Genetic and Environmental Factors Affecting the Incidence of Coronary Artery Disease in Heterozygous Familial Hypercholesterolemia

J.S. Hill, M.R. Hayden, J. Frohlich, and P.H. Pritchard

This study explores the influence of selected genetic and environmental factors on the clinical expression of heterozygous familial hypercholesterolemia (FH). A detailed examination of the physical and biochemical features of FH was performed in a large cohort of 208 females and 156 males. Females with FH had higher levels of total, low density lipoprotein (LDL), and high density lipoprotein (HDL) cholesterol when compared with males, although the concentration of HDL cholesterol was significantly lower for both sexes when compared with normals. The reported incidence of coronary artery disease (CAD) was 31% for men and 13% for women, which was lower when compared with figures from previous studies. The average age of onset of coronary symptoms was delayed in females, with a mean age of 55 years compared with 48 years for males ($p<0.05$). A greater risk of developing CAD in men was associated with lower levels of HDL cholesterol and a history of smoking. In women, however, CAD was associated with elevated triglycerides and the presence of hypertension. The frequencies of the $e_2$, $e_3$, and $e_4$ alleles of apolipoprotein E in 125 unrelated FH subjects did not differ significantly from the normal population. In addition, there was no apparent relation between apo E4 and the concentration of any of the parameters in the plasma lipid profile; however, the presence of the $E_2$ isoform was associated with significantly elevated triglycerides in both sexes. This study has allowed us to identify those factors, which, in addition to total cholesterol levels, are associated with the development of premature coronary atherosclerosis in heterozygous FH. (Arteriosclerosis and Thrombosis 1991;11:290-297)

Familial hypercholesterolemia (FH) is an autosomal dominant disorder in which the primary defect is a mutation in the low density lipoprotein (LDL) receptor. Heterozygous FH is among the most common inborn errors of metabolism and occurs in approximately one in 500 persons; affected individuals can usually be identified from birth by elevated levels of plasma LDL cholesterol (LDL-C). The accumulation of this LDL-derived cholesterol frequently results in its deposition in tendons and skin, producing xanthomas, in addition to its contribution to premature coronary artery disease (CAD). In contrast, individuals who are homozygous for this genetic defect have a distinctly different clinical expression, which is considerably more serious. They present with severe hypercholesterolemia at birth and develop cutaneous xanthomas in early childhood. The prognosis for homozygotes is poor, and they often die of coronary events before 30 years of age.

Although all patients who are heterozygous for FH present with high serum cholesterol levels, the severity of the disease in terms of coronary symptoms is varied and not necessarily correlated with serum cholesterol levels. Even reports of single kindreds with FH have demonstrated considerable individual variation with respect to cholesterol levels and CAD. This phenotypic variation could be influenced by the variability of the underlying mutation; however, the effects of gender, obesity, hypertension, smoking, and possibly other forms of genetic polymorphism are likely to contribute to this poorly understood clinical heterogeneity. For example, a recent study of lipoprotein(a) (Lp[a]) levels and apolipoprotein (a) (apo[a]) phenotype in 115 FH patients indicated that this polymorphism was a significant independent risk factor for the development of coronary heart disease.

In addition, the well-described polymorphisms of apolipoprotein E structure and function may be an-
other factor that determines diversity in the clinical expression of FH. The genetic locus for plasma apo E has three common alleles (e2, e3, e4), which encode for the three major apo E isoforms found in plasma, E2, E3, and E4, respectively, resulting in the expression of six apo E phenotypes. Several studies have established that in a normal population, apo E4 and apo E2 have opposite effects on the concentrations of total cholesterol (TC) and LDL-C.6,7 In addition, it has been shown that the incidence of the e2 and e4 alleles is greater in patients with ischemic heart disease.11 Although some previous reports have attempted to study the effects of coinheritance of these different apo E alleles on the phenotypic expression of FH, no clear pattern has been established.12-15

The current clinical and biochemical features of heterozygous FH have been based on a number of different population studies. However, many of these investigations differ with respect to size, selection criteria, and genetic background, making it difficult to definitively describe the characteristics of FH. In the present study, we have used specific selection criteria to perform a detailed examination of the physical and biochemical features of a large cohort of individuals with heterozygous FH. A comparative analysis was made between males and females and between those with and without CAD through the investigation of lipids, lipoproteins, and apoproteins as well as other potential risk factors, including the polymorphism of apo E. This study has allowed us to identify those factors that, in addition to TC levels, are associated with the development of premature coronary atherosclerosis in heterozygous FH.

