Deletion of Exon 15 of the LDL Receptor Gene
Is Associated With a Mild Form
of Familial Hypercholesterolemia

FH-Espoo

Pekka V.I. Koivisto, Ulla-Maija Koivisto, Petri T. Kovanen, Helena Gylling,
Tatu A. Miettinen, Kimmo Kontula

We describe a mutation of the low-density lipoprotein (LDL) receptor gene, designated familial hypercholesterolemia (FH)–Espoo, which deletes exon 15 of the LDL receptor gene. The mutant receptor is predicted to lack 57 amino acids, including 18 serine and threonine residues, which are the sites of the clustered O-linked sugars of the receptor. Studies on 10 carriers of this gene revealed that FH-Espoo is associated with an exceptionally mild form of FH. Thus, in conditions in which cell proliferation was rendered dependent on the function of LDL receptors, lymphocytes from the patients with the FH-Espoo allele had a growth rate intermediate between those from healthy subjects and patients with the FH-Helsinki gene, a mutation known to abolish LDL receptor function. The in vivo fractional catabolic rate of LDL apolipoprotein B was lower than normal in the two FH-Espoo heterozygotes studied. Although higher than those in healthy controls, the serum LDL cholesterol concentrations in patients with the FH-Espoo gene were significantly lower than those in patients with the FH-Helsinki mutation. The thickness of the Achilles tendons was within the normal limits in subjects with the FH-Espoo gene. Our study suggests that moderate varieties of hypercholesterolemia, ie, those not considered to represent FH, may occasionally be due to subtle LDL receptor gene mutations. (Arterioscler Thromb. 1993;13:1680-1688.)

KEY WORDS • apolipoprotein B • apolipoprotein E • cholesterol • DNA • Finland • LDL receptor gene • familial hypercholesterolemia

Familial hypercholesterolemia (FH) is characterized by a lack of functional low-density lipoprotein (LDL) receptors on the cell surface and is caused by mutations of the LDL receptor gene. These mutations include a wide variety of DNA alterations ranging from single nucleotide substitutions to large deletions and insertions. This wide spectrum at the DNA level is reflected in the considerable phenotypic variation of the mutant receptors. In most populations mutations of the LDL receptor gene vary in their characteristics from family to family. In some populations, more homogeneous in genetic terms, only one or a few LDL receptor gene mutations have been enriched; examples include the French-Canadians, Lebanese Christian Arabs, South African Afrikanders, and Finns. More than 60% (in eastern parts of the country up to 90%) of the heterozygous FH patients in Finland are carriers of one of the two “Finnish-type” LDL receptor gene mutations, FH-Helsinki or FH-North Karelia. The FH-Helsinki mutation is a 9.5-kb deletion eliminating exons 16 through 18 of the LDL receptor gene; in the FH-North Karelia gene seven nucleotides from exon 6 are deleted. Both of these Finnish-type LDL receptor mutations result in a typical clinical picture of FH, with elevated serum LDL concentration, tendon xanthomatosis, and premature coronary heart disease (CHD). There appear to be no differences in serum lipid levels between patients with these two mutation types.

In our recent study on the concordance of clinical and molecular genetic diagnosis of FH we encountered another LDL receptor gene mutation, designated FH-Espoo. Preliminary data suggested that the FH-Espoo gene most likely results from deletion of exon 15 of the LDL receptor gene. Exon 15 is of special interest in that it encodes the domain with O-linked sugars situated extracellularly between the membrane-spanning region and the epidermal growth factor homology domain of the LDL receptor protein. Davis et al used oligonucleotide-directed mutagenesis to delete the cDNA segment encoding this receptor domain with clustered serine and threonine residues. When transfected into hamster fibroblasts, the mutated cDNA codes for a receptor protein functionally indistinguishable from the normal receptor. Although the proband with the FH-Espoo mutation in our preliminary study was originally identified from a pool of FH patients, two young
members of the same family were found to have relatively low serum LDL concentrations. These findings prompted us to characterize this mutation in more detail as well as to clarify whether the associated clinical syndrome would turn out to be different from the classic form of heterozygous FH, exemplified by carriers of the FH-Helsinki mutation.8,10

Methods

Patients

The proband, a 64-year-old woman with a 15-year history of hypercholesterolemia and angina pectoris and small subperiosteal xanthomas at the olecranon processes on both sides, but without unequivocal tendon xanthomas, was identified in our earlier study.10 The proband, all her siblings, and their children and grandchildren over 6 years of age were invited to the outpatient department of the Meilahti University Hospital, where 12-hour fasting blood samples were drawn and a clinical examination was performed. Of the 32 subjects invited, 29 volunteered; two subjects were temporarily abroad and one did not respond to the invitation. Eleven of these 29 also volunteered for our earlier study.10 Data on the clinical characteristics and serum lipid levels of the FH-Espoo patients and their non-FH relatives were compared with those of the FH-Helsinki patients and their non-FH family members examined in the earlier study.10

