Response to HMG CoA Reductase Inhibitors in Heterozygous Familial Hypercholesterolemia Due to the 10-kb Deletion (“French Canadian Mutation”) of the LDL Receptor Gene

Lina Karayan, Shiqiang Qiu, Christine Betard, Robert Dufour, Ghislaine Roederer, Anne Minnich, Jean Davignon, Jacques Genest, Jr

Abstract The 10-kb deletion (“French Canadian mutation”) of the low-density lipoprotein (LDL) receptor gene is the most common mutation causing familial hypercholesterolemia among subjects of French Canadian descent. In affected subjects, it results in a null allele of the LDL receptor gene and provides a unique opportunity to examine single-allele regulation of this gene in humans. We sought to ascertain the response of inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase in subjects with the French Canadian mutation of the LDL receptor gene and to correlate this response with biochemical variables and the haplotype of the nondeletion LDL receptor allele. The prevalence of nonresponders to high doses of HMG CoA reductase inhibitors (defined as <15% decrease in LDL cholesterol [LDL-C] from baseline values after dietary intervention) was ascertained in 105 patients heterozygous for the 10-kb deletion after excluding first-degree relatives and those on combined lipid-lowering therapy or other lipid-lowering agents. Lipoprotein cholesterol levels were examined after a diet period (30% calories as fat) and after receiving HMG CoA reductase inhibitors as monotherapy for a minimum of 3 months. The mean reduction in total cholesterol was 45±23%, in LDL-C 33±15%, and in triglycerides 32±49% (all P<.005). There was a slight increase in high-density lipoprotein cholesterol of 8.5±18% (P>.05). Overall, 68.4% of patients had more than a 30% decrease in LDL-C levels and 23% had a decrease ranging from 15% to 30%; 8.6% of patients failed to respond, and some even showed an increase in their LDL-C levels (mean change, 1.2±11.9%). This response was independent of age, gender, triglycerides, or high-density lipoprotein cholesterol levels. There was no significant overall effect of the apolipoprotein E phenotype in predicting the degree of total cholesterol or LDL-C reduction. Haplotypes of the LDL receptor gene were determined with the use of five polymorphic markers. The 10-kb deletion is known to be present on a single haplotype, allowing the haplotype determination of the nondeletion allele. Analysis of the nondeletion allele of the LDL receptor did not reveal a difference between responders and nonresponders, suggesting that a defect in the nondeletion allele of the LDL receptor may not be the cause of this phenomenon. (Arterioscler Thromb. 1994;14:1258-1263.)

Key Words • familial hypercholesterolemia • LDL receptor • HMG CoA reductase inhibitors

Familial hypercholesterolemia (FH) is a genetic disorder characterized by elevated plasma levels of total cholesterol due to elevated low-density lipoprotein (LDL) cholesterol (LDL-C) and cutaneous lipid deposits (xanthelasmas, xanthomas, and corneal arcus) as well as the presence of premature coronary artery disease in probands and family members.1,2 Mutations within the gene coding for the LDL receptor have been identified as the cause of FH.3 Multiple mutations have been described,4 and five classes of phenotypes at the cellular level have been established. Class 1 defects do not produce LDL receptor protein (null allele); class 2 defects encode proteins that do not bind normally to LDL; class 4 defects encode receptors that are not recycled to the cell surface in a normal fashion.3,4 A defect in the ligand for the LDL receptor, apolipoprotein (apo) B, is phenotypically indistinguishable from FH5,6 and is seen in approximately 1/500 subjects. In the province of Québec, Canada, the prevalence of FH is approximately 1/270, with geographical clusters having a frequency as high as 1/80.7 Based on the prevalence of homozygotes with FH, the number of heterozygotes in the province of Québec (population approximately 6 million) has been estimated at 26 000.

