Phenotypic Variation Among Familial Hypercholesterolemics Heterozygous for Either One of Two Afrikaner Founder LDL Receptor Mutations


Two common founder-related gene mutations that affect the low-density lipoprotein receptor (LDLR) are responsible for ~80% of familial hypercholesterolemia (FH) in South African Afrikaners. The FH Afrikaner-1 (FH1) mutation (Asp^ to Glu; GAC to GAG) in exon 4 results in defective receptors with ~20% of normal activity, whereas the FH Afrikaner-2 (FH2) mutation (Val^ to Met; GTG to ATG) in exon 9 completely abolishes LDLR activity (<2% normal activity). We analyzed the contribution of these mutations and other factors on the variation of hypercholesterolemia and clinical features in Afrikaner FH heterozygotes. The type of FH mutation, plasma triglyceride levels, and age of patients each contributed significantly to the variation in hypercholesterolemia, whereas smoking status, high-density lipoprotein cholesterol levels, and gender had no influence. Although all FH heterozygotes had frank hypercholesterolemia, patients with the FH1 mutation had significantly lower cholesterol levels than those with the FH2 mutation. FH1 heterozygotes also tended to have milder clinical features. The differences between the two FH groups could not be explained by a difference in the common apolipoprotein E variants. This study demonstrates that mutational heterogeneity in the LDLR gene influences the phenotypic expression of heterozygous FH. (Arterioscler Thromb. 1993;13:1460-1468.)

Key Words • familial hypercholesterolemia • LDL receptor • heterogeneity • phenotypic variation • apolipoprotein E

Familial hypercholesterolemia (FH) is a common autosomal dominant disease caused by mutations in the low-density lipoprotein receptor (LDLR) gene. Characteristic phenotypic features of FH are raised low-density lipoprotein (LDL) cholesterol (C) levels, the presence of tendon xanthomata, and the premature development of coronary heart disease (CHD). These features are more striking and their age of onset earlier in FH heterozygotes who inherit two mutant LDLR gene alleles. The mutational heterogeneity of FH explains most of the phenotypic variation found among FH homozygotes, in whom a strong correlation is found between residual receptor activity and the severity of the disease.1-2 A similar correlation for FH heterozygotes has not been shown.

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The founder-related basis for the high prevalence of FH in the Afrikaans-speaking white population of South Africa (Afrikaners) enabled us to study the degree of phenotypic variability caused by different LDLR gene mutations. Two of the three founder mutations identified in the Afrikaner population, which together account for ~80% of FH in Afrikaners,3,7 have different effects on the cellular expression of the LDLR. The FH Afrikaner-1 (FH1) mutation (Asp^ to Glu; GAC to GAG) in exon 4 of the LDLR gene results in the formation of functionally distinct forms of the mutant receptor; one form exhibits normal receptor activity, whereas another is unable to bind lipoprotein ligands.8,9 As a result, fully upregulated cells homozygous for this mutation express about 20% of normal receptor activity. The FH Afrikaner-2 (FH2) mutation (Val^ to Met; GTG to ATG) in exon 9 causes the receptor to be rapidly degraded and results in very low receptor activity (<2% of normal receptor activity).9

Studies have been carried out on the effect of other genes, such as apolipoprotein (apo) (a),10-12 apo B,14,15 and apo E,16-18 on the phenotypic expression of FH. There is, however, no consistent or complete explanation for the considerable variation in the phenotypic expression of heterozygous FH. This may in part be due to differences in selection criteria, size, and genetic background of the various populations studied or to
heterogeneity in expression of the many different FH mutant alleles. To assess the contribution of the mutant LDLR allele on phenotypic variation in FH, we compared the manifestations of FH in patients heterozygous for either one of the two common Afrikaner LDLR gene mutations. The phenotypic expression was found to be correlated, independent of the effects of apo E genotype or age, with the severity of the receptor defect.

**Methods**

**Patients and Control Subjects**

A total of 276 Afrikaans-speaking patients from 166 families with heterozygous FH and 203 normal control subjects were the subjects of the study. Sixty-four patients, who were unrelated at the level of first or second cousin, attended the lipid clinic at Tygerberg Hospital and 26 attended the lipid clinics at Groote Schuur Hospital and Red Cross War Memorial Children’s Hospital (all three in the Cape Province). Twenty-seven unrelated patients attended the Johannesburg Hospital Lipid Disorders Clinic (Transvaal Province). The remaining 49 unrelated individuals and 110 affected family members responded to a request in an Afrikaans newspaper for study participants, or they were referred for molecular diagnosis of FH at Tygerberg Hospital by general practitioners or the Department of National Health and Population Development. Blood was taken after obtaining informed consent and with ethical approval by the appropriate institution.