Physical Examination

During interview of the family members, earlier illnesses and medications were recorded. Subjects were classified to have CHD if a diagnosis of myocardial infarction or angina pectoris had been established earlier or if they had had exercise electrocardiographic findings compatible with CHD.10 The presence of tendon and subperiosteal xanthomas was evaluated by manual palpation. Achilles tendon thickness was measured with a ruler, holding the Achilles tendon between the thumb and index finger.10 All the clinical data were collected by the same investigator, and the results were recorded before the laboratory studies were performed.

Lipoprotein Measurements

Serum cholesterol14 and triglyceride15 concentrations were measured by enzymatic methods using commercial kits obtained from Boehringer, Mannheim, FRG. The concentration of high-density lipoprotein cholesterol was measured enzymatically after precipitation of LDL and very-low-density lipoprotein fractions with dextran sulfate and magnesium chloride.10 The concentration of LDL cholesterol (LDL-C) was calculated by using the equation of Friedewald formula.17 The proband with the FH-Espoo mutation and 14 of the adult control subjects with the FH-Helsinki mutation10 had been on hypolipidemic treatment. They were asked to stop the medication at least 6 weeks before measurement of the lipid levels. The sister of the FH-Espoo proband, also a bearer of the FH-Espoo mutation, had been operated on because of breast cancer and was taking tamoxifen at the time of clinical examination was performed. Of the 32 subjects invited, 29 volunteered; two subjects were temporarily abroad and one did not respond to the invitation. Eleven of these 29 also volunteered for our earlier study.10 Data on the clinical characteristics and serum lipid levels of the FH-Espoo patients and their non-FH relatives were compared with those of the FH-Helsinki patients and their non-FH family members examined in the earlier study.10

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A.

![Diagram of DNA sequence showing partial sequence of cDNA corresponding to the mutated low-density lipoprotein (LDL) receptor gene in a familial hypercholesterolemia (FH)-Espoo patient.](image)

B.

![Diagram of predicted amino acid sequence of the mutated protein](image)

Fig 1. A, Autoradiograph showing partial sequence of the cDNA corresponding to the mutated low-density lipoprotein (LDL) receptor gene in a familial hypercholesterolemia (FH)-Espoo patient. B, Predicted amino acid sequence of the mutated protein. For comparison the amino acid sequence of the normal LDL receptor protein is also shown (from Reference 11). Numbers underneath denote amino acid numbers of the normal and FH-Espoo receptors. The amino acids belonging to the membrane-spanning sequence are underlined. Vertical lines indicate exon boundaries.

primers as sequencing primers and reagents of the fmol kit (Promega Biotec, Madison, Wis). The temperature profile was 95°C for 30 seconds and 70°C for 30 seconds for 30 cycles. The sequencing reaction products were electrophoresed on urea-containing polyacrylamide gels, and the results were visualized by autoradiography.

**Determination of the Activity of LDL Receptors on Lymphocytes**

The activity of LDL receptors was determined on lymphocytes from 8 patients with the FH-Espoo mutation, from 12 age-matched patients with the FH-Helsinki mutation selected from an earlier study population, and from 20 healthy control subjects of similar age. At the time of the study, all subjects had stopped hypolipidemic treatment for at least 4 weeks. The functional LDL receptor assay was carried out essentially as described by Cuthbert et al. In brief, peripheral blood mononuclear cells were isolated and then suspended in a medium supplemented with lipoprotein-deficient serum. The cells were incubated in microtiter wells with 0.5 μg/mL phytohemagglutinin to induce cell proliferation and 0.5 μmol/L lovastatin to block cellular cholesterol synthesis. LDL (d = 1.020 to 1.050 g/mL), which was isolated by ultracentrifugation from the plasma of healthy normcholesterolemic subjects, was added at various concentrations to provide the cells with an exogenous source of cholesterol. The concentrations of LDL-C (up to 1.15 μg/mL) were all well below the concentration that would have saturated the LDL receptors, ensuring that uptake of LDL-C by the dividing cells was LDL receptor dependent. After incubation for 72 hours, [3H]thymidine was added to the medium. After an additional incubation for 18 hours, the cells were harvested and measured for their content of 3H radioactivity. Plots showing the ability of increasing concentrations of exogenous LDL to reverse the lovastatin-mediated suppression of lymphocyte proliferation were constructed as described. In addition, the concentration of LDL necessary to reduce the lovastatin-mediated inhibition of lymphocyte proliferation by 50% was determined.