In the French Canadian population approximately 75% of subjects with FH have one of five mutations of the LDL receptor gene. The most frequent, accounting for 60% of FH cases in the Montréal metropolitan region, is a >10-kb deletion of the 5′ region of the LDL receptor gene (the “French Canadian mutation”). The deletion includes part of the second intron, the first exon, the first intron, and the 5′ regulatory region. In homozygotes with the 10-kb deletion, no mRNA is detected, and the mutation results in a null allele.8,9 In heterozygotes the expression of the LDL receptor on

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before their introduction in 1990. Subjects on concomitant therapy with niacin, probucol, bile acid sequestrants, or fibric acid derivatives were excluded from the study. Using these criteria, we selected 115 subjects (56 women and 59 men; mean age, 45.5±11.5 years). None of the study subjects were on an HCRi for at least 3 months before treatment was initiated; all underwent dietary intervention with a professional dietitian and were advised to follow an American Heart Association phase I or II diet. All subjects took lovastatin (40 mg, n=19; 60 mg, n=5; 80 mg, n=61), simvastatin (20 mg, n=6; 30 mg, n=1; 40 mg, n=9), or pravastatin (40 mg, n=4) per day for at least 3 months. The clinician treating the patient was not constrained to increase drug dosage if the clinical response was considered satisfactory. The mean interval of time between blood sampling was 1.68±0.82 months (range, 1 through 3 months). The duration of follow-up on HCRi monotherapy was 12.7±9.72 months (range, 2.5 through 38 months). Approximately 44% of patients were on drug study protocols that included regular clinic visits as well as pill counts.

**Lipid and Lipoprotein Measurements**

Blood was collected in tubes containing EDTA to a final concentration of 1.2 mg/mL. Plasma was separated by centrifugation at 3000 rpm for 20 minutes at 4°C. Total cholesterol, triglycerides, and high-density lipoprotein cholesterol (HDL-C) were determined. Plasma levels of LDL-C were determined after ultracentrifugation at d=1.006 g/mL and determined as d<1.006 g/mL cholesterol minus HDL-C. ApoE isoforms were determined by using the technique of Bouhiller as reported in Xhignesse et al.13 DNA Analysis and LDL Receptor Haplotype Determination

Human chromosomal DNA was isolated from peripheral blood. The diagnosis of the 10-kb deletion was ascertained by a double digest of the DNA by the restriction enzymes Xba I and EcoRV under conditions recommended by the manufacturer. The DNA fragments were then separated by electrophoresis on 0.7% agarose gels and transferred to nylon membranes (Hybond-N, Amersham). The nylon filters were hybridized with a 650-bp EcoRI-Pst I fragment of the LDL receptor gene (American Type Culture Collection) and subcloned in the vector pGEM-3 (Pharmacia). The sequence of the insert was checked by direct sequencing. Haplotype analysis followed the methodology and nomenclature of Betard et al18 and used the restriction enzymes Xba I, Stu I, Apa LI, Pvu II, and Nco I. The 10-kb deletion is present only on the B haplotype.10 The haplotype of the nondeletion allele can thus be determined by simple subtraction of the B allele from the complete haplotype, assuming that no rearrangements of the LDL receptor gene had occurred in the subjects examined. The presence of other mutations of the LDL receptor gene known to be present in French Canadians (5-kb deletion and point mutations within exons 3, 4, and 14) was also investigated.8,12 Statistical Analysis