Methods

Subjects

A total of 364 patients from 283 families with heterozygous FH were identified among a population in the University Hospital Lipid Clinic. The ethnic origin of this cohort was very diverse, with at least 38 different countries represented. FH was diagnosed if subjects satisfied both of the following criteria: 1) a level of LDL-C greater than the 95th percentile corrected for both age and sex and 2) tendon xanthomas in the patient or a first-degree relative.

The criteria for CAD were the presence of angina (history of typical exercise-associated chest pain) or myocardial infarction (MI, proven by electrocardiogram and/or serum enzyme changes) or angiographically proven disease or a history of coronary bypass surgery. The frequency for each of these findings is indicated in Table 3, where more than one of the CAD indicators may occur in a single patient. Smoking was defined in both former and current smokers who had a history of smoking of at least 5 pack-years, where 1 pack-year is equivalent to smoking 1 pack/day for 1 year. Hypertension was indicated if clinically documented, even if patients were currently on antihypertensive medication. The body mass index (BMI) was calculated as body weight in kilograms divided by the square of the height in meters. Plasma samples from 125 unrelated FH subjects from the larger patient population were randomly chosen for apo E phenotype determination. In addition, specimens from a randomly selected normal population of 203 subjects aged 18-78 years living in the Vancouver area were analyzed for lipids and apo E phenotype.

Laboratory Methods

Venous blood was collected from all subjects after an overnight fast of 12-16 hours. The EDTA/plasma was separated from cells by low-speed centrifugation (1,200g, 20 minutes) and was analyzed immediately or frozen at -70°C. TC and triglycerides (TGs) were measured by established enzymatic techniques. High density lipoprotein cholesterol (HDL-C) was determined as the amount of cholesterol remaining after precipitation of apo B-containing lipoproteins with heparin/MnCl₂. LDL-C was calculated from the formula [TC - (HDL-C)] - [TG/2.2], where all values were measured in millimoles per liter. Plasma apo A-I and apo B were measured by rate nephelometry using a Beckman Immunochemistry System, Beckman Instruments, Ontario, Canada. Apo E phenotypes were determined as previously described in plasma that was neuraminidase treated, delipidated, and focused in vertical polyacrylamide gels. After immunoblotting, apo E was visualized with a polyclonal goat anti-apo E antibody followed by a protein G-peroxidase conjugate.

Data Analysis

Statistical analysis was performed using data obtained on the patient's first visit to the lipid clinic to ensure that the lipid values represented were obtained before treatment. Patients with hypothyroidism or poorly controlled diabetes and those on medication affecting lipoprotein metabolism were excluded from analysis. The significance of difference between two means was determined by Student's t test. The statistical significance of the differences in proportion between two groups was determined by the χ² test (employing Yates' correction for continuity).

Results

Age and Sex Distribution

A total of 364 patients (208 females and 156 males) with FH were identified from 283 families. The age distribution of this population is shown in Figure 1. The mean age for males was 40.3±17 years and 45.4±17 years for women. This age difference was statistically significant (p<0.01) with a larger proportion of women identified between the ages of 50 and 69 years.

Plasma Lipids, Lipoproteins, and Apoproteins

Table 1 compares the lipid parameters between males and females with FH and contrasts this patient group with the randomly selected population. As expected, in both sexes the levels of TC, LDL-C, and apo B were greatly elevated in comparison with the
normal population. In addition, the levels of HDL-C and apo A-I were consistently lower in all FH patients when compared with normals \((p<0.001)\). Also, the levels of plasma TGs were elevated in FH females compared with normals \((p<0.005)\) although the concentration within the FH population did not differ significantly between the sexes. However, Table 1 shows several differences among other variables between males and females with FH. The levels of TC, LDL-C, and HDL-C were all significantly elevated in FH females compared with FH males. The mean cholesterol value for females was 9.05±1.7 mmol/l and for males, 8.48±1.5 mmol/l \((p<0.001)\).