**LDL Turnover In Vivo**

LDL turnover studies were performed in two male FH-Espoo heterozygotes as described in detail with autologous LDL (d = 1.019 to 1.063 g/mL) isolated by ultracentrifugation. LDL apoB was labeled with 125I, the...
labeled lipoprotein was injected into the patients, and blood samples were obtained for 14 days thereafter. ApoB in LDL was measured turbidimetrically using anti-human apoB antiserum (Orion Diagnostica, Espoo, Finland). The fractional catabolic rate and production rate of LDL apoB were calculated using a two-pool model.33 The results of the FH-Espoo patients were compared with those of five FH-Helsinki patients studied during the same time in our laboratory and with 27 healthy middle-aged men consuming a cholesterol-lowering diet (from Reference 34; two subjects with the rare apoE 2/2 phenotype were excluded).

**Statistical Methods**

Statistical significances of differences between groups were evaluated by using one-way ANOVA, Student’s *t* test, or the *χ*² test (BMDP Statistical Software, Inc, Los Angeles, Calif).

**Results**

**Characterization of the FH-Espoo Mutation**

Our earlier study10 suggests that the FH-Espoo mutation involves an approximately 6-kb deletion extending from intron 14 through intron 15, thus deleting exon 15. For screening of the members of the kindred with the FH-Espoo mutation, the DNA samples were digested with *BamH*I before hybridization analysis to reveal the unique 11-kb fragment characteristic of this deletion.10

When poly(A)-enriched RNA preparations from fibroblasts of two FH-Espoo heterozygotes were subjected to Northern blot analysis, only the normal-sized 5.3-kb mRNA species hybridizable with a ³²P-labeled LDL receptor cDNA probe was visualized (data not shown). Because the stretch encoded by exon 15 comprises only 171 nucleotides, the mutant mRNA may have been superimposed on the normal mRNA. To deduce the consequences of the deletion on the structural characteristics of the mutant mRNA and the corresponding receptor protein, we prepared cDNA molecules corresponding to the area of the mutation from total fibroblast RNA from the patients and sequenced them. In the mutant DNA the intact 3' end of exon 14 merged with the intact 5' end of exon 16, with a selective deletion of the entire exon 15 (Fig 1). The data thus demonstrated that mRNA splicing occurs between the normal splice sites at the 3' end of exon 14 and at the 5' end of exon 16. Accordingly, in the mature mRNA only exon 15 is deleted, and the overall normal reading frame is maintained (Fig 1B). The mutant FH-Espoo LDL receptor protein, if actually synthesized, should be 57 amino acids shorter than the normal one because amino acids from Glu 693 through Gin 749 are deleted, but the amino acid sequence should otherwise follow that of the normal LDL receptor.

**The Activity of the Mutant LDL Receptor in Mitogen-Stimulated Lymphocytes**

The impact of the FH-Espoo mutation on the activity of the LDL receptors on proliferating blood lymphocytes was evaluated in vitro under conditions in which endogenous cholesterol biosynthesis was blocked by lovastatin to render cellular proliferation dependent on exogenous LDL-C.30 The results showed that for phytohemagglutinin-induced proliferation, lymphocytes from patients with the FH-Espoo mutation needed more LDL than lymphocyte.
cytes from healthy control subjects, but less than lymphocytes from patients with the FH-Helsinki mutation (Fig 2A). The approximate LDL concentrations that would have given proliferation rates of half the maximal rates were estimated from the proliferation curves. For patients with the FH-Espoo mutation this concentration was 0.71±0.06 (mean±SEM) μg/mL, an intermediate value between the values for control subjects (0.50±0.02 μg/mL) and for patients with the FH-Helsinki gene (0.88±0.05 μg/mL) (Fig 2B). The intermediate functional activity of the LDL receptors on lymphocytes carrying the FH-Espoo mutation was also reflected in the overlap of values between patients and control subjects, which was greater for the FH-Espoo mutation than for the FH-Helsinki mutation (Fig 2B).

