Clinical, Biochemical, and Genetic Features in Familial Disorders of High Density Lipoprotein Deficiency

Ernst J. Schaefer

This review assesses current knowledge of the clinical, genetic, and biochemical features of familial high density lipoprotein (HDL) deficiency syndromes. The focus is on HDL deficiency states occurring in the absence of severe hypertriglyceridemia or lecithin/cholesterol acyltransferase deficiency. Specific entities falling within this category include Tangier disease, familial HDL deficiency with planar xanthomas, familial apolipoprotein A-I and C-III deficiency (formerly known as apolipoprotein A-I absence), familial deficiency of apolipoprotein A-I and C-III, fish-eye disease, familial hypoproteinemia, and apolipoprotein A-I variants (apo A-I Stuwe, apo A-Iwahshi, and apo A-Imunotl T-3). Diffuse corneal opacification and premature coronary artery disease are common features in many of these kindreds. No striking clinical abnormalities have been noted in patients with currently known apolipoprotein A-I variants, possibly because these subjects are heterozygotes for their respective defects. The HDL deficiency in many of these disorders has been associated with abnormalities or deficiencies of apolipoprotein A-I. Further research will undoubtedly define the defects in all the disorders that have been described, uncover new mutations, as well as provide additional insights into the precise relationship between HDL deficiency and atherosclerosis. (Arteriosclerosis 4:303–322, July/August 1984)

| Plasma high density lipoproteins (HDL, density = 1.063 – 1.21 g/ml) mostly have alpha mobility on lipoprotein electrophoresis, and are composed (weight %) of approximately 50% protein, 25% phospholipid, 20% cholesterol (mainly esterified), and triglyceride. Fluctuations in HDL levels have been associated largely with alterations in HDL (d = 1.063 – 1.125 g/ml). Cholesterol is the HDL constituent commonly measured (following precipitation of other lipoproteins), and decreased plasma HDL cholesterol concentrations have been associated with premature coronary artery disease (CAD). The normal values for this parameter are given in Table 1. |

<table>
<thead>
<tr>
<th>Table 1. Plasma High Density Lipoprotein Cholesterol Concentration</th>
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<tbody>
<tr>
<td>Normal values (mg/dl)</td>
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<tr>
<td><strong>Age (yrs)</strong></td>
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<tr>
<td>5-9</td>
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<td>15-19</td>
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<tr>
<td>65-69</td>
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</table>

Values are based on Lipid Research Clinics population studies in the U.S. and Canada, 3524 while males and 2545 while females (non-sex-hormone users) as derived from NIH Publication 80-1527, 1980. All subjects were sampled in the fasting state.

— indicates no data because there were less than 100 cases in the cell.

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Table 2. Plasma Apolipoprotein Metabolic Parameters

<table>
<thead>
<tr>
<th>Apolipoprotein</th>
<th>Plasma concentration (mg/dl)</th>
<th>Percentage within HDL (%)</th>
<th>Synthesis rate (mg/kg day)</th>
<th>Plasma residence time (days)</th>
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<tbody>
<tr>
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<td>120</td>
<td>90</td>
<td>11.0</td>
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<td>A-II</td>
<td>35</td>
<td>95</td>
<td>2.8</td>
<td>5.0</td>
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<tr>
<td>B</td>
<td>90</td>
<td>1-5</td>
<td>14.4</td>
<td>2.2</td>
</tr>
<tr>
<td>C-I</td>
<td>7</td>
<td>50</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>C-II</td>
<td>4</td>
<td>50</td>
<td>1.6</td>
<td>1.0</td>
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<td>C-III</td>
<td>13</td>
<td>50</td>
<td>5.2</td>
<td>1.0</td>
</tr>
<tr>
<td>E</td>
<td>5</td>
<td>50</td>
<td>5.0</td>
<td>0.4</td>
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<tr>
<td>Lp(a)</td>
<td>10</td>
<td>60</td>
<td>2.0</td>
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</table>

Approximate normal metabolic parameters are derived from references 58-80, 159.
— indicates no data available.

Apolipoproteins (apo) A-I and A-II are the major protein constituents of HDL, while apolipoproteins B, Lp(a), C-I, C-II, C-III, D, E, F, and G are minor constituents.12-21 Decreased plasma apo A-I may provide even better information about CAD risk than HDL cholesterol.22-27 Apo A-I and apo C-I both reportedly activate lecithin/cholesterol acyltransferase (LCAT), while apo A-II enhances hepatic lipase activity.28-30 Apo C-II activates lipoprotein lipase, while apo C-III inhibits hepatic chylomicron remnant uptake.31-32 Apo B-containing particles bind to a specific LDL receptor on the cell surface, are internalized, and inhibit the activity of HMG CoA reductase, the rate-limiting enzyme in cholesterol synthesis.33-35 Apo E-containing lipoproteins also bind to this receptor, and in addition apo E appears essential for hepatic receptor-mediated chylomicron remnant uptake.32,36 A specific receptor for HDL apolipoproteins A-I and A-II was reported on the surface of skin fibroblasts and arterial smooth muscle cells.36 HDL constituents can be derived from direct HDL synthesis by the liver or the intestine, as a result of the catabolism of chylomicrons and very low density lipoproteins (VLDL); they can also pick up lipid constituents in the periphery.39-55 Both the liver and kidneys appear to play an important role in HDL catabolism.56,57 Metabolic parameters for the various apolipoproteins found within the HDL density region are given in Table 2.58-60

The purpose of this review is to summarize the existing data on the clinical, biochemical, and genetic features of familial HDL deficiency syndromes. It will focus on genetic disease states characterized by HDL cholesterol levels below the 10th percentile in the absence of severe hypertriglyceridemia or the elevated free total cholesterol ratio in plasma as observed in LCAT deficiency.83,84 Disease entities falling within this category include the familial apolipoprotein A-I and C-III deficiency states,85-86 Tangier disease,87,88 HDL deficiency with planar xanthomas,89,90 apo A-I absence,91-93 fish-eye disease,94,95 familial hypoalphalipoproteinemia,96-100 apo A-I101 apo A-II102 These disorders have arbitrarily been grouped starting with the lowest plasma apo A-I values and moving to the highest concentrations. The clinical features, plasma lipoprotein values, and reported apolipoprotein concentrations are summarized in Tables 3-5.