The magnitude of this difference was reflected in LDL-C, 6.99±1.6 mmol/l for females and 6.63±1.5 mmol/l for males \((p<0.05)\), and HDL-C, 1.26±0.3 mmol/l for females and 1.09±0.2 mmol/l for males \((p<0.001)\). Also, there was a significantly greater concentration of apo B and apo A-I in females compared with males \((p<0.001)\).

The concentration of lipids and apoproteins was also analyzed for each age group within each sex (Table 2). The values of TC and LDL-C increased steadily with age in both sexes. Higher levels of TC were observed in females for each age group. The concentration of HDL-C after age 30 years appeared to decline for men but to increase for women, with lower values found in males for the remaining age groups. Although there was no significant difference between TG values between the sexes in the whole group, differences could be detected when the separate age groups were analyzed. For males, the concentration of TGs increased with age and peaked between the ages of 30 and 49 years and then

<table>
<thead>
<tr>
<th>Variable</th>
<th>Males</th>
<th>FH</th>
<th>Females</th>
<th>FH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal ((n=97))</td>
<td>FH ((n=156))</td>
<td>Normal ((n=101))</td>
<td>FH ((n=208))</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>44.5±18</td>
<td>40.3±17</td>
<td>41.8±17</td>
<td>45.4±17*</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.37±1.1</td>
<td>8.48±1.5†</td>
<td>5.26±1.2</td>
<td>9.05±1.7†</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>3.50±0.9</td>
<td>6.63±1.5†</td>
<td>3.30±1.1</td>
<td>6.99±1.6†</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.20±0.3</td>
<td>1.09±0.2†</td>
<td>1.40±0.3†</td>
<td>1.26±0.3†</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.45±0.8</td>
<td>1.53±0.9</td>
<td>1.20±0.8†</td>
<td>1.48±0.8†</td>
</tr>
<tr>
<td>Apoprotein B (g/l)</td>
<td>0.89±0.2</td>
<td>1.35±0.5†</td>
<td>0.81±0.2†</td>
<td>1.52±0.4†</td>
</tr>
<tr>
<td>Apoprotein A-I (g/l)</td>
<td>1.42±0.3</td>
<td>1.24±0.2†</td>
<td>1.55±0.3†</td>
<td>1.36±0.3†</td>
</tr>
</tbody>
</table>

FH, familial hypercholesterolemia; LDL, low density lipoprotein; HDL, high density lipoprotein. Values are given as mean±SD.

*Significance of difference between males and females with FH \((p<0.05)\).
†Significance of difference between normal and FH groups \((p<0.001)\).
‡Significance of difference between males and females in the normal population \((p<0.05)\).
TABLE 2. Mean Values for Lipids, Lipoproteins, and Apoproteins for Each Age Division in Familial Hypercholesterolemia

<table>
<thead>
<tr>
<th>Variable</th>
<th>0–9 (n = 12)</th>
<th>10–19 (n = 9)</th>
<th>20–29 (n = 19)</th>
<th>30–39 (n = 28)</th>
<th>40–49 (n = 35)</th>
<th>50–59 (n = 32)</th>
<th>60–69 (n = 19)</th>
<th>70–79 (n = 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>7.24±1.5</td>
<td>7.63±1.5</td>
<td>8.54±1.3</td>
<td>8.49±1.3</td>
<td>8.81±1.6</td>
<td>8.63±1.2</td>
<td>8.84±1.7</td>
<td>6.91±0.1</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>5.66±1.4</td>
<td>5.77±1.4</td>
<td>6.90±1.3</td>
<td>6.39±1.6</td>
<td>6.97±1.6</td>
<td>6.88±1.2</td>
<td>6.86±1.4</td>
<td>5.39±0.4</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.14±0.2</td>
<td>1.16±0.2</td>
<td>1.11±0.2</td>
<td>1.09±0.2</td>
<td>1.04±0.3</td>
<td>1.05±0.2</td>
<td>1.15±0.2</td>
<td>0.92±0.1</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>0.99±0.4</td>
<td>0.75±0.3</td>
<td>1.20±0.7</td>
<td>1.88±1.2</td>
<td>1.84±0.8</td>
<td>1.57±0.7</td>
<td>1.45±0.7</td>
<td>1.43±0.4</td>
</tr>
<tr>
<td>Apoprotein A-I (g/l)</td>
<td>1.15±0.3</td>
<td>1.09±0.2</td>
<td>1.30±0.4</td>
<td>1.35±0.4</td>
<td>1.37±0.7</td>
<td>1.50±0.3</td>
<td>1.38±0.4</td>
<td>1.41±0.1</td>
</tr>
<tr>
<td>Apoprotein A-I (g/l)</td>
<td>1.22±0.1</td>
<td>1.30±0.2</td>
<td>1.16±0.1</td>
<td>1.24±0.2</td>
<td>1.18±0.3</td>
<td>1.25±0.2</td>
<td>1.34±0.2</td>
<td>1.31±0.03</td>
</tr>
</tbody>
</table>