**Design of the Study**

Affected individuals were diagnosed during an ongoing screening of hypercholesterolemia Afrikaners for LDLR gene mutations. From a total of 276 subjects with one of the two most common Afrikaner founder mutations, pretreatment lipid levels could be obtained in 249 subjects, and these were selected to compare total cholesterol (TC) levels in different age groups. No dietary information was available on these patients, but those who were following low-cholesterol diets were excluded. After observation of a significant difference in TC levels between the FH1 and FH2 mutation groups, 148 FH heterozygotes who were unrelated to each other were selected for detailed comparison of lipid profiles. To investigate the possible influence of allelic variation at the apo e locus, genotypes for these subjects were also analyzed for the three most common apo E isoforms. Since the frequency and role of different apo e alleles have not been determined in the normal Afrikaner population, a total of 203 normal Afrikaners were also studied for comparison. A total of 130 unrelated FH individuals for whom clinical data were available were selected to compare the frequency of tendon xanthomata and CHD in the two mutation groups. Clinical features and lipid levels were also compared in 92 probands between the ages of 20 and 50 years.

**Laboratory Methods**

Genomic DNA was extracted from peripheral blood samples. The point mutations at bases 681 (FH1) and 1285 (FH2) of the LDLR gene were analyzed by polymerase chain reaction (PCR)–based methods as described previously.6,7 Apo e genotypes were determined by PCR amplification of genomic DNA by using oligonucleotide primers F4 and F6,19 restriction enzyme digestion with Hha I, and gel electrophoresis.20 Plasma lipid levels for TC, high-density lipoprotein cholesterol (HDLC), and triglycerides (TG) were determined in unrelated FH individuals and normal control subjects after an overnight fast of 12 to 16 hours as described previously.7,21 LDLC levels were calculated according to the Friedewald formula. Since it was not possible to obtain fasting blood samples from all family members, they were studied only with respect to their TC levels.

The presence or absence of tendon xanthomatas and CHD was recorded in 130 FH heterozygotes. Patients who had a myocardial infarction or suffered angina pectoris were recorded as CHD-positive cases.

**Statistical Methods**

Apo e allele frequencies were estimated by gene counting. The paired t test and the Wilcoxon signed-rank test were used to test the significance of any differences in proportion between paired observations. The statistical significance of the differences in proportion between two groups was determined by the χ² test (employing Yates’ correction for continuity). The analysis of variance and the Kruskal-Wallis test were used to determine whether average levels and responses were different among genotypes. In every case, the results were concordant. The R² from the analysis of variance was used to estimate the proportion of the total phenotypic variance accounted for by a genetic or environmental factor.

**Results**

**Age and Sex Distribution**

A total of 276 heterozygous FH patients (140 female and 136 male) with either the FH1 or FH2 LDLR gene mutation were identified from 166 families. Fig 1 shows the age distribution of this population. This distribution was similar for the two mutation groups as well as for males and females. The mean age for females and males was 38±18 and 34±16 years, respectively. In the FH1 group, ages ranged from 5 to 84 years for males (mean...
age, 35±17 years) and from 5 to 82 years for females (mean age, 38±18 years). In the FH2 group, ages ranged between 2 and 49 years in males (mean age, 30±14 years) and between 1 and 72 years in females (mean age, 39±20 years).

Plasma Lipid and Lipoprotein Levels in FH and Normal Populations

Pretreatment TC levels for all age groups were higher in the FH2 mutation group compared with the FH1 group (Fig 2). The distribution of pretreatment TC levels in male and female FH1 heterozygotes is contrasted with the normal population described by Rossov and coworkers (Fig 3). The number of patients analyzed in the FH2 group was too small to allow a similar comparison between the sexes. The TC levels varied with age in approximately the same way in normal and FH individuals and, as expected, affected individuals show markedly higher cholesterol levels in comparison with the control subjects.