The reductions in plasma lipid and lipoprotein levels were expressed as a percentage of baseline levels, defined as [(baseline−treatment/baseline levels)×100]. Men and women were first examined separately and then as a group after we determined that the magnitude of change in lipoprotein cholesterol was not affected by gender. Normality of each variable was checked by Kolmogorov-Smirnov analysis. A Student’s t test was used to compare lipid and lipoprotein levels before and after treatment for those variables with a normal distribution, and a Mann-Whitney rank-sum test was used for the variables that were not normally distributed. χ² analysis was used to compare the frequency of discrete variables. Pearson’s correlation coefficients were determined, and on those variables showing a significant correlation a linear regression
TABLE 1. Clinical Characteristics of the 105 Study Subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Initial</th>
<th>Final</th>
<th>Change, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC, mmol/L</td>
<td>9.84±1.90</td>
<td>6.89±1.36</td>
<td>-45±23*</td>
</tr>
<tr>
<td>Trig, mmol/L</td>
<td>1.62±1.10</td>
<td>1.29±0.71</td>
<td>-32±49*</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>7.92±1.46</td>
<td>5.22±1.22</td>
<td>-33±15*</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>0.98±0.28</td>
<td>1.05±0.29</td>
<td>9±18</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>67.4±14.5</td>
<td>68.6±15.4</td>
<td>1.5±4</td>
</tr>
</tbody>
</table>

TC indicates total cholesterol; Trig, triglycerides; LDL-C, low-density lipoprotein cholesterol; and HDL-C, high-density lipoprotein cholesterol. Values are mean±SD. P<.005.

Results

Analysis was performed by the least-squares fit method. A Pearson's regression was performed on the variables with a normal distribution, and Spearman's regression was used on data not showing a normal distribution. The data were analyzed with the SIGMA STAT statistical software (Jandel Scientific).

An index case is shown in Fig 1. Compared with a subject showing a 47% reduction of LDL-C on high-dose lovastatin (subject ICM 09), one subject (ICM 06) showed no response to lovastatin. The clinical and biochemical characteristics of the 105 subjects are shown in Table 1.

Despite the presence of the 10-kb deletion, subjects taking HCRLs had a significant decrease in total cholesterol (from 9.84±1.90 to 6.89±1.36 mmol/L; mean decrease, 45.1±22.9%, P<.005) and LDL-C levels (from 7.92±1.46 to 5.22±1.22 mmol/L; mean decrease, 33±15%, P<.005). Triglycerides decreased significantly by 31.9±48.9% (from 1.62±1.10 to 1.29±0.71 mmol/L, P<.005). There was a nonsignificant increase (8.5±18.3%) in HDL-C levels (from 0.98±0.28 to 1.05±0.29 mmol/L). There was no significant change in weight during the study period (67.4±14.5 to 68.6±15.4 kg; mean change, 1.5±4.2%, P=.516).

Fig 2 shows the frequency distribution of the percent decrease in LDL-C. The mean percent decrease was 33%; the median decrease was 36%. Over two thirds of subjects (68%) had a decrease of ≥30% in LDL-C, and 23% had a decrease between 15% and 30% of baseline LDL values. Interestingly, the frequency distribution of the percent decrease in LDL-C did not follow a normal distribution but was skewed to the left.

We defined a lack of response to HCRL as less than a 15% reduction in LDL-C levels after treatment. We considered that a 10% response could represent biological variability and that a 20% reduction represented a true response. With this criterion, 9/105 (8.6%) subjects were defined as nonresponders (Figs 2 and 3).

We determined whether baseline characteristics influenced the degree of reduction in LDL-C levels. Correlation coefficients were determined between the degree of reduction in LDL-C and gender, age, baseline total cholesterol, LDL-C, HDL-C, and triglyceride levels (Table 2). A significant inverse Spearman's correlation was found only for baseline total cholesterol and LDL-C levels (r=-.288 and r=-.399, P<.05, respectively). Despite the statistical association, baseline levels of total cholesterol or LDL-C were not useful biochem-

TABLE 2. Correlation Between Baseline Parameters and Degree of LDL-C Reduction

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LDL-C Reduction, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.130</td>
</tr>
<tr>
<td>Gender</td>
<td>-0.026</td>
</tr>
<tr>
<td>TC</td>
<td>-0.288*</td>
</tr>
<tr>
<td>Trig</td>
<td>0.071</td>
</tr>
<tr>
<td>LDL-C</td>
<td>-0.399*</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.022</td>
</tr>
<tr>
<td>Weight</td>
<td>-0.011</td>
</tr>
</tbody>
</table>