Familial High Density Lipoprotein Deficiency States

Familial Apolipoprotein A-I and C-III Deficiency

The proband in this kindred from northwest Alabama in the United States (originally described as apolipoprotein A-I absence) was a 45-year-old white woman who had had mild corneal opacification since age 42, angina pectoris, significant three-vessel...
coronary artery disease, and marked HDL deficiency. She had no history of hypertension or smoking, but did have a salpingo-oophorectomy and hysterec-
tomy at 26 years of age. She died shortly after coro-
nary artery bypass grafting surgery. Autopsy re-
vealed significant atherosclerosis in the descending
aorta, carotid, pulmonary, and coronary arteries
(Figure 1), normal tonsils, and lack of lipid deposition
in the reticuloendothelial cells of the liver, spleen,
and bone marrow. All grafts were found to be patent,
but significant, left ventricular contraction band nec-
crosis was observed consistent with decreased in-
traoperative coronary perfusion. No xanthomas
were noted. Diffuse extracellular granular lipid depo-
sition was observed in the corneal stroma (Figure 1).
Of 38 kindred members tested, 17 were heterozy-
gotes, none of whom had premature CAD or corneal
opacification before age 40. Two heterozygotes de-
veloped clinical evidence of CAD before the age of
60, and one died at the age of 56 of a myocardial
infarction. (He was also diabetic and hypertensive.)
The biochemical abnormalities noted in the pro-
band included marked HDL deficiency, undetectable
levels of plasma apo A-I and apo C-III, an apo A-II
value which was 11% of normal, apo B-rich LDL, a
slightly prolonged prothrombin time, and a deficiency
of plasma vitamin E (alpha tocopherol) and linoleic
acid (C18:2). Apolipoproteins C-I, C-II, D, E, and F
were present in the proband’s plasma at reduced
centration (Tables 1, 2). Apo A-I and C-III were
assayed by radioimmunoassay, and other apolipo-
proteins, by radial immunodiffusion or electroimmu-
noassay. The ratio of free to total cholesterol was
normal in the proband’s plasma, and LCAT activity
and mass, as well as cholesterol esterification rate,
were all approximately 40% of normal. Heterozy-
gotes (n = 17) had plasma HDL cholesterol, apo A-I
and apo C-III concentrations which were 54%, 58%,
and 83% of normal, respectively (E.J. Schaefer, un-
published observations, see Tables 1 and 2).
The defect in this disease entity appears to be an
inability to synthesize apo A-I and apo C-III. When
DNA was isolated from the white cells of the two
offspring of the proband, subjected to restriction en-
zyme digestion (EcoRI, Pst-1) and Southern blot
analysis using a radiolabeled nick-translated apo A-I
insert DNA, no apo A-I gene abnormality was detect-
ed (E.J. Schaefer, unpublished observations). The
mode of genetic inheritance in this kindred is auto-
sonal codominant.

### Table 4. Plasma Lipid and Lipoprotein Cholesterol Concentrations

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<tr>
<th>Disease</th>
<th>Plasma (mg/dl)</th>
<th>Cholesterol</th>
<th>Triglyceride</th>
<th>VLDL</th>
<th>LDL</th>
<th>HDL</th>
<th>Reference</th>
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<td>Cholesterol</td>
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<td>62</td>
<td>4</td>
<td>106</td>
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<td>186 ± 41</td>
<td>131 ± 99</td>
<td>23 ± 16</td>
<td>136 ± 35</td>
<td>27 ± 6</td>
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<td>Heterozygotes</td>
<td>n = 1088</td>
<td>189 ± 40</td>
<td>87 ± 43</td>
<td>16 ± 11</td>
<td>123 ± 35</td>
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<td>33 ± 8</td>
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<td>68 ± 21</td>
<td>198 ± 90</td>
<td>19 ± 13</td>
<td>48 ± 19</td>
<td>2 ± 2</td>
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<tr>
<td>Heterozygotes</td>
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<td>167 ± 25</td>
<td>187 ± 134</td>
<td>36 ± 20</td>
<td>114 ± 17</td>
<td>27 ± 12</td>
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<tr>
<td>Normals</td>
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<td>120-330</td>
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<td>165 ± 38</td>
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<td>115 ± 35</td>
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<td>177 ± 19</td>
<td>89 ± 26</td>
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<td>107 ± 23</td>
<td>51 ± 9</td>
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</table>

Values are means ± sd.

*Normal values as cited in reference 81.
† Also, E.J. Schaefer, unpublished observations.
Table 5. Plasma Apolipoprotein Concentrations

<table>
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<th>Disease</th>
<th>Concentrations (mg/dl)</th>
<th>References</th>
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<tr>
<td></td>
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<td>Apo A-II</td>
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<td>Familial apo A-I and C-III deficiency</td>
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<tr>
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<td>37 ± 4</td>
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<td>Tangier disease</td>
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<tr>
<td>Homozygote (n = 8)</td>
<td>0.65 ± 0.27</td>
<td>2.2 ± 0.6</td>
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<td>Normal</td>
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<td>Affected (n = 6)</td>
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<tr>
<td>Normal (n = 11)</td>
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Values are means ± SD. ND is not detectable; — is not reported.