Of the 249 FH heterozygotes studied, 148 were unrelated at the level of first or second cousins. The FH1 mutation was present in 112 (76%) and the FH2 mutation in 36 (24%) of these individuals. The mean TC and LDLC levels, as expected, were significantly higher in the FH groups when compared with the control group, while the mean HDLC and TG levels were higher in the control group (Table 1). Significantly higher mean TC and LDLC levels were also observed in individuals with the FH2 mutation compared with individuals with the FH1 mutation (P<.0001). There were also significant differences in TC levels between these two mutation groups when either males or females were compared (data not shown). The contribution of variation in certain variables to the variation in TC was determined by using analysis of variance and multiple

FIG 2. Line plot showing distribution of pretreatment total cholesterol (TC) levels in FH1 and FH2 heterozygotes combined in different age groups (n=249). Error bars indicate SD. FH indicates familial hypercholesterolemia.

FIG 3. Line plot showing distribution of pretreatment total cholesterol (TC) levels in male and female FH1 heterozygotes (■, □) in comparison with the normal Afrikaner population (▲, ▼) for different age groups. FH indicates familial hypercholesterolemia.
Frequency and Effects of Apo E Polymorphism in FH

The plasma lipid levels in the FH1 and FH2 groups and their age composition (P = .47) were compared in Table 1. The FH1 and FH2 groups were also compared according to apo e genotype (Table 3) (four control subjects and one FH patient were not considered because of their e2/4 genotype). The apo e allele frequencies were relatively lower in the FH2 group (67%) than the FH1 (49%) group. Although none of the differences between the FH1 and FH2 groups reached statistical significance, the differences between the FH1 group and the FH2 group with CHD and non-CHD patients in either mutation group were evident at a younger age, as indicated by the fact that 43% of individuals in the younger FH2 group were affected with CHD, compared with 30% of individuals in the older FH2 group. The plasma lipid levels in the FH1 group were lower than in the FH2 group in both mutation groups, and the FH2 patients had higher cholesterol levels and TG. Most importantly, when only the e3/3 patients were compared, the mean TC levels differed significantly between the FH1 and FH2 groups (P = .0001) (Table 3). The apo E polymorphism was also shown to be noncontributory to the variation in TC between the FH1 and FH2 groups by analysis of variance and multiple regression models.

Clinical Manifestations

The LDLC levels and ages of 130 unrelated probands with and without CHD or xanthomata are shown in Table 4. In both mutation groups the frequency of CHD and xanthomata increased with age. The effects of gender and e alleles on the presence of CHD were not significant (data not shown). No CHD in either mutation group was evident in any proband under the age of 20 years. The frequency of CHD in the over-50-year age group reached about 63% for both the FH1 and FH2 groups. In the FH2 group there were no males older than 50 years. Given the lack of CHD in the younger individuals and its high frequency in the older group together with the absence of males in the older FH2 patients, the 20- to 50-year-old heterozygotes were specifically selected for a more detailed analysis (Table 4). The FH2 group appeared to be affected at a younger age, as indicated by the fact that 43% of individuals in the 20- to 50-year bracket had CHD, compared with only 23% in the corresponding FH1 group (Table 4). Similarly, the frequency of xanthomata was higher in the FH2 (67%) than in the FH1 (49%) group. Although none of the differences between the FH1 and FH2 groups mentioned above reached statistical significance, they indicate a tendency that FH1 heterozygotes are less severely affected clinically than are FH2 heterozygotes.

The plasma lipid levels in the FH1 and FH2 groups (20 to 50 years of age) were compared in patients with or without CHD or xanthomata (Table 4). No significant difference in either LDLC or TC was observed between the CHD and non-CHD patients in either mutation group (or in the combined group). The same observations were made when males and females were analyzed separately (data not shown). Plasma cholesterol levels therefore do not appear to be a good predictor of CHD in these heterozygous groups. In similar comparisons,
The high frequency (about one in 80) of FH in the Afrikaans-speaking white population of South Africa\(^3\)\(^-\)\(^2\) is the result of three founder-related LDLR gene defects.\(^3\)\(^-\)\(^5\) In this study, the phenotypic expression of FH was initially analyzed in 276 individuals (from 166 families) who were heterozygous for one of the two most common mutations. Analysis of the age distribution showed that there was a greater proportion of women than men in the older age groups, possibly due to earlier coronary death in men with FH. This was also observed when the FH1 and FH2 groups were analyzed separately (results not shown). It is noteworthy that all the FH2 heterozygous men identified were younger than 50 years old. Similar age distributions were observed for the two sexes when a single proband from each family was analyzed, indicating that these results do not reflect other genetic factors that accumulate in certain families (results not shown).