LDL-C indicates low-density lipoprotein cholesterol; TC, total cholesterol; Trig, triglycerides; and HDL-C, high-density lipoprotein cholesterol. *P<.05.
genotype data, the nondeletion allele could be ascertained. Differences in the magnitude of LDL-C reduction and age, gender, baseline triglyceride levels, or HDL-C levels were noted in the nonresponders (six men and three women; mean age, 46.5±11 years), defined as those subjects showing a <15% decrease in LDL-C, are shown in Table 3. This group's baseline lipid and lipoprotein cholesterol levels did not differ significantly from the rest of the group of 96 FH subjects with the >10-kb deletion who were defined as responders. No significant changes in total cholesterol, LDL-C, or HDL-C levels were noted in the nonresponders, although a nonsignificant reduction in triglyceride levels was observed. The haplotype of the nondeletion allele of the LDL receptor gene was determined in 101 subjects (see "Methods") for whom the genotype data were consistent with the presence of the B haplotype. In the other four subjects (3.8%), all of whom responded to HRCI therapy, the complete haplotype could not be reliably determined. By "subtracting" the B allele from the genotype data, the nondeletion allele could be ascertained. We used the nomenclature of Betard et al. for whom the genotype data were consistent with the presence of the F haplotype10; n=36 subjects) was 33%. The next most frequent haplotype was the B haplotype (n=19 subjects), which was associated with a 37% reduction in LDL-C levels. Nonresponders are identified in Fig 4; haplotype F was found in 5 subjects, and haplotypes G, J, L, and P in 1 subject each.

**TABLE 3. Clinical Characteristics in the Nine Nonresponders**

<table>
<thead>
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<td>9.25±5.6</td>
<td>6.1±14.5</td>
<td></td>
</tr>
<tr>
<td>Trig</td>
<td>3.64±2.34</td>
<td>2.38±1.1</td>
<td>-25.9±35.1</td>
</tr>
<tr>
<td>LDL-C</td>
<td>7.03±1.56</td>
<td>7.15±1.9</td>
<td>1.2±11.9</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.93±0.36</td>
<td>0.94±0.29</td>
<td>5.6±0.21</td>
</tr>
</tbody>
</table>

TC indicates total cholesterol; Trig, triglycerides; LDL-C, low-density lipoprotein cholesterol; and HDL-C, high-density lipoprotein cholesterol. Values are mean±SD and are given as millimoles per liter. Nonresponders are those study subjects who showed <15% decrease from baseline LDL-C in response to high-dose 3-hydroxy-3-methylglutaryl coenzyme A inhibitors.

The effects of the apoE phenotype on the percent LDL-C decrease were ascertained. No phenotyping was performed for seven patients. The distribution of the apoE phenotypes was as follows: E2/2, 1.02%; E3/2, 9.18%; E3/3, 57.14%; E4/2, 2.08%; and E4/4, 4.08%. In subjects with the presence of the apoE2 allele (excluding subjects with the E4/2 genotype), the mean LDL-C reduction was 28.6±20.2% (n=10 subjects); subjects with the E3/3 genotype (n=56) had a mean LDL-C reduction of 34.4±12.3%, and in those with the E4 allele (excluding the E4/2 genotype), the degree of LDL-C reduction was 32.9±10.5% (n=30). In this analysis, no significant effects of gender and apoE phenotype were observed on the degree of LDL-C or HDL-C change. Thus, overall, no significant effect of the apoE phenotype was shown on the degree of LDL-C reduction. The number of subjects in each group is small, however, and an effect of the apoE phenotype may not have been detectable.

The clinical characteristics of the nonresponders (six men and three women; mean age, 46.5±11 years), defined as those subjects showing a <15% decrease in LDL-C, are shown in Table 3. This group's baseline lipid and lipoprotein cholesterol levels did not differ significantly from the rest of the group of 96 FH subjects with the >10-kb deletion who were defined as responders. No significant changes in total cholesterol, LDL-C, or HDL-C levels were noted in the nonresponders, although a nonsignificant reduction in triglyceride levels was observed.