Values are given as mean±SD except for the male age group of 70–79 years, for which data are expressed as mean±Vi the range.

TABLE 3. Clinical Data for Each Age Division in Familial Hypercholesterolemia

<table>
<thead>
<tr>
<th>Clinical finding</th>
<th>0–9 (n = 21)</th>
<th>10–19 (n = 8)</th>
<th>20–29 (n = 18)</th>
<th>30–39 (n = 64)</th>
<th>40–49 (n = 30)</th>
<th>50–59 (n = 45)</th>
<th>60–69 (n = 45)</th>
<th>70–79 (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tendon xanthoma</td>
<td>0</td>
<td>12 (63%)</td>
<td>25 (89%)</td>
<td>32 (91%)</td>
<td>31 (97%)</td>
<td>18 (95%)</td>
<td>2 (100%)</td>
<td></td>
</tr>
<tr>
<td>Corneal arcus</td>
<td>1 (5%)</td>
<td>7 (37%)</td>
<td>11 (39%)</td>
<td>31 (89%)</td>
<td>25 (78%)</td>
<td>17 (89%)</td>
<td>2 (100%)</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
<td>0</td>
<td>5 (18%)</td>
<td>6 (17%)</td>
<td>11 (34%)</td>
<td>8 (42%)</td>
<td>1 (50%)</td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td>0</td>
<td>0</td>
<td>2 (7%)</td>
<td>6 (17%)</td>
<td>6 (19%)</td>
<td>5 (26%)</td>
<td>2 (100%)</td>
<td></td>
</tr>
<tr>
<td>Bypass surgery</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>7 (20%)</td>
<td>9 (28%)</td>
<td>3 (16%)</td>
<td>1 (50%)</td>
<td></td>
</tr>
<tr>
<td>Angiographically documented disease</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (7%)</td>
<td>11 (31%)</td>
<td>5 (16%)</td>
<td>3 (16%)</td>
<td>2 (100%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (3%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Values are given as absolute numbers (and as percentages in parentheses) of the total number for each age group.

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...declined after age 50. In contrast, females generally showed a steady increase in the concentration of TGs with age. Between the ages of 30 and 49, men had significantly higher TG levels than did women, 1.85±0.9 mmol/l compared with 1.26±0.9 mmol/l (p<0.001). The values of apo B for all ages were consistently higher in females. In contrast, apo A-I levels were similar for both sexes until the age of 40 years, at which point they increased significantly in women (p<0.002).

Clinical Features of Familial Hypercholesterolemia

The frequency of specific clinical findings in FH for each age group is listed in Table 3. Tendon xanthomas begin to appear most commonly after age 20, and their frequency increases with age. The total...
The incidence of tendon xanthomas was greater in females (89%) compared with males (77%) \( (p<0.01) \). The frequency of corneal arcus also increased with age but was more common in males (60%) than in females (46%) \( (p<0.05) \). After age 30, the clinical findings related to CAD first appeared and became more prevalent with increasing age. The occurrence of MI was much greater in men over 30 (27%) than in women of the same age \( (p<0.001) \). Angina was also more frequent in men (18%) than in women \( (p<0.05) \). Stroke or cerebrovascular disease occurred in only one man and six women between the ages of 50 and 69.

