit of immunoturbidimetry (<1 mg/dL) and electroimmunodiffusion (<0.5 mg/dL), respectively. Fig 1 shows a rocket electrophoresis pattern demonstrating the extremely low concentration of apoA-I in the proband's serum by comparing it with serum from a patient with Tangier disease. Serum concentrations of triglycerides were low, and total cholesterol and LDL cholesterol were normal, while the relative amount of unesterified cholesterol was slightly increased compared with normal control subjects. More-detailed analysis of lipoproteins isolated from plasma by ultracentrifugation revealed the presence of an HDL-like particle that contained predominantly apoA-II (Table 3). This particle showed pre-β-mobility upon agarose gel electrophoresis (Fig 2). Moreover, the patient's LDL contained the majority of plasma phospholipids and triglycerides.

Direct sequencing of PCR-amplified exon 3 of the patient's apoA-I gene identified a homozygous C-T transition in codon 32 yielding a nonsense mutation [Q32X] (Fig 3). This mutation creates a recognition site for the restriction endonuclease Mae I, which is unique in the PCR fragment created by primers 3 and 4 (Fig 4). This RFLP was used in the patient's family to identify additional carriers of the mutation (Fig 5). Table 2 shows that subjects heterozygous for the Q32X mutation had serum concentrations of HDL cholesterol (25.7±3.6 mg/dL) and apoA-I (83.0±9.9 mg/dL) that were markedly lower than in unaffected family members (49.3±7.5 and 123.8±8.1 mg/dL, respectively).
Homozygosity for the premature termination codon in the apoA-I gene should prevent the synthesis of a full-length polypeptide but may allow the synthesis of a truncated protein encompassing the 55 aminoterminal amino acids of preproapoA-I. IEF and 2D SDS-PAGE in combination with anti-apoA-I immunoblotting with several different monoclonal antibodies were used to detect the truncated apoA-I polypeptide or its processing products in the plasma as well as in different lipoprotein fractions. We failed to identify the gene products with calculated molecular masses of 5081 D and 4090 D for the hypothetical propeptide and the hypothetical mature peptide, respectively. Surprisingly, we detected an anti–apoA-I immunoreactive protein with an isoelectric point and a molecular mass of mature wild-type apoA-I. This protein was present in HDL in extremely small amounts (Fig 6). Blank experiments have been carried out in parallel and helped to rule out contamination as a possible cause of artifacts. Also, antibodies used in this study were the same that have been used in the immunoblot analysis of a previously reported case of apoA-I deficiency in which a frameshift mutation moved the gel position of the mutant protein by seven charge units.12 No unexplained immunoreactive bands were detected in the area of the pi of normal apoA-I; this observation further reduces the probability of artifact detection by these antibodies. We attempted to purify the protein to homogeneity from 1 L plasma by

**TABLE 2. Lipid Values and ApoA-I Concentrations In a Family With HDL Deficiency**

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Sex/Age</th>
<th>Cholesterol, mg/dL</th>
<th>Triglycerides, mg/dL</th>
<th>HDL Cholesterol, mg/dL</th>
<th>LDL Cholesterol, mg/dL</th>
<th>ApoA-I, mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homozygote patient</td>
<td>IIc*</td>
<td>f/31</td>
<td>129.5±9.5</td>
<td>39.6±4.2</td>
<td>3.3±0.5</td>
<td>117.8±10.0</td>
</tr>
<tr>
<td>Heterozygote patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>la</td>
<td>m/72</td>
<td>210</td>
<td>123</td>
<td>31</td>
<td>155</td>
<td>98</td>
</tr>
<tr>
<td>lb</td>
<td>f/71</td>
<td>249</td>
<td>299</td>
<td>22</td>
<td>167</td>
<td>74</td>
</tr>
<tr>
<td>lib</td>
<td>f/41</td>
<td>192</td>
<td>95</td>
<td>22</td>
<td>151</td>
<td>92</td>
</tr>
<tr>
<td>IId</td>
<td>f/17</td>
<td>165</td>
<td>85</td>
<td>28</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>Illc</td>
<td>m/9</td>
<td>160</td>
<td>55</td>
<td>24</td>
<td>125</td>
<td>76</td>
</tr>
<tr>
<td>IIff</td>
<td>m/4</td>
<td>133</td>
<td>97</td>
<td>27</td>
<td>87</td>
<td>82</td>
</tr>
<tr>
<td>Mean±SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ila</td>
<td>m/45</td>
<td>275</td>
<td>109</td>
<td>44</td>
<td>209</td>
<td>120</td>
</tr>
<tr>
<td>Illa</td>
<td>m/23</td>
<td>192</td>
<td>58</td>
<td>44</td>
<td>136</td>
<td>114</td>
</tr>
<tr>
<td>IIib</td>
<td>f/21</td>
<td>210</td>
<td>50</td>
<td>60</td>
<td>137</td>
<td>131</td>
</tr>
<tr>
<td>IIic</td>
<td>m/10</td>
<td>207</td>
<td>86</td>
<td>49</td>
<td>141</td>
<td>130</td>
</tr>
<tr>
<td>Mean±SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| *Mean±SD from six independent blood drawings.  
*P was calculated by Student’s t test; comparisons were made between heterozygote patients and normal control subjects. †P<.05; ‡P<.001.