**Normal apo A-I values for males = 98 ± 10 mg/dl; for females = 115 ± 20 mg/dl.
†Same normal values as for familial apolipoprotein A-I and C-III deficiency.
§Represents HDL apo A-I.
§Also, E.J. Schaefer, unpublished observations.

Familial Deficiency of Apoproteins A-I and C-III

The probands for this kindred were two sisters from the Detroit area of Michigan in the United States. The first proband was a 33-year-old white woman who had yellow-orange, indurated plaques on her trunk, neck, eyelids, chest, arms, and back since adolescence, significant three-vessel coronary artery disease, a decreased left ventricular ejection fraction, and mild diffuse corneal opacification (first noted in the periphery of the cornea at 31 years of age). A biopsy of one skin xanthoma revealed perivascular histiocytic lipid deposition. Her tonsils were normal, and she had symptoms of dyspnea, orthopnea, and palpitations. Coronary artery bypass surgery was performed, and there was an improvement of her symptoms and her left ventricular ejection fraction. Her sister, 31 years old, had a history of yellow plaques on the arms and eyelids since age 9, removal of a tendinous xanthoma from the lateral aspect of the left foot at age 30 (pathology showed vacuolated histiocytes), and congestive heart failure first diagnosed at age 25 before the delivery of her second child. Coronary artery catheterization at age 29 revealed occlusion of the right coronary artery, marked stenosis of the circumflex coronary artery, and diffuse left ventricular hypokinesis. Her tonsils had been removed. Peripheral corneal opacification was noted at the same age, and by age 31 this process had become diffuse. The mother of the probands had a plaque on one eyelid at age 50; no family member (father, age 45; brother, age 25; and five offspring, ages 1–9) had clinical evidence of CAD.
Figure 1. Proband for familial apoprotein A-I and C-III deficiency.  

A. Coronary atherosclerosis (×4).  

B. Corneal lipid deposition (oil red 0 stain, ×10).
Biochemical abnormalities noted in the two probands included marked HDL deficiency, trace amounts of plasma apo A-I detected by radioimmunoassay, plasma apo C-III undetectable by electroimmunoassay, triglyceride-rich LDL, and a normal ratio of free to total cholesterol in plasma (0.29), but not in HDL (0.50). The LCAT activity was 40% of normal in the two probands, and plasma apo A-II levels were 51% of normal. Apo C-I, C-II, E, and F were present in the plasma of the probands. Heterozygotes (n = 8) had plasma HDL cholesterol and apo A-I levels which were 67% and 59% of normal respectively. Apo C-III levels in heterozygotes were not reported, and the apo A-II values were normal.

Following an infusion of 75 ml of normal plasma into each proband, the decay of HDL protein (as assessed by an antiserum which reacted against both apo A-I and apo A-II) in each subject’s plasma was followed for 2 to 3 days, was fitted by inspection, and was found to yield an HDL protein half-life of 3 days. The defect in this disease appears to be an inability to synthesize apo A-I and apo A-II. When DNA was isolated from the white cells of the two probands, subjected to EcoRI digestion, and analyzed by Southern blot analysis by using an apo A-I gene probe, the probe hybridized to a unique 6.5 kb band in contrast to the normal 13 kb band. Similar experiments in heterozygotes demonstrated the presence of both the normal 13 kb band and the abnormal 6.5 kb band. Recent data has documented that the apo C-III gene is approximately 2.6 kilobases downstream of the 3’ end of the apo A-I gene, accounting for the observed genetic linkage. The mode of inheritance in this kindred is autosomal codominant.

### Tangier Disease

The original two probands for Tangier disease were a brother and sister, aged 5 and 6 years, respectively, from Tangier Island, Virginia, in the southern Chesapeake Bay area of the United States. These children had enlarged yellow-orange tonsils, mild hepatosplenomegaly, and lymphadenopathy. Both subjects had had their tonsils removed, and pathology revealed vacuolated histiocytes containing increased amounts of cholesterol ester. Similar pathology has been noted in the bone marrow, tonsils, skin, rectal mucosa, liver, spleen, lymph nodes, omentum, and conjunctiva of Tangier patients (Figures 2 to 5). The two original probands developed mild transient peripheral neuropathy in adolescence for a 6- to 12-month period, but both probands are alive and well at ages 27 and 28, with no evidence of CAD. They have mild diffuse corneal opacification, but no xanthomas.

Since the original description of this kindred, 23 other patients from 20 kindreds with clinical and laboratory features consistent with homozygous Tangier disease have been described. The prevalence of CAD and other clinical features in homozygous and heterozygous Tangier disease were recently reviewed. The clinical features noted in homozygotes included yellowish pharyngeal mucosal plaques or lymphoid follicles in 81%, splenomegaly in 63%, peripheral neuropathy in 63%, hepatomegaly in 37%, and lymphadenopathy in 22%. Diffuse corneal infiltration was observed in 40% of the homozygotes who had a slit-lamp examination, and in all homozygotes over age 40. No xanthomas were noted in homozygotes except in one subject who developed transient eruptive xanthomas following splenectomy. This patient subsequently developed marked lipid deposition in the reticuloendothelial cells in the omentum. None of these abnormalities have been observed in heterozygotes.