The cumulative frequency of CAD in FH as a function of age is shown in Figure 2. Males had a much higher incidence of disease, with a frequency of 31% for the total male population as compared with 13% for females \( (p<0.001) \). Angina was also more frequent in men (18%) than in women (9%) for this age group \( (p<0.05) \). Smoking was associated with the presence of CAD in men \( (p<0.005) \) but not in women. However, a higher frequency of hypertension was observed in women with CAD but not among men \( (p<0.025) \). A higher percentage of men with CAD had HDL-C levels in the lower quartile of this population \( (p<0.025) \). Conversely, significantly fewer men with HDL-C levels in the upper quartile were positive for CAD \( (p<0.025) \). Similar trends were observed for women, but these differences were not statistically significant. There was no difference in BMI between those with and without CAD for both sexes.

### Table 4. Lipid, Lipoprotein, and Apoprotein Levels in Familial Hypercholesterolemia Patients With and Without Coronary Artery Disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>CAD-</th>
<th>CAD+</th>
<th>CAD-</th>
<th>CAD+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>n</td>
<td>68</td>
<td>47</td>
<td>147</td>
<td>26</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>45.5±10</td>
<td>48.2±9</td>
<td>49.7±12</td>
<td>54.7±12</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>8.47±1.3</td>
<td>8.96±1.6</td>
<td>9.10±1.6</td>
<td>9.68±2.1</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>6.51±1.4</td>
<td>7.13±1.5*</td>
<td>7.01±1.6</td>
<td>7.25±2.0</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.13±0.2</td>
<td>0.99±0.2†</td>
<td>1.29±0.3</td>
<td>1.22±0.4</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.70±1.0</td>
<td>1.70±0.7</td>
<td>1.46±0.7</td>
<td>2.09±1.41</td>
</tr>
<tr>
<td>Apoprotein B (g/l)</td>
<td>1.33±0.4</td>
<td>1.51±0.5*</td>
<td>1.53±0.4</td>
<td>1.59±0.6</td>
</tr>
<tr>
<td>Apoprotein A-1 (g/l)</td>
<td>1.28±0.2</td>
<td>1.18±0.22</td>
<td>1.40±0.3</td>
<td>1.31±0.3</td>
</tr>
</tbody>
</table>

CAD, coronary artery disease; LDL, low density lipoprotein; HDL, high density lipoprotein. Values are given as mean±SD. Significance of difference between CAD+ and CAD- groups for males and females is *\( p<0.05 \), †\( p<0.001 \), ‡\( p<0.01 \).
**Apolipoprotein E and Familial Hypercholesterolemia**

The apo E phenotype distribution and allele frequency for both FH and normal populations are shown in Table 6. Although not statistically significant, the frequency of the E4/3 phenotype was higher in FH patients (33.6%) compared with normals (24.6%), while the E3/2 incidence was lower, 8.0% compared with 12.3%. These differences were also reflected for the individual allele frequencies. In FH, they were 0.056 for e2, 0.744 for e3, and 0.200 for e4, and in normals, 0.086 for e2, 0.761 for e3, and 0.153 for e4.

This FH population was separated into two sets of two groups: those who had a phenotype containing the apo E4 or the apo E2 isoform and those who did not. Clinical data for these patients were compared between these two groups, and no significant difference was observed for the incidence of tendon xanthomas, corneal arcus, smoking, or hypertension. The only observable difference was found in the frequency of CAD, 29% for those with E4 and 19% for those without, but this difference did not reach statistical significance. It should be noted that there was no difference between these patient groups with CAD with respect to mean age, sex distribution, or frequency of smoking and hypertension (data not shown). Table 7 displays the lipid and lipoprotein data for the same categories, where the only significant difference found was a distinct elevation of TGs associated with the E2 isoform ($p<0.001$). It should be recognized that the ratio of males to females in each group was similar, and that a separate analysis for males and females revealed the same relations observed in Table 7 (data not shown).

**Discussion**

The detailed analysis of this large population of subjects with heterozygous FH has revealed a relatively low incidence of CAD in the presence of a gender-specific response to selected risk factors.

When the lipid and lipoprotein data of males and females with FH were analyzed, several differences were observed. For the first time, we have shown that females with FH have significantly higher mean levels of TC and LDL-C than males. This finding did not appear to be influenced by an age difference alone, as the TC levels were higher in every age group (Table 2). In addition, this finding was well correlated with the higher frequency of tendon xan-
thomas in females, especially those aged less than 30 years (Table 3).