The mean TC and LDL levels were compared between the two mutation groups, and the FH2 group was shown to have higher levels at all ages than the FH1 group. Comparison of TC levels for different age groups in the normal population and FH1 heterozygotes showed a similar trend of increased levels with age. Contrary to a previous report on another group of FH patients with various LDLR mutations,\(^18\) TC levels in females were generally not found to be higher than those in males, although in the age group over 55 years, these levels tended to be somewhat higher in women than in men.

Of the factors considered that might contribute to the variation in the hypercholesterolemia in FH patients, the type of mutation, TG level, and age each contributed significantly to about 10% of the variation. This was the case whether univariate or multivariate analysis was considered. These factors together explain \(\approx 30\)% of cholesterol variation in FH heterozygotes. Smoking status, HDL levels, and gender were noncontributory. The contribution of age, as previously noted,\(^18\) was expected, but the reason(s) for the contributions of the mutation and TG level is unclear. It is possible that the lower level of plasma cholesterol associated with the FH1 mutation reflects the known retention of some receptor activity of this mutant protein. In cultured fibroblasts, the FH1 mutant protein expresses 10% to 20% of normal receptor activity, compared with the normal LDLR protein. It is known that the LDLR functions as an oligomer,\(^20\) and the FH2 mutant protein, which is extremely unstable and rapidly degraded, might influence the stability and consequently the activity of the normal receptor.

The distribution of the common apo \(\epsilon\) allele frequencies in the normal Afrikaner control group was similar to that reported for most other populations.\(^27\) The effects of the apo \(\epsilon\) alleles on cholesterol levels in this group follow the expected pattern. Apo \(\epsilon 2\) alleles were associated with low cholesterol levels, while \(\epsilon 4\) alleles were associated with raised levels. Interestingly, while

### Table 3. Lipid and Lipoprotein Concentrations in Afrikaner Control Subjects and Proband Chromosomal Hypercholesterolemia Two Familial Hypercholesterolemia Males Groups According to Apolipoprotein E Genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Controls (n=199)</th>
<th>FH1 (n=112)</th>
<th>FH2 (n=35)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>TC, mmol/L</td>
<td>TC, mmol/L</td>
<td>TC, mmol/L</td>
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<tr>
<td>E2</td>
<td>40.1±14.0</td>
<td>43.9±13.9</td>
<td>43.7±13.9</td>
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<tr>
<td></td>
<td>9.4±1.99</td>
<td>9.5±1.3</td>
<td>9.6±1.3</td>
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<tr>
<td></td>
<td>7.6±1.9</td>
<td>7.9±1.3</td>
<td>7.9±1.3</td>
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<tr>
<td></td>
<td>1.4±0.3</td>
<td>1.1±0.4</td>
<td>1.2±0.4</td>
</tr>
<tr>
<td></td>
<td>1.0±0.9</td>
<td>1.2±0.4</td>
<td>1.2±0.4</td>
</tr>
<tr>
<td>E3</td>
<td>44.3±13.4</td>
<td>40.1±14.0</td>
<td>43.7±13.9</td>
</tr>
<tr>
<td></td>
<td>9.4±1.99</td>
<td>9.5±1.3</td>
<td>9.6±1.3</td>
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<tr>
<td></td>
<td>7.6±1.9</td>
<td>7.9±1.3</td>
<td>7.9±1.3</td>
</tr>
<tr>
<td></td>
<td>1.4±0.3</td>
<td>1.1±0.4</td>
<td>1.2±0.4</td>
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<tr>
<td></td>
<td>1.0±0.9</td>
<td>1.2±0.4</td>
<td>1.2±0.4</td>
</tr>
<tr>
<td>E4</td>
<td>31.7±22.7</td>
<td>43.7±14.1</td>
<td>43.7±14.1</td>
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<tr>
<td></td>
<td>11.0±1.4</td>
<td>11.3±1.7</td>
<td>11.3±1.7</td>
</tr>
<tr>
<td></td>
<td>9.3±1.4</td>
<td>9.2±1.5</td>
<td>9.2±1.5</td>
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<tr>
<td></td>
<td>1.2±0.3</td>
<td>1.2±0.3</td>
<td>1.2±0.3</td>
</tr>
<tr>
<td></td>
<td>1.6±0.5</td>
<td>1.9±0.6</td>
<td>1.9±0.6</td>
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</tbody>
</table>

TC indicates total cholesterol; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TG, triglyceride; FH, familial hypercholesterolemia. Values are given as mean±SD.