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**Discussion**

FH individuals are at increased risk of cardiovascular disease. It is estimated that by age 50, nearly 50% of men will have developed cardiovascular disease; in women, the onset of the disease is delayed by approximately 10 years. Early and aggressive treatment to lower increased LDL-C levels in FH subjects leads to decreased complications from cardiovascular disease. The Program on Surgical control of Hyperlipidemias (POSHEL trial) has shown14 that the use of ileal bypass to reduce cholesterol levels results in marked cholesterol reductions and a significant reduction in cardiac events. In subjects with a left ventricular ejection fraction >45%, total mortality was reduced in the treatment group.15 The clinical trial by Kane et al16 has shown that aggressive cholesterol reduction in subjects with marked hypercholesterolemia results in decreased cardiac complications compared with control subjects. These and other studies strongly suggest that the reduction of elevated cholesterol is beneficial in preventing the progression of coronary artery disease and prevents (or delays) clinical manifestations such as myocardial infarction, the need for revascularization procedures, and cardiac death.

Modalities of treatment in subjects with FH include bile acid–binding resins and HRCIs. In the majority of cases diet alone may be insufficient to correct the lipoprotein profile. Furthermore, the effects of currently recommended diets on plasma total cholesterol and LDL-C levels in subjects with type II hyperlipoproteinemia are, on average, less than can be obtained with HRCI therapy.17 The recent introduction of HRCIs has been a landmark in the treatment of patients with FH. In the province of Québec the majority of subjects with FH (>60% in the Montréal metropolitan region)
have the French Canadian mutation, a >10-kb deletion at the 5' end of the LDL receptor gene. Studies by Hobbs et al and Leitersdorf et al show that approximately 60% of FH subjects from the eastern part of the province also have a >10-kb deletion of the LDL receptor gene. This latter deletion removes part of the first intron, the first exon, and the promoter region and results in a null allele type of mutation. Since the regulatory region of the gene is deleted in subjects with the 10-kb deletion, no mRNA is produced from this allele, and homozygotes for the mutation do not synthesize any LDL receptor protein.

Our results show that despite the presence of a mutation with an important effect on lipoprotein metabolism, patients heterozygous for the French Canadian mutation of the LDL receptor gene respond to HCRIs with mean decreases of 45%, 33%, and 32%, respectively, in total cholesterol, LDL-C, and triglyceride levels and a 9% mean increase in HDL-C level. In addition, two thirds of subjects responded with a >30% reduction in total cholesterol. We also noted that approximately 9% of our subjects failed to respond to HCR1 monotherapy (defined as <15% decrease in LDL-C).

We postulate at least four possible mechanisms to explain our findings. First, a lack of compliance to the medication regimen seems unlikely. In many instances, subjects participated in clinical study protocols and pill counts were routinely made; most subjects were patients followed for many years by one of us (R.D., G.R., J.D., and J.G.) at either of our institutions. Second, drug malabsorption, although possible, seems unlikely. None of the subjects presented with any medical condition associated with malabsorption syndromes. We did not, however, perform detailed drug absorption or pharmacokinetic studies on any of our subjects. Third, the prevalence of other mutations of the LDL receptor could explain our findings. None of the nonresponders showed the 5-kb deletion or the point mutations at exons 3, 4, and 14 seen in French Canadians. We propose that the results observed may be the result of defective upregulation of the LDL receptor gene from the nondeletion allele in the nonresponders. Multiple mechanisms could account for this, including a defective response to intracellular cholesterol depletion in the nondeletion allele or an abnormal upregulation of the HMG CoA reductase gene. This latter deletion removes part of the 5' end of the LDL receptor gene. Studies by Hobbs et al and Leitersdorf et al show that approximately 60% of FH subjects from the eastern part of the province also have a >10-kb deletion of the LDL receptor gene. This latter deletion removes part of the first intron, the first exon, and the promoter region and results in a null allele type of mutation. Since the regulatory region of the gene is deleted in subjects with the 10-kb deletion, no mRNA is produced from this allele, and homozygotes for the mutation do not synthesize any LDL receptor protein.