Fig 1. Quantification of apoA-I by electroimmunodiffusion. Agarose contained 0.5% polyclonal anti–apoA-I antibody and 3% polyethylene glycol. Sera from the homozygous proband (A) and from a patient with Tangier disease (T) were used undiluted, whereas the serum of a normal control (C) was diluted 50-fold. A standard serum containing 123 mg/dL apoA-I was diluted 160-, 80-, 40-, and 20-fold and used in the first four slots.

Fig 2. Agarose gel electrophoresis of plasma from a patient with apoA-I deficiency and a normolipidemic control. Part a demonstrates the identification of lipoproteins by staining with Ponceau red; part b, the identification of apoA-II-containing lipoproteins by anti–apoA-II immunoblotting. P denotes the patient and C, a normolipidemic control. Note the absence of α-lipoproteins and the presence of an abnormal apoA-II–containing lipoprotein with electrophoretic pre-β-mobility in the patient’s plasma.
Table 3. Lipid and Apolipoprotein Composition of Lipoprotein Fractions of the Homozygous Patient’s Plasma Compared With Control Subject’s Plasma

<table>
<thead>
<tr>
<th></th>
<th>Plasma</th>
<th>Control Subject</th>
<th>Patient</th>
<th>Control Subject</th>
<th>Patient</th>
<th>Control Subject</th>
<th>Patient</th>
<th>Control Subject</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VLDL, d&lt;1.006</td>
<td>LDL, 1.006&lt;d&lt;1.063</td>
<td>HDL2, 1.063&lt;d&lt;1.125</td>
<td>HDL3, d&gt;1.25 g/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>108</td>
<td>187</td>
<td>4</td>
<td>13</td>
<td>85</td>
<td>118</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>Cholesterol ester</td>
<td>66</td>
<td>129</td>
<td>2.5</td>
<td>8</td>
<td>50</td>
<td>82</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Free cholesterol</td>
<td>42</td>
<td>58</td>
<td>1.5</td>
<td>5</td>
<td>35</td>
<td>36</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>45</td>
<td>151</td>
<td>12</td>
<td>107</td>
<td>24</td>
<td>13</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Phospholipids</td>
<td>91</td>
<td>165</td>
<td>9</td>
<td>23</td>
<td>53</td>
<td>39</td>
<td>9.5</td>
<td>28</td>
</tr>
<tr>
<td>ApoA-I</td>
<td>&lt;1</td>
<td>142</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>35</td>
</tr>
<tr>
<td>ApoA-II</td>
<td>11</td>
<td>32</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8.5</td>
</tr>
<tr>
<td>ApoB</td>
<td>51</td>
<td>79</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>38</td>
<td>60</td>
<td>2.5</td>
</tr>
</tbody>
</table>

*Plasma of a normolipemic individual was fractionated as a within-run control. Lipoprotein fractions were characterized in parallel to those of the patient.

†All measurements in mg/dL.

ultracentrifugation of HDL, gel filtration of HDL apolipoproteins, and subsequent reversed-phase HPLC. The HPLC chromatogram revealed the presence of a protein with the retention time of apoA-I, which exhibited the electrophoretic properties of normal apoA-I (Fig 7). In subsequent analyses the so-purified protein, probably as a consequence of low mass, yielded no detectable signals in both amino-acid sequence analysis and UV-LDI MS.12

Discussion

In this study we identified a novel mutation in the apoA-I gene, apo A-I:Gln32End, as the molecular basis of familial HDL deficiency. The hypothetical translation product of the mutant mRNA is a 55-amino-acid-residue-long polypeptide representing the aminoterminal proportion of preproapoA-I. Neither this truncated protein nor hypothetical processing products were detectable in the patient’s plasma. We did, however, identify very small amounts of an anti-apoA-I-immunoreactive protein with the isoelectric point and the molecular mass of wild-type apoA-I. Attempts to isolate this protein for sequence determination or mass spectrometry analysis have been unsuccessful, probably as the result of the protein’s extremely low plasma concentration. Because this protein is indistinguishable from wild-type apoA-I by molecular mass, isoelectric point, immunoreactivity with polyclonal as well as with a mixture of monoclonal anti-apoA-I antibodies, its retention time in reversed-phase HPLC, and by its presence in the HDL density range, we cannot currently exclude the presence of extremely small amounts of apoA-I in the proband patient’s plasma even though she is homozygous for a nonsense mutation.