\(\ast\)E2 vs E4; \(P<.05\).\n
\(\dagger\)E2 vs E3; \(P<.05\).\n
\(\ddagger\)E3 vs E4; \(P<.05\).\n
\(\natural\)FH1 vs FH2; \(P<.0001\).

There were no differences in HDL or TG levels were found between CHD and non-CHD patients. With respect to the presence of xanthomata, a significant difference was observed specifically in the FH1 group, in which LDL and TC levels were higher in patients with than in patients without these characteristics.

To assess further the possible effects of the two mutations and LDL levels on the frequency of CHD, patients were divided into high (>8 mmol/L) and low- (<8 mmol/L) LDL levels. Analysis of the age distribution showed that there was a greater frequency of CHD than the corresponding low-LDL levels. This analysis, however, involved relatively small numbers of patients, and none of these differences reached statistical significance.

**Discussion**

The high frequency (about one in 80) of FH in the Afrikaans-speaking white population of South Africa\(^3\)\(^-\)\(^2\) is the result of three founder-related LDLR gene defects.\(^3\)\(^-\)\(^5\) In this study, the phenotypic expression of FH was initially analyzed in 276 individuals (from 166 families) who were heterozygous for one of the two most common mutations. Analysis of the age distribution showed that there was a greater proportion of women than men in the older age groups, possibly due to earlier coronary death in men with FH. This was also observed when the FH1 and FH2 groups were analyzed separately (results not shown). It is noteworthy that all the FH2 heterozygous men identified were younger than 50 years old. Similar age distributions were observed for the two sexes when a single proband from each family was analyzed, indicating that these results do not reflect other genetic factors that accumulate in certain families (results not shown).

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the apo e allele frequencies in the FH2 group are similar to the control group, the frequencies in the FH1 group differ significantly. In contrast with Eto and coworkers, who found a higher frequency of the apo e4 allele in the FH compared with the normal population, this allele was lower in the Afrikaner FH1 population compared with control subjects and the FH2 group. The apo e2 allele frequency was also clearly lower in the FH1 group compared with the other groups. Different underlying apo e allele frequencies were thus found in the two "founder" FH groups. This was possibly due to a coincidental enrichment of the apo e3 allele with the FH1 mutation during the genetic drift that presumably contributed to the "founding" phenomenon responsible for FH1 enrichment in Afrikaners.

The contrasting effects of the e2 allele in the normal and FH1 groups are probably explained by the small numbers analyzed and, as mentioned by Hill and colleagues, the likelihood that LDLR mutations will affect cholesterol metabolism to such an extent that any influence of apo e alleles on cholesterol concentration would not be evident in FH patients. This view is supported by De Knijff et al and O'Malley and Illingworth, who could not demonstrate any significant effect of apo E polymorphism on baseline levels of TC and LDL in FH patients. Therefore, we conclude that variation at the apo E locus does not contribute in a major way to the variation in hypercholesterolemia in our FH population or to the difference between the two mutation groups.

Limitations of the present study include the fact that comparisons were made of index cases, who may be more severely affected than heterozygotes not presenting at the lipid clinics. The possible effects of diet have not been considered, and the influences of lipoprotein(a) levels and variation in the apo B gene have also not been assessed. No clear pattern has been estab-
### TABLE 4. Lipid and Lipoprotein Levels in Familial Hypercholesterolemic Probands Aged Between 20 and 50 Years With and Without Coronary Heart Disease/Tendon Xanthomas