No premature CAD or cerebrovascular disease has been noted in Tangier heterozygotes or homozygotes before age 40. Of eight homozygotes over age 40, five (63%) had evidence of CAD or cerebrovascular disease. One homozygote with a history of angina, hypertension, and smoking died suddenly at age 48 of a suspected myocardial infarction. His brother, with no risk factors other than markedly reduced HDL, developed angina at age 59, and underwent coronary artery bypass surgery for significant CAD at age 61. Another homozygote developed angina pectoris at age 43. Two homozygotes developed "strokes" in their fifth decade of life; one died at age 58 (G. Utermann, personal communication), and the other died at age 69 of probable cerebrovascular disease. Three other homozygotes are alive and well in their fourth and fifth decades of life. Seven of 14 (50%) heterozygotes over age 40 had evidence of premature coronary artery disease.

Biochemical abnormalities noted in Tangier homozygotes include plasma cholesterol, LDL cholesterol, and HDL cholesterol values which are approximately 37%, 34%, and 4% of normal, respectively. Plasma triglyceride and VLDL cholesterol values were normal or moderately increased in homozygotes, and triglyceride-rich LDL of abnormal electrophoretic mobility has been reported. The ratio of free to total cholesterol and LCAT activity in homozygotes were normal, and plasma apo A-I and apo A-II concentrations were about 1.0% and 8.8% of normal respectively, while mean levels of apo B, C-I, C-II, apo C-III, D, and E were 84%, 59%, 62%, 50%, 22%, and 54% of normal, respectively. Heterozygotes had plasma HDL cholesterol, apo A-I, and apo A-II concentrations that were approximately 50% of normal. Other apolipoprotein values were in the normal range (Tables 1, 2).

The precise molecular defect in Tangier disease remains to be elucidated. Early studies suggested that homozygotes not only had marked HDL deficiency, but that their HDL had an abnormal composition and mobility on immunoelectrophoresis (apo A-I/apo A-II ratio was 1:12; while normal is 3:1). Subsequently, an HDL particle containing apo A-II, but no apo A-I, was noted in Tangier homozygotes after...
Figure 2. Subjects with homozygous Tangier disease. A. Enlarged tonsils. B. Mild corneal opacification demonstrated on slit-lamp examination. C. Omental mass. D. Liver with stippled lipid infiltrated surface. (Photographs of tonsils from original kindred, reproduced from reference 87 with permission.)

HDL isolation by ultracentrifugation. In addition, it was reported that a large fraction of apo A-I in Tangier plasma was found in the 1.21 g/ml infranate. Other studies confirmed this finding, but also reported that 28% of apo A-I and 91% of apo A-II in the plasma of homozygotes was found in the 1.063 g/ml superate. Radiolabeled HDL, apo A-I, and apo A-II kinetic studies performed in homozygotes studied under steady state conditions revealed apo A-I and apo A-II residence times of 5% and 18% of normal. For heterozygotes, these parameters were 66% and 84% of normal, respectively. This hypercatabolism of HDL protein constituents also occurred in homozygotes following infusion of large amounts of HDL. In one infusion study, HDL2a and HDL2b were catabolized much more rapidly than HDL, (with some conversion of HDL2b to HDL2a); HDL apo A-I, triglyceride, and cholesterol were more rapidly catabolized than were HDL, apo A-II, and phospholipid.

Recent data suggest that Tangier homozygotes produce a variant apo A-I (apo A-I_Tangier) with an abnormal amino acid composition, increased proapo A-I on isoelectric focusing, abnormal uptake by rat liver Kupffer cells, and a fractional catabolic rate enhanced threefold in normal subjects compared to normal apo A-I. No such abnormalities have been observed for apo A-II isolated from Tangier plasma. It has been suggested that the defect is due to a lack of conversion of proapo A-I to apo A-I. However, an increased ratio of proapo A-I to apo A-I has also been reported in other patients with decreased HDL (cerebrotendinous xanthomatosis). Moreover, the sequence of the 6 amino-acid propeptide in Tangier disease is identical to normal. An alternative view is that there is a normal rate of apo A-I production and conversion of proapo A-I to apo A-I, and then hypercatabolism of the abnormal apo A-I, resulting in a relative enrichment of the preprotein in plasma.
Figure 3. Tangier homozygote. A. Soft tissue granuloma with cholesterol clefts in the omental mass surrounded by chronic inflammatory cells (×25). B. Lipid-laden macrophages with interspersed lymphocytes in omental mass (×25). C. Lipid-laden macrophages in omental mass (oil red O stain, ×125). D. Lipid-laden Kupffer cells in liver. (Reproduced from reference 110 with permission, ×200.)
Figure 4. A Tangier homozygote. A liver sinusoid with Kupffer cells containing numerous phagosomes. Free cytoplasmic lipid droplets (*) are seen and the fusion of a lipid droplet with phagosomes is depicted (arrow). (Reproduced from reference 110 with permission, ×12,000; inset: ×20,000.)
Figure 5. A Tangier homozygote. Lipid-laden macrophages and cholesterol cleft (see arrow and *) in omental mass. (Reproduced from reference 110 with permission, ×6000.)
HDL Deficiency with Planar Xanthomas

The proband in this kindred was a 48-year-old white Swedish woman with a history of widespread yellow skin discoloration, especially around the eyes and in the groin since early childhood (Figure 7). She also had a history of hypothyroidism, angina pectoris, and a transient facial neuralgia. Corneal opacification was noted on slit-lamp examination, and ischemic changes were observed on her electrocardiogram. Physical examination revealed diffuse yellow discoloration around the eyes and mouth.
over the neck, upper chest, axillae, antecubital fossa, inguinal regions, vulva, perineum, perianal region, and also of the soft palate mucosa of the floor of the mouth. Both upper eyelids were thickened and infiltrated with small firm nodules, especially at the margins (Figure 7 A). Histochemical tests revealed intracellular histiocytic deposition of free and esterified cholesterol in skin lesions and rectal mucosa (Figure 7 B). Moderate hepatomegaly was noted. The patient’s tonsils were normal. The patient’s mother also had yellow skin discoloration and died at age 72 shortly after a cholecystectomy. The patient had no siblings, and of six cousins, two men had reduced HDL cholesterol values of 29 and 35 mg/dl, respectively.