Of the different reasons that might provide an explanation for this unexpected finding, the presence of somatic mosaicism is unlikely because both parents are mutation carriers. Linton et al29 observed the synthesis Fig 3. Sequence analysis of exons 2 to 4 of the apolipoprotein A-I gene from the apoA-I-deficient patient. The bottom shows a schematic drawing of the apoA-I gene in which the shadowing indicates the pre-pro-segment. The positions and processing directions of primers are indicated with arrows. Amplification primers 1 to 5 and 10 were also used as sequencing primers. Other primers were used for sequencing only. The sequences in panels A and B show the area around codon 32 of an unaffected individual and the apoA-I-deficient proband. For convenience, the autoradiographs have been flipped to allow sequence reading in upper strand format, although primer 4 has been used as the sequencing primer.
of a full-length apoB together with truncated forms of this protein in an individual who is a compound heterozygote for mutations predictive to form abbreviated apoB. As the underlying mechanism, these authors identified the introduction into RNA of a nucleotide during transcription that restored the reading frame destroyed in genomic DNA. Also, mechanisms that circumvent the functional effectivity of stop codons by processing errors at the ribosomal site have been described. These include ribosomal frame-shifting and codon hopping. Also, stop codons do not always have a 100% efficiency in the termination of protein synthesis. Translational readthrough events have been observed not only in viruses and bacteria but also in eukaryotic cells. Local tRNA availability, tRNA mutations, and specific suppressor tRNAs (e.g., the selenocysteine tRNA) have been shown to contribute to this phenomenon. In addition, Brown et al. in several eukaryotic and prokaryotic species identified an important role for the stringency of a termination signal of the base following the termination codon. Using the same blotting procedure that has been used to identify the apoA-I-immunoreactive band in our proband patient in normal subjects, we see no signal above the proapoA-I band, indicating the absence of a protein expected from a readthrough of the natural stop codon. It is thus tempting to speculate that the nucleotide context of the mutant stop codon may allow very-low-level readthrough events. Unfortunately, our attempts to test this hypothesis via sequencing amino acid 32 were not successful.

Numerous epidemiological and clinical studies revealed an inverse correlation between apoA-I and HDL plasma concentrations and the risk of myocardial infarction. The identification of HDL as a potent acceptor of cholesterol from cells in culture has led to the reverse cholesterol transport model, in which HDLs are the starting point of several alternative mechanisms and routes for transporting excess cellular cholesterol from peripheral cells to the liver (reviewed in Reference 41). To date, it is a matter of debate whether or not familial HDL deficiency puts affected individuals at an increased risk for cardiovascular disease.

In four different families, homozygote patients for different apoA-I null alleles suffered from myocardial infarction at relatively young ages. By contrast, CHD was absent in an apoA-I-deficient patient with planar xanthomas described by Lackner et al. and in an HDL-deficient patient with a homozygous frameshift mutation in codon 202 of apoA-I. Also, in the patient described in this study, clinical signs of atherosclerosis have not been observed. Part of this variation may be a
HDL deficiency in CHD formation is low case numbers. Although in familial forms of HDL deficiency heterozygote mutation carriers usually have HDL cholesterol concentrations below the commonly used risk threshold of 35 mg/dL, their often young age does not allow a reliable risk assessment. Even a severalfold increase in CHD prevalence is likely to remain undetected in individuals <50 years old when the number of studied cases is small as in most family analyses. Usual lifespan and absence of CHD from the cause-of-death list, as is the case in the family of our proband patient, may be more meaningful.

In addition to the aforementioned possibilities to underestimate CHD risk, there are also mechanisms for overestimation. Screening for HDL deficiency in individuals who have been admitted to hospitals because of CHD is a frequent cause for this. Despite these insecurities in phenotype assignment, the existence of homozygous familial HDL deficiency with and without associated CHD suggests that this familial disorder is not predisposing to young-age CHD with the same constancy that is observed in homozygous familial hypercholesterolemia.