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If we extrapolate our findings at the level of the population in the province of Quebec, where approximately 26,000 subjects have heterozygous FH, and assume that 60% of FH subjects have the 10-kb deletion and that of those, 8.6% are nonresponders, approximately 1300 subjects with FH would have the 10-kb deletion and would not respond to medications. This number would greatly strain our resources in terms of health budgets and treatment facilities with extracorporeal LDL elimination. The use of extracorporeal LDL-removal techniques remains controversial in subjects with heterozygous FH. LDL apheresis or filtration techniques are not widely available, and the cost of LDL filtration in our institution is currently approximately $12,300 Canadian per year. Although the sole modality for treatment in these subjects is extracorporeal LDL removal, the prospect for widespread use of this technology is, in the current economic context, difficult. The prevalence of FH in a group of subjects with premature coronary artery disease is approximately 3% to 4% in a group of French Canadian subjects with angiographically documented coronary artery disease, the prevalence of FH is approximately 5% (J. Genest, unpublished data, 1994), close to the prevalence reported by Goldstein et al. It seems, therefore, that judicious use of extracorporeal LDL elimination in the secondary prevention of coronary artery disease may be more cost-effective than its widespread use in asymptomatic subjects who do not respond to aggressive lipid-lowering pharmacological therapy.

We were not able to show a clinically significant correlation between baseline characteristics such as age, weight, and HDL-C or triglyceride levels and the degree of LDL-C reduction on HCRIs (a weak correlation was found for baseline total cholesterol and LDL-C). Similarly, haplotype analysis of the nondeletion allele of the LDL receptor gene did not reveal a segregation of the lack of response with any single allele. It is conceivable that the transcriptional rate of individual alleles of the LDL receptor may differ in response to altered intracellular cholesterol, but our study was not designed to assess in vitro gene regulation. We did not show a significant effect of the apoE polymorphism in the response to HCRIs. This finding differs from a previous report by Carmena et al, in which 67 of 98 subjects with FH were from the same clinic as those reported here. This difference can be explained by the fact that the study design and the baseline lipid and lipoprotein cholesterol differed between the two studies.

Although in the study of Carmena et al 28.7% did not have the 10-kb deletion, all subjects were taking the same drug (lovastatin) at a dose of 80 mg/d, and 85% of the patients were studied as part of a clinical pharmacology protocol.

A caveat of the current study lies in the fact that our subject population is inherently biased. Cases are referred for severe hyperlipoproteinemia, for failure of control of a lipid disorder, or for the presence of coronary artery disease. Therefore, it is not known how many subjects with the 10-kb deletion respond in a satisfactory fashion out-
side our clinic. Furthermore, since we did not consider those subjects who responded adequately with lower doses of HCRIs or bile acid-binding resins, our number of nonresponders may be overestimated. Nevertheless, our data suggest that some subjects with null allele mutations of the LDL receptor may not respond to conventional drug therapy. One previous study has examined the response to drug-lowering therapy in FH with defined mutations of the LDL receptor gene. 26 It is of interest that the magnitude of LDL reduction observed in our subjects with the >10-kb deletion was greater than that observed in the study of Leitersdorf et al, 27 in which the drug fluvastatin was used. This may reflect differences in drug efficacy rather than effects of a mutation. Interestingly, we found no differences in the degree of LDL reduction in subjects taking lovastatin 40 mg (31±11% reduction), 60 mg (34±16% reduction), or 80 mg (34±16% reduction, P=NS). The physiological and molecular mechanisms underlying the lack of response in our nine nonresponders remain to be determined. Elucidating such mechanisms may allow novel methods of therapy in these subjects who, for the present time, fail to respond to conventional drug therapy.

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