The proband had elevated plasma triglyceride and VLDL cholesterol values, a normal LDL cholesterol level, and an HDL cholesterol level which was 6% of normal. Her plasma apo A-I, apo A-II, apo B, and apo C-III concentrations were 1%, 19%, 128% and 136% of normal respectively. Apo D and apo E levels were 40% and 140% of normal values (Tables 1 and 2). Of note was that 75% of both plasma apo A-II and apo D were found within LDL, and 85% of apo A-I was found in the 1.21 g/ml infranate. The ratio of free to total cholesterol and LCAT activity was normal, as was plasma fatty acid composition. The patient also had normal adipose tissue lipoprotein lipase activity. The defect in this condition remains to be defined.

Apo A-I<sub>Milan</sub>

The proband was a 49-year-old Italian man with no clinical evidence of coronary artery disease, a history of irregular bowel habits ("irritable colon") and several "tonsillectomies" for recurrent streptococcal infections.91 92 The proband also reported numerous episodes of bronchitis and lymphadenopathy, and underwent a total gastrectomy at age 36 for a bleeding duodenal ulcer. No corneal opacification, xanthomas, or hepatosplenomegaly were reported. He had one brother, age 37, who was apparently in good health, and another brother who died at age 26 of an unspecified cause. The proband had three offspring, aged 19, 13, and 12 years, and all were in good health. The mother of the proband, aged 73 years, had sustained a stroke. The proband's father was in good health at age 79. Coronary disease was noted in one of the proband's cousins (age not specified).

Five subjects in this kindred (proband, father, one brother, and two offspring) had reduced levels of HDL lipid constituents, hypertriglyceridemia, and abnormal apo A-I as determined by isoelectric focusing.93 Mean plasma triglyceride, HDL cholesterol, and LDL apo A-I concentrations in mg/dl were 243, 11, and 13, respectively (Tables 1, 2). Both LDL and HDL were triglyceride-rich in affected kindred members. The ratio of plasma free to total cholesterol was normal at 0.32. HDL cholesterol values correlated negatively with plasma triglyceride. Post-heparin plasma lipoprotein lipase levels were normal in three affected subjects, and LCAT activity was normal or slightly increased. Analysis of apo A-I from the proband indicated an abnormal amino acid composition since cysteine was present, resulting in the formation of apo A-I–apo A-I and apo A-I–apo A-II dimers.92 Moreover, isoelectric focusing analysis suggested that both abnormal and normal apo A-I was present in the proband.101 More recent data145 confirmed this finding and indicated that the percentages of normal apo A-I in two subjects with apo A-I<sub>Milan</sub> were 16% and 26%. Partial sequence analysis of apo A-I<sub>Milan</sub> from one subject indicated a cysteine-for-arginine substitution at residue 173. These data indicate that subjects with apo A-I<sub>Milan</sub> are heterozygotes and that the mode of inheritance is autosomal codominant. Apo A-I<sub>Milan</sub> reportedly has an enhanced in vivo catabolism and increased hepatocyte uptake as compared to normal apo A-I.

Fish-Eye Disease

Two Swedish kindreds have been reported with HDL deficiency and severe corneal opacification causing visual impairment (Figure 8). The index case for the first kindred was a 68-year-old white woman who had had corneal cloudiness since her teens, resulting in gradual bilateral visual impairment. A corneal transplant on her left eye was performed at age 64 with marked visual improvement.94 95 When examined by a biomicroscope, the corneal cloudiness appeared as small dotlike, grey-white-yellow opacities in a mosaic pattern. Analysis of the removed cornea demonstrated vacuoles in the stroma and Bowman’s layer and a significantly increased cholesterol content (mainly free cholesterol) as compared to normal corneas. The transplanted cornea has thus far remained clear. The patient also had acrodermatitis on her hands and left forearm which responded to penicillin therapy. A chest x-ray revealed aortic calcifications. An exercise stress test performed at age 63 resulted in ST-segment depression on ECG consistent with coronary insufficiency, as well as an intermittent left bundle branch block. Physical examination revealed mild hypertension, normal tonsils, and no hepatosplenomegaly.

The proband’s father and two sisters were also afflicted with marked corneal opacification. The father died at age 76 of a probable myocardial infarction, and one affected sister died at age 37 from an accident. The proband’s mother died at age 69 of unknown causes. The other affected sister of the proband had a history of corneal cloudiness since her teens. Her corneal findings were similar to the proband’s. She complained of intermittent arthralgia since age 46. A physical examination showed she had normal tonsils, spleen and liver, with bruits over the left carotid and right femoral arteries. She suffered a myocardial infarction at age 77 and died suddenly 6 months thereafter. None of these three affected sisters had offspring. The proband had two additional siblings who were in good health, one sis-
Figure 8. Marked corneal opacification as observed in homozygous fish-eye disease. (Reproduced from reference 95 with permission.)

In the first kindred, a 75-year-old white man had marked corneal cloudiness, mild hypertension, and decreased HDL cholesterol levels of 27 and 29 mg/dl respectively. The proband for the second kindred was a 74-year-old white woman who had a long history of marked corneal cloudiness similar in appearance to other fish-eye cases. She had decreased visual acuity. An electrocardiogram showed mild ST segment depression (anterior leads) and an x-ray showed no aortic calcification. The patient had mild hypertension, normal tonsils, and no hepatosplenomegaly. Her mother had died at age 91, but her father was alive at 93 and had an HDL cholesterol level of 28 mg/dl. The proband had one healthy 38-year-old daughter, who had an HDL cholesterol level of 39 mg/dl.