The reported incidence of CAD of 31% for males and 13% for females was lower when compared with those of other studies16-18; however, this may have been affected by the lower mean age of this population compared with the mean age associated with the first symptoms of CAD. The age of onset of coronary symptoms and its delay for women, 55 years, compared with 48 years for men, has been shown to be a remarkably consistent feature in several different FH populations.16,19-21

The levels of TC in either sex did not distinguish between those patients with and those without CAD. This was particularly evident in females who had higher plasma cholesterol levels than males but who still had a very low incidence of CAD. However, for males, the concentration of both LDL-C and HDL-C had a greater predictive value. This observation was also confirmed in the measurement of apo concentration, with lower values of apo A-I and higher values of apo B being more often associated with CAD. Although other reports have shown that low HDL-C in FH is associated with CAD in both sexes,18,28 our study found that it was a good indicator for males only. In contrast, the only difference seen for females was higher concentrations of TG for those positive for CAD, an observation also made by Hirobe et al.18 This elevation in TGs was remarkably consistent feature in several different FH populations.16,19-21

The differences between the sexes still remained after additional risk factors were assessed. Smoking was found to have a profound effect in males, where as much as 70% of the CAD-positive males were smokers. An increased risk of CAD has been associated with smoking in other FH studies,5,19 especially for males,19 but it remains unclear why female smokers are not similarly affected. Instead, hypertension, which was seen with greater frequency in females, was associated with CAD. Having been reported in other studies,19,21 this observation confirms that hypertension is an independent risk factor for females with FH.

When HDL-C levels were divided into quartiles, the relation between low values and CAD was confirmed in males. Also, it was interesting to note that a higher percentage of patients with an HDL-C value in the upper quartile were negative for CAD. This observation, also reported by Hirobe et al,18 suggests that higher levels of HDL-C offer a degree of protection against CAD even in the presence of hypercholesterolemia.

The analysis of the apo E polymorphism in 125 unrelated FH subjects revealed several similarities to the study of Eto et al,15 of 50 Japanese patients with FH. In their study, there was also a tendency of the E2 allele to have a higher frequency in FH compared with the normal population. In addition, the prevalence of ischemic heart disease was greater in those patients who were positive for apo E4, while the frequency of other risk factors did not differ between the two groups. However, an important difference in our study, as well as others,13-15 was the lack of a relation between apo E4 and the concentration of any of the parameters in the plasma lipid profile. Since the locus for both the apo E and LDL receptor genes is found on chromosome 19,29-31 their distant locations would not indicate a functional relation.30 It is likely that in most cases, a mutation in the LDL receptor gene would affect cholesterol metabolism to such an extent that the influence of the different apo E alleles on cholesterol concentration seen in the normal population would not be evident in those with FH. However, it is of interest that those patients who have phenotypes containing the E2 isoform have elevated TGs, an observation sometimes seen in the normal population.31,32 Yet, it appears that the TG-raising effect associated with the E2 isoform is more dramatic in FH.15

One genetic factor that has not been assessed by the present study is the influence of Lp(a) levels and apo(a) phenotype. As previously mentioned, the levels of Lp(a) have been found to be independent risk factors for the development of coronary heart disease in FH.7 The analysis of Lp(a) levels and apo(a) phenotype has been initiated in our laboratory, and the data are currently being collected to be presented in a subsequent manuscript.

In this study, we have assessed the influence of selected genetic and environmental factors on the phenotypic expression of FH. We have established that the dissimilarity in clinical expression between
males and females is related to differences between the impact of known risk factors and the incidence of CAD. Even in the presence of a genetic mutation causing overt hypercholesterolemia, the expression of this disease is markedly affected by gender, lipid profile, smoking, and hypertension. In our study, only a small number of females with FH had symptoms of CAD; however, the risk of developing CAD in females was significantly increased in the smaller fraction of patients who had hypertension or elevated TGs. In contrast, males had a higher general frequency of disease but were at a much greater risk if they had lower HDL-C values and a history of smoking. In fact, the presence of CAD was almost always associated with one or more of these risk factors. Considering these observations, it may be necessary to reevaluate the conditions of treatment for the general FH population. From this investigation, it is apparent that an individualized assessment to consider the differences between males and females, including the effects of these risk factors, should be emphasized when treating and predicting the development of CAD in patients with FH.

References

Key Words • familial hypercholesterolemia • coronary artery disease • plasma lipids • smoking • apolipoprotein E • hypertension
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