<table>
<thead>
<tr>
<th>Subgroup/Variable</th>
<th>CHD−</th>
<th>CHD+</th>
<th>XMTA−</th>
<th>XMTA+</th>
</tr>
</thead>
<tbody>
<tr>
<td>FH1 heterozygotes (n=71)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>55 (77%)</td>
<td>16 (23%)</td>
<td>36 (51%)</td>
<td>35 (49%)</td>
</tr>
<tr>
<td>Male/female</td>
<td>23/32</td>
<td>9/7</td>
<td>13/23</td>
<td>19/16</td>
</tr>
<tr>
<td>Age, y</td>
<td>35±8.3</td>
<td>38±4.8</td>
<td>35±8.3</td>
<td>37±6.9</td>
</tr>
<tr>
<td>TC, mmol/L</td>
<td>9.3±1.5</td>
<td>9.7±1.6*</td>
<td>8.8±1.5†</td>
<td>9.9±1.3*</td>
</tr>
<tr>
<td>LDLC, mmol/L</td>
<td>7.6±1.6</td>
<td>8.0±1.4*</td>
<td>7.1±1.5†</td>
<td>8.2±1.4</td>
</tr>
<tr>
<td>HDLC, mmol/L</td>
<td>1.14±0.4</td>
<td>1.1±0.4</td>
<td>1.15±0.4</td>
<td>1.1±0.3</td>
</tr>
<tr>
<td>TG, mmol/L</td>
<td>1.2±0.6</td>
<td>1.4±0.7</td>
<td>1.33±0.7</td>
<td>1.2±0.4*</td>
</tr>
</tbody>
</table>

| FH2 heterozygotes (n=21) | | | | |
| Total | 12 (57%) | 9 (43%) | 7 (33%) | 14 (67%) |
| Male/female | 5/7 | 6/3 | 2/5 | 9/5 |
| Age, y | 34±6.9 | 37.8±8.6 | 32±10.3 | 38±5.3 |
| TC, mmol/L | 10.6±1.7 | 11.3±1.4 | 10.9±1.4 | 10.9±1.7 |
| LDLC, mmol/L | 8.8±1.5 | 9.4±1.4 | 9.15±1.2 | 9.0±1.6 |
| HDLC, mmol/L | 1.17±0.2 | 1.07±0.3 | 1.2±0.2 | 1.09±0.3 |
| TG, mmol/L | 1.7±0.6 | 1.3±0.6 | 1.2±0.5 | 1.6±0.6 |

| FH1 and FH2 heterozygotes (n=92) | | | | |
| Total | 67 (73%) | 25 (27%) | 43 (45%) | 49 (53%) |
| Male/female | 28/39 | 15/10 | 15/28 | 26/21 |
| Age, y | 35±8.0 | 38±6.2 | 34±8.6 | 37±6.5 |
| TC, mmol/L | 9.5±1.6 | 10.3±1.7 | 9.2±1.7† | 10.2±1.5 |
| LDLC, mmol/L | 7.8±1.6 | 8.5±1.5 | 7.4±1.6 | 8.5±1.5 |
| HDLC, mmol/L | 1.14±0.3 | 1.09±0.3 | 1.2±0.4 | 1.1±0.3 |
| TG, mmol/L | 1.25±0.6 | 1.5±0.6 | 1.3±0.7 | 1.3±0.5 |

CHD indicates coronary heart disease; −, without; +, with; XMTA, tendon xanthoma; FH, familial hypercholesterolemia; TC, total cholesterol; LDLC, low-density lipoprotein cholesterol; HDLC, high-density lipoprotein cholesterol; TG, triglyceride. Values are given as mean±SD.

*FH1 vs FH2: P<.01.†XMTA− vs XMTA+: P<.01.

A comparison of the clinical manifestations in FH1 and FH2 heterozygotes has shown a tendency of the FH2 group to be more severely affected, since relatively more FH2 heterozygotes presented with CHD and tendon xanthoma. Previous studies have shown that some FH1 heterozygotes, even those with high TC and LDLC levels, may remain clinically asymptomatic throughout their lives, while the majority of deaths by cardiovascular disease in FH2 heterozygotes, particularly in males, occurs between 40 and 50 years of age. Interestingly, it was shown that heterozygous FH patients with the FH2 mutation responded better to simvastatin treatment than those with the FH1 mutation. The tendency for FH2 heterozygotes to be more severely affected is consistent with the higher cholesterol levels found in the FH2 group. This suggests that LDLC may be as good a predictor of clinical outcome as is knowledge of the LDLR gene defect. To test this hypothesis, we compared the cholesterol levels between patients with and without clinical manifestations of FH. TC and LDLC levels did not discriminate significantly between patients with and without CHD and neither did the mutation type, although the tendencies observed were that higher CHD frequencies were associated with the FH2 mutation as well as with higher cholesterol values. Although greater numbers of FH patients are needed for a more accurate statistical analysis of these groups, knowledge of both LDLC levels and LDLR...
mutation type may therefore offer the best means of identifying those FH patients with the highest risk of developing premature CHD.

Acknowledgments

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