Lipoprotein abnormalities noted in homozygous fish-eye disease included hypertriglyceridemia, increased VLDL constituents, triglyceride-rich LDL, and marked HDL deficiency (the mean HDL cholesterol values were 10% of normal). The heterozygotes had normal plasma lipids and lipoprotein values except for reduced HDL cholesterol with mean HDL cholesterol values which were 46% of normal. Mean plasma apo A-I and A-II concentrations in the homozygotes were 22% and 12% of normal values respectively (Tables 1 and 2). No other apolipoprotein values were reported for the heterozygotes. Further analysis revealed that almost all the HDL in homozygotes was found in HDL₃, that a ratio of free total cholesterol was slightly increased at 0.40 (normal, 0.3), and that there was normal LCAT activity. The defect in fish-eye disease remains to be determined.

Familial Hypoalphalipoproteinemia

The proband for this kindred from Milano, Italy, was a 39-year-old white man who sustained a documented myocardial infarction at age 37, and had a reduced HDL cholesterol level. One brother, aged 44 years, who had sustained a myocardial infarction at age 41, also had a reduced HDL cholesterol level. Three sisters and all four female offspring of the two affected brothers had normal HDL cholesterol concentrations. The proband's father died at age 57 of a myocardial infarction, and three (all male) of the father's five siblings died suddenly at ages 49, 51, and 58. The sibling who died at age 49 had one son with decreased HDL cholesterol. The sibling (paternal uncle of proband) who died at age 58 had five offspring: two sons died suddenly at 36 and 51 years, one son had sustained a myocardial infarction at age 48 and had a reduced HDL cholesterol level, and two daughters were in good health with normal lipoprotein levels. Two (both male) of the five offspring of the two sons (proband's paternal cousins) had reduced HDL cholesterol levels. Whether any of these affected kindred members had corneal opacification, xanthomas, abnormal tonsils, or hepatosplenomegaly is not mentioned.

Plasma lipid and lipoprotein cholesterol levels in the affected kindred members were normal except for reduced HDL cholesterol values (51% of normal) and plasma apo A concentrations (combined determination of apo A-I and apo A-II, 78% of normal).
Analysis of apolipoprotein A-I isolated from the plasma of the proband of this kindred indicated a normal apo A-I isoform pattern and amino acid composition, and normal in vivo apo A-I kinetics as tested in two normal volunteers and in this kindred. Observations, Ghiselli G, Schaefer EJ, Vergani C, Brewer HB, Jr. These data suggest that these patients do not have an apo A-I abnormality. Apo B concentrations, post-heparin lipoprotein lipase and hepatic lipase activities, and CETP activities were normal in the affected kindred members. The mode of inheritance was felt to be autosomal dominant, and the precise molecular defect remains to be defined. Additional studies suggest that the prevalence of familial hypoalphalipoproteinemia in patients with premature CAD may be quite high. These various kindreds may have quite different molecular defects. In addition familial HDL deficiency has been associated with strokes in children.

Apo A-I Variants

Several additional apo A-I variants have been reported. apo A-I(Munster), apo A-I(Milano), and apo A-I(Milano 2) have been found in various kindreds. Recently reported amino acid substitutions on these variants are summarized in Table 6. Aapo A-I(Munster) was identified by isoelectric focusing in a patient with hypertriglyceridemia and a low HDL cholesterol. One major and one minor species occurred in the positions of normal apo A-I components. Another major and minor band were present in abnormal positions, and were demonstrated by immunoprecipitation to be apo A-I. This pattern suggested that this subject was a heterozygote for apo A-I(Munster). An additional apo A-I variant (apo A-I(Giessen)) was found in a healthy blood donor who showed two normal apo A-I bands on isoelectric focusing, and one additional major apo A-I band in an abnormal alkaline (pI 5.67) position. The isoelectric focusing patterns of these mutant proteins were not affected by reduction with disulfide reducing agents.

Table 6. Apolipoprotein A-I Variants

<table>
<thead>
<tr>
<th>Name</th>
<th>Substitution</th>
<th>Residue</th>
<th>Charge difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-I(Milano)</td>
<td>Arg → Cys</td>
<td>173</td>
<td>-1</td>
</tr>
<tr>
<td>A-I(Munster 3A)</td>
<td>Asp → Asn</td>
<td>103</td>
<td>+1</td>
</tr>
<tr>
<td>A-I(Munster 3B)</td>
<td>Pro → Arg</td>
<td>4</td>
<td>+1</td>
</tr>
<tr>
<td>A-I(Munster 3C)</td>
<td>Pro → His</td>
<td>3</td>
<td>+1</td>
</tr>
<tr>
<td>A-I(Giessen)</td>
<td>Pro → Arg</td>
<td>143</td>
<td>+1</td>
</tr>
<tr>
<td>A-I(Munster 2)</td>
<td>Lys → O</td>
<td>107</td>
<td>-1</td>
</tr>
</tbody>
</table>

Values are based on references 101, 102, 145, 147.

*Deficient in LCAT-activating ability (reference 147).