**LDL Kinetics In Vivo**

Two adult FH-Espoo patients (sons of the proband and her sister) volunteered to take part in the kinetic study. Their fractional catabolic rates of LDL apoB were low compared with those of healthy control subjects, being in the range of the five FH-Helsinki patients studied (Table 1). The concentrations and the production rates of LDL apoB in the two FH-Espoo heterozygotes were relatively low compared with the corresponding values in the FH-Helsinki heterozygotes. These kinetic data showed that the in vivo catabolism of LDL is subnormal in FH-Espoo patients, but they did not demonstrate a significant difference in the LDL catabolism between patients with the FH-Espoo and FH-Helsinki varieties of the LDL receptor gene mutations.

### Clinical Expression of the FH-Espoo Gene

The presence of the FH-Espoo mutation in the volunteers of the kindred was determined by the Southern blot technique using the restriction enzyme BamHI to generate informative fragments. The proposita and her sister as well as four of their children and four of their grandchildren had the FH-Espoo mutation. The kindred was screened for other causes of hypercholesterolemia, and none were found.
TABLE 2. Characteristics of the FH-Espoo Patients Compared With Nonaffected Relatives

<table>
<thead>
<tr>
<th></th>
<th>FH-Espoo</th>
<th>Non-FH</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects (male/female)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults (≥18 y)</td>
<td>6 (3/3)</td>
<td>12 (6/6)</td>
<td></td>
</tr>
<tr>
<td>Children (&lt;18 y)</td>
<td>4 (3/1)</td>
<td>7 (5/2)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>47 ± 6</td>
<td>36 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>Children</td>
<td>11 ± 1</td>
<td>12 ± 1</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>27 ± 1</td>
<td>23 ± 1</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Children</td>
<td>17 ± 1</td>
<td>19 ± 1</td>
<td>NS</td>
</tr>
<tr>
<td>Serum cholesterol, mmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>8.8 ± 0.7</td>
<td>5.1 ± 0.4</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Children</td>
<td>5.0 ± 0.3</td>
<td>4.2 ± 0.2</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>6.9 ± 0.6</td>
<td>3.2 ± 0.3</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Children</td>
<td>3.4 ± 0.2</td>
<td>2.4 ± 0.2</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>1.23 ± 0.15</td>
<td>1.42 ± 0.12</td>
<td>NS</td>
</tr>
<tr>
<td>Children</td>
<td>1.23 ± 0.12</td>
<td>1.51 ± 0.05</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Serum triglycerides, mmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>1.58 ± 0.15</td>
<td>1.23 ± 0.17</td>
<td>NS</td>
</tr>
<tr>
<td>Children</td>
<td>0.81 ± 0.16</td>
<td>0.67 ± 0.10</td>
<td>NS</td>
</tr>
</tbody>
</table>

FH indicates familial hypercholesterolemia; NS, not significant (P > .05); LDL, low-density lipoprotein; and HDL, high-density lipoprotein. Values are mean ± SEM. Diagnosis of the carrier status for the FH-Espoo gene was based on DNA analysis.

Additional evidence suggesting that the FH-Espoo mutation is associated with a relatively mild form of FH came from clinical examination of the patients. The mean Achilles tendon thickness among the affected and nonaffected members of the FH-Espoo family was similar, but the Achilles tendons of the FH-Helsinki patients were significantly thicker than those of the FH-Espoo heterozygotes (Fig 4).

**Discussion**

This study demonstrated that the FH-Espoo mutation is an in-frame deletion of exon 15 of the LDL receptor gene, and it also showed that the hypercholesterolemia associated with this deletion is less severe than that caused by the FH-Helsinki allele, a mutation very common in Finland and associated with a typical clinical picture of heterozygous FH. Studies with mitogen-
TABLE 3. Comparison of Patients With Heterozygous ApoE allele frequencies

<table>
<thead>
<tr>
<th>Parameter</th>
<th>FH-Espoo</th>
<th>FH-Helsinki</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects (male/female)</td>
<td>10 (6/4)</td>
<td>23 (13/10)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>33±7</td>
<td>38±3</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23±2</td>
<td>26±1</td>
<td>NS</td>
</tr>
<tr>
<td>Serum cholesterol, mmol/L</td>
<td>7.3±0.8</td>
<td>9.7±0.5</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>5.5±0.7</td>
<td>8.0±0.4</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>ApoE allele frequencies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ε2</td>
<td>0.05</td>
<td>0.13</td>
<td>NS</td>
</tr>
<tr>
<td>ε3</td>
<td>0.70</td>
<td>0.52</td>
<td>NS</td>
</tr>
<tr>
<td>ε4</td>
<td>0.25</td>
<td>0.35</td>
<td>NS</td>
</tr>
<tr>
<td>ApoB allele frequencies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X1</td>
<td>0.65</td>
<td>0.83</td>
<td>NS</td>
</tr>
<tr>
<td>X2</td>
<td>0.35</td>
<td>0.17</td>
<td>NS</td>
</tr>
<tr>
<td>Xanthomas, n (%)</td>
<td>2 (33%)</td>
<td>14 (70%)</td>
<td>NS</td>
</tr>
<tr>
<td>CHD, n (%)</td>
<td>2 (33%)</td>
<td>7 (35%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

FH indicates familial hypercholesterolemia; LDL, low-density lipoprotein; NS, not significant (P>.05); apo, apolipoprotein; and CHD, coronary heart disease. Values are mean±SEM. For xanthomas and CHD, n indicates the number of adult patients affected.