The difficulties in phenotype assignment in familial HDL deficiency are also reflected in biological experiments: apoA-I deficiency in transgenic mice did not cause atherosclerosis, while overexpression was reported to prevent atherosclerosis. In attempting to understand the different clinical consequences that have been found associated with complete HDL deficiency, we have previously speculated that traces of apoA-I may be sufficient to trigger functionally important reverse cholesterol transport mechanisms. Also in LCAT deficiency, fish-eye disease, and Tangier disease, low but detectable concentrations of apoA-I in plasma

![Figure 6](image1.png)

**Fig. 6.** Isoelectric focusing (IEF) of lipoproteins from a patient with apoA-I-deficiency. IEF was performed as described by Menzel et al. In the upper part, proteins were identified by Coomassie blue staining; in the lower part, apo A-I was detected by immunoblotting with monoclonal anti-human apoA-I antibodies, biotinylated antiserum, and streptavidin horseradish peroxidase. N denotes the plasma of a normal control subject; a, b, c, d, and e denote VLDL, LDL, HDL1, HDL2, and lipoprotein-depleted serum, respectively. Arrowheads point to areas where apoA-I usually is located (pro apoA-I [top arrow], mature apoA-I [big arrow], deamidized apoA-I [bottom arrow]). Note the presence in HDL2 and HDL3 of small amounts of an anti-apoA-I-immunoreactive protein with the isoelectric point of normal apoA-I, which is not seen in the Coomassie blue-stained gel, likely reflecting the low apoA-I concentration in the proband patient's plasma.

![Figure 7](image2.png)

**Fig. 7.** Demonstration of apoA-I in an apoA-I-deficient patient by reversed-phase high-performance liquid chromatography (HPLC) of HDL apolipoproteins. HPLC of HDL was performed as described previously. Proteins from HPLC fractions 1, 2, and 3 were analyzed by isoelectric focusing. Insert a shows a gel after staining with Coomassie blue; insert b, an anti-human apoA-I immunoblot. Fraction 1 contained apoA-I; fraction 2, apoA-I and apoA-II; and fraction 3, apoA-I. The chromatographic heterogeneity of apoA-I and apoA-II is a consequence of oxidized methionine residues.
coincide with the frequent absence of CHD from these individuals.\textsuperscript{10} The case reported in this study might also be understood on the basis of this speculation. There are different mechanisms conceivable that may help to maintain a flux of cholesterol from peripheral cells to the liver even in HDL deficiency. First, one may speculate that even trace amounts of normal or mutant apoA-I are sufficient for triggering the translocation of cholesterol from intracellular pools to cell membranes by signal transduction (reviewed in References 5 and 47) and the uptake into the plasma compartment. Second, one has to take into account that apolipoproteins other than apoA-I can also fulfill important functions in reverse cholesterol transport. For example, apoA-IV–containing particles without apoA-I were shown to enhance LCAT and cholesterol ester transfer protein activities and to promote cholesterol eflux from cells in vitro.\textsuperscript{48-50} Plasma of patients with Tangier disease and apoA-I deficiency contain an HDL-like lipoprotein with apoA-II but without apoA-I, which promotes cholesterol eflux.\textsuperscript{51} A similar particle was also identified in the plasma of our patient. Most recently, our laboratory has demonstrated that a solely apoE-containing plasma lipoprotein, \textit{\gamma}-LpE, releases cholesterol from cells.\textsuperscript{52} Actually, this lipoprotein is also regularly present in the plasma of the apoA-I–deficient patient described here (von Eckardstein et al, unpublished data) and may thus allow reverse cholesterol transport by an alternative route.

Acknowledgements

The project was sponsored by grants from Deutsche Forschungsgemeinschaft to H.F. (Fu 179/1-1) and A. von E. (Ec 116/1-1). We thank A. Roetrige, A. Merschjann, and A. Reckwerth for expert technical assistance and M. Opalka for help with the photos. We are grateful to Prof Dr F. Spener (Institut fur Biochemie, Westfälische Wilhelms-Universität Münster) for supervision of the thesis work of R.R.

References

30. Romling et al 1991
32. With the photos. We are grateful to Prof Dr F. Spener (Institut fur Biochemie, Westfälische Wilhelms-Universität Münster) for supervision of the thesis work of R.R.


A nonsense mutation in the apolipoprotein A-I gene is associated with high-density lipoprotein deficiency and periorbital xanthelasmas.

R Römling, A von Eckardstein, H Funke, C Motti, G C Fragiacomo, G Noseda and G Assmann

Arterioscler Thromb Vasc Biol. 1994;14:1915-1922
doi: 10.1161/01.ATV.14.12.1915

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1994 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/14/12/1915