Corneal Opacification

Normal HDL cholesterol values, apolipoprotein concentrations, and metabolic parameters are summarized in Tables 1 and 2. Clinical features in various familial HDL deficient are listed in Table 3, and biochemical features are given in Tables 4–6. Diffuse corneal opacification has been observed in the probands for the familial apolipoprotein A-I and C-III deficiency states, Tangier disease, HDL deficiency with planar xanthomias, and fish-eye disease, but not in subjects affected with apo A-I(Milano) or familial hypoalphalipoproteinemia. In all these kindreds, corneal opacification was only noted in homozygotes, did not effect visual acuity, and developed in the third and fourth decade of life; an exception was in fish-eye disease where this finding was observed in the teenage years and led to a marked diminution in acuity. This latter condition can be effectively treated with corneal transplantation. The corneal opacification in fish-eye disease is readily visible and much more striking than that observed in other HDL deficient kindreds (except LCAT deficiency). In fish-eye disease, vacuolization was noted in the stroma and Bowman’s layer of the cornea, and was associated with a twofold increase in cholesterol content (mainly unesterified) as compared to normal corneas. In familial apolipoprotein A-I and C-III deficiency, granular lipid deposition was noted in extracellular locations in the stroma. In the probands for familial deficiency of apolipoproteins A-I and C-III, the corneal opacification was first observed in the periphery of the cornea, and subsequently moved toward the central area to affect the entire cornea. The data are consistent with the concept that marked HDL deficiency leads to an increased free cholesterol content in extracellular locations in the corneal stroma over time, possibly due to a lack of free cholesterol efflux caused by HDL deficiency. In contrast, corneal arcus due to increased cholesterol ester deposition in the peripheral, well vascularized portions of the cornea...
is associated with plasma LDL excess, as well as with the aging process.

**Xanthomas and Tissue Cholesterol Deposition**

Yellow-orange planar xanthomas due to lipid-laden histocytes have been observed in familial deficiency of apolipoproteins A-I and C-III and in HDL deficiency with planar xanthomas, but not in other HDL-deficient syndromes. Abnormal tonsils, hepatosplenomegaly, lymphadenopathy, and peripheral neuropathy associated with lipid deposition in reticuloendothelial and Schwann cells in these tissues have only been observed in Tangier disease. One hypothesis for the observed cholesterol ester deposition in these cells is the lack of HDL to promote efflux. An alternative explanation would be that these subjects, especially Tangier homozygotes, produce lipoproteins containing an abnormal lipid composition and apo A-I, which results in the uptake of these particles by reticuloendothelial cells.134, 150 In support of this latter concept are observations110 in one Tangier homozygote who developed marked omental reticuloendothelial lipid deposition following splenectomy.

**Premature Coronary Artery Disease**

Coronary artery disease before age 60 years has been observed in most HDL-deficient kindreds, but not in patients with apo A-II Milano or fish-eye disease. In this latter condition, CAD has been observed in individuals over 60. In the proband for familial apolipoprotein A-I and C-III deficiency, autopsy examination of the coronary arteries revealed typical atherosclerosis with smooth muscle cell proliferation, and lipid deposition (Figure 1). HDL deficiency has also been associated with strokes in children. Epidemiologic data would suggest that a decreased HDL level may be even more important as a CAD risk factor when combined with hypertension, smoking, or an increased LDL concentration. Therefore, while there are no formulated treatment regimens for HDL-deficient patients, efforts to minimize other risk factors should be undertaken for these individuals (i.e., maintenance of ideal body weight, treatment of hypertension when present, cessation of smoking, and a prudent low-saturated-fat, low-cholesterol diet). Drugs that may be effective in raising HDL levels in these subjects include niacin and gemfibrozil.129, 151–153 The presence of essential fatty acid or vitamin E deficiency should be excluded in subjects with marked HDL deficiency. Patients with significant coronary artery and angina pectoris unresponsive to medical therapy should be referred for coronary artery bypass grafting. Splenectomy appears to be contraindicated in Tangier homozygotes as it markedly enhances lipid deposition in reticuloendothelial cells in the omentum.110 The hemolytic anemia, proteinuria, and renal failure observed in familial LCAT deficiency has not been observed in other HDL-deficient states.93, 94

**Plasma Lipid and Lipoprotein Concentrations**

The plasma lipid, lipoprotein cholesterol, and lipoprotein concentrations reported for subjects with various types of familial HDL deficient states are summarized in Tables 4 and 5. An initial blood screening to detect these disorders should include determination of plasma cholesterol, triglyceride, and HDL cholesterol concentrations. If HDL cholesterol levels are below the 10th percentile (Table 1), then in addition to repeat analysis, lipoprotein electrophoresis and quantitation of lipoprotein lipids by ultracentrifugation are indicated as confirmatory tests. Measurement of free cholesterol is also important for assessment of LCAT deficiency.93, 94 If HDL levels are decreased and the patient has normal plasma lipids and tendinous xanthomas, a diagnosis of cerebrotendinous xanthomatosis should be considered.142 HDL levels are also decreased in severe hypertriglyceridemia. Additional studies required for diagnosis include measurement of plasma apolipoproteins A-I, A-II, B, and C-III, as well as isoelectric focusing of HDL apolipoproteins. Research studies that are of interest in these patients include amino acid composition and sequencing of apo A-I, radiolabeled HDL or apolipoprotein A-I and A-II kinetic studies, and analysis of DNA from white cells of affected subjects to detect possible gene defects utilizing appropriate probes.