Exon 15 comprises 171 nucleotides and encodes 57 amino acids, of which 18 are threonine or serine residues. Most of the O-linked carbohydrate side chains of the LDL receptor protein are attached on these serine and threonine residues. This domain is situated immediately extracellularly between the membrane-spanning and epidermal growth factor homology regions. A similar region is also conserved in the LDL receptors of other mammals. Davis et al evaluated the functional role of the domain with O-linked sugars by deleting 144 nucleotides encoding 48 amino acids (Thr700 through Ser745), including all serine and threonine residues of this domain, from the human LDL receptor gene. Transfected and expressed in hamster fibroblasts, this deleted cDNA construct encoded LDL receptors whose function was indistinguishable from that of the normal LDL receptor. In the FH-Espoo mutation the whole exon 15 is deleted, and accordingly the deletion is 27 nucleotides larger than the in vitro construct studied by Davis et al. Provided that the FH-Espoo gene is expressed as a mature protein, the distance from the membrane-spanning region to the last cysteine residue in the epidermal growth factor homology region will be shortened from 77 to only 20 amino acids (Fig 1). It is possible that a radical shortening of this distance may disturb the normal folding of the extracellular domains of the LDL receptor and thus its normal functioning.

The mildness of the clinical features of FH associated with the FH-Espoo gene compared with those of the FH-Helsinki carriers was reflected in the LDL-C concentrations and in the differences in Achilles tendon affection. The total cholesterol and LDL-C concentrations were significantly lower in the FH-Espoo than in the FH-Helsinki patients (Table 3 and Fig 4). This difference was most pronounced among children. In the FH-Espoo children the mean serum LDL-C concentrations remained below the age- and sex-specific 95th percentile in all cases. Compared with the FH-Helsinki children (LDL-C, 5.3 mmol/L) or the heterozygous FH children studied by Kwiterovich et al (LDL-C, 6.3 mmol/L), the mean serum LDL-C concentration in the FH-Espoo children (3.4 mmol/L) was strikingly low.

The measurement of the Achilles tendon thickness is a useful aid in the diagnosis of FH, and it probably reflects the lifelong mean of serum LDL-C concentrations for an individual. The Achilles tendons of the FH-Espoo patients were not, however, thicker than those of their nonaffected relatives, in contrast with the FH-Helsinki patients, most of whom had thickened xanthomatous Achilles tendons. The prevalence of CHD in the adult FH-Espoo patients was not different from that in the FH-Helsinki group (Table 3), but the numbers were small, and any conclusions on differences in the risk for CHD should await more detailed cardiological as well as follow-up studies in larger cohorts of patients. It should be emphasized that all the FH-Espoo patients were from a single kindred, whereas the FH-Helsinki patients originated from nine different families. We have not conducted comparative studies in our FH-Helsinki kindreds to find out whether any of them would turn out to be less severely affected.
Our clinical and biochemical data provided convincing evidence for the assumption that certain LDL receptor mutations, when present in a heterozygous state, may cause only a moderate elevation of serum LDL-C level, and that "mild" forms of FH exist. An idea got some support from earlier studies in homozygous FH patients in whom the residual function of the cellular LDL receptors was related to the clinical severity of the disease.11-22 Furthermore, Bilheimer et al13,14 reported on an FH family in which obligate heterozygotes had normal cholesterol levels and a family history of unusual longevity. This mutation (designated FH-Denver-2) was subsequently found to result from a substitution of adenine for guanine in exon 6 of the LDL receptor gene, causing an aspartic acid→asparagine change at codon 283.4

In conclusion, this study showed that elimination of the carbohydrate-containing portion of the LDL receptor molecule causes a partial deterioration of receptor functioning and a clinical picture of hypercholesterolemia intermediate between the normal condition and heterozygous FH. If additional reports on partial mutations of the LDL receptor gene appear, the diagnostic criteria of FH may have to be re-evaluated.

Acknowledgments

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