**Triglyceride-Rich LDL**

Triglyceride-rich LDL appears to be a common feature in many of the HDL-deficient states reported. The probands for the familial apolipoprotein A-I and C-III deficiency states had somewhat decreased plasma concentrations of triglyceride. In contrast, patients with Tangier disease, HDL deficiency with planar xanthomas, fish-eye disease, or apo A-II Milano tended to have increased triglyceride levels. It is possible that the apo C-III deficiency in the former two kindreds results in enhanced catabolism of triglyceride-rich particles, since apo C-III reportedly142 inhibits hepatic uptake of chylomicron remnants. The hypertriglyceridemia observed in some HDL-deficient kindreds may be due to genetic abnormalities of apo C-III as well as apo A-I.104, 149

**LDL Cholesterol**

LDL cholesterol reportedly is normal in all HDL-deficient states except in homozygous Tangier disease (Table 4), where mean LDL cholesterol levels are 34% of normal. Variations in LDL levels, as well as HDL concentrations, may account for some of the observed heterogeneity in CAD prevalence in these kindreds. Decreases in HDL constituents are often the only lipid abnormalities detectable in heterozygotes for these various conditions. The ratio of free total cholesterol appears to be close to normal in all HDL-deficient states except familial LCAT deficiency which is not included in this review.
Apolipoprotein Measurement

Apolipoprotein measurements provide a reasonable means to distinguish among these various disorders. Plasma apo A-I was not detectable in the proband for familial apolipoprotein A-I and C-III deficiency, and only trace amounts were observed in the patients with homozygous familial deficiency of apolipoprotein A-I and C-III. In other HDL-deficient states, apo A-I values ranged between approximately 1 and 38 mg/dl. Plasma apo A-II concentrations were 10%, 51%, 7%, 33% and 11% of normal, respectively, in the probands for familial apolipoprotein A-I and C-III deficiency, familial deficiency of apolipoprotein A-I and C-III, Tangier disease, HDL deficiency with planar xanthomas, and fish-eye disease. Heterozygotes for the apolipoprotein A-I and C-III deficiency states had reduced apo A-I plasma levels, while Tangier heterozygotes had reductions of both apo A-I and apo A-II.

Differences in the distributions of apo A-I and A-II among lipoprotein density fractions in these various kindreds have also been observed. In the apo A-I and C-III deficiency states, almost all plasma apo A-II was found within the HDL density region, whereas in both homozygous Tangier disease and HDL deficiency with planar xanthomas, a large percentage of plasma apo A-I was found within the 1.21 g/ml infranate, and a significant fraction of apo A-II and some apo A-I were found in the 1.063 g/ml supernate following ultracentrifugation. These latter abnormal distributions may be a reflection of possible apo A-I abnormalities.

Apo B concentrations in these various disorders are in the normal range, with the lowest values being reported for homozygous Tangier disease. Apo C-III was undetectable in the apolipoprotein A-I- and C-III-deficient states, while in Tangier disease and HDL deficiency with planar xanthomas, values of 50% and 136% of normal, respectively, have been reported.

Apo A-I isoform analysis, as well as amino acid composition and sequence analysis,147,158 has been useful in detecting apo A-I abnormalities in Tangier disease, apo A-I_Munro, apo A-I_Munro, apo A-I_GiesSEN, and apo A-I_Munro, 1-3. Specific amino acid substitutions have been documented in many of these variants (Table 6), and substitutions undoubtedly will be documented in other HDL-deficient states. HDL and apolipoprotein kinetics have also been useful in understanding the pathophysiology of these disease states with enhanced fractional catabolism being reported for apo A-I_Munro and apo A-I_1cabin. In contrast, relatively normal HDL decay was observed in homozygous familial deficiency of apolipoproteins A-I and C-III, indicating lack of synthesis.

Genetic Pattern

The genetic pattern observed in these HDL deficient states appears to be most consistent with an autosomal codominant mode of inheritance in which the biochemical abnormality observed in homozygotes is partially expressed in heterozygotes. Subjects with apo A-I_Munro, apo A-I_Munro, apo A-I_GiesSEN, and apo A-I_Munro, 1-3 all appear to be heterozygotes. Familial hypophosphatoproteinemia reportedly has an autosomal dominant mode of inheritance; however, the subjects reported may all be heterozygotes since their lipoprotein values are similar to those reported for heterozygotes in other HDL deficient kindreds (Table 5). Until specific biochemical and genetic defects have been established for all these disease states, it may be exceedingly difficult to distinguish heterozygotes with one specific disorder from those of another.

Molecular biology techniques are increasingly being applied to genetic disorders of lipoprotein metabolism.103,104,156-158 A specific apo A-I gene abnormality has been reported based on the Southern blot analysis in familial deficiency of apolipoproteins A-I and C-III.103,104 No such abnormality exists in familial apolipoprotein A-I and C-III deficiency or Tangier disease. However, most genetic defects cannot be detected by DNA restriction enzyme digestion and Southern blot analysis using specific gene probes, but require DNA sequence analysis. In addition, some HDL-deficient states will undoubtedly not be due to apo A-I abnormalities, but to other molecular defects.

Genetic mutations often provide insights into normal metabolism that are difficult to obtain in other ways. Observations made in the various HDL-deficient states reviewed provide support for the following concepts: 1) decreased HDL is a primary risk factor for premature CAD in some kindreds but not in others; 2) apo A-I is not essential for LCAT activation and cholesterol esterification; 3) apo A-I and apo C-III are genetically linked; 4) apo A-I and/or C-III may be important for essential fatty acid and vitamin E intestinal absorption; and 5) apo A-I appears to be essential for normal HDL formation. Future research will undoubtedly uncover new genetic mutations associated with HDL deficiency, define the precise molecular and genetic defects in the disorders that have been described, as well as provide new insights into the relationship between decreased plasma HDL and atherosclerosis.

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GENETIC HDL DEFICIENCY

Schaefer


Index Terms: high density lipoprotein • high density lipoprotein deficiency • atherosclerosis • apolipoprotein A-I • apolipoprotein A-II
Clinical, biochemical, and genetic features in familial disorders of high density lipoprotein deficiency.
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