The spectrum of premature atherosclerosis: from single gene to complex genetic disorder
Trip, M.D.

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A frequent mutation in the lipoprotein lipase gene (D9N) exacerbates the biochemical and clinical phenotype of Familial Hypercholesterolemia.

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Abstract

The D9N substitution is a common mutation in the lipoprotein lipase (LPL) gene. This mutation has been associated with reduced levels of HDL cholesterol and elevated triglycerides (TG) in a wide variety of patients. We investigated the influence of this D9N mutation on lipid and lipoprotein levels and risk for cardiovascular disease (CVD) in patients with familial hypercholesterolemia (FH). A total of 2091 FH heterozygotes, all of Dutch extraction, were screened for the D9N mutation using standard polymerase chain reaction techniques, followed by specific enzyme digestion. A total of 94 FH subjects carried the D9N mutation at a carrier frequency of 4.5%. Carriers of other common LPL mutations, such as the N291S and the S447X were excluded. Clinical data on 80 FH individuals carrying the D9N were available and were compared with a FH control group matched for age, sex, and body mass index (n=203). Analysis revealed significantly higher TG (p=0.01) and lower HDL-cholesterol levels (p=0.002). Dyslipidaemia was more pronounced in D9N carriers with higher body mass index. Moreover, FH patients carrying the common LPL mutation were at higher risk for CVD, (odds ratio=2.8; 95% CI, 1.43 to 5.32; p=0.002). The common D9N LPL mutation leads to increased TG and decreased HDL plasma levels in patients with FH. These effects are most apparent in those FH heterozygotes with an increased body mass index. Furthermore, this mutation, present in 4.5% of Dutch FH heterozygotes, leads to increased risk for CVD.

Introduction

The association between elevated triglyceride levels (TG) and the incidence of coronary artery disease is well established. As triglycerides themselves do not accumulate in atherosclerotic lesions, their atherogenicity must be related to the associated adverse quantitative and qualitative changes in other circulating lipoproteins. In particular, decreased levels of high-density lipoprotein (HDL) cholesterol and increased levels of both small, dense, low-density lipoprotein (LDL) and remnant particles are thought to contribute towards this propensity for atherosclerotic vascular disease. TG-rich lipoproteins, both chylomicrons and VLDLs, are catabolized by the rate limiting enzyme in TG metabolism, lipoprotein lipase (LPL). LPL is a dimeric plasma enzyme that acts at the endothelial surface of extrahepatic capillaries,
providing parenchymal cells with fatty acids for direct energy use or storage. This lipolytic process is central to lipoprotein metabolism and to the removal of lipoproteins from the circulation.

LPL has also been proposed as a key protein in the retention of lipoproteins in the arterial wall by enabling their adherence to extracellular matrix. Moreover, local secretion of LPL by macrophages and its postulated function as a monocyte adhesion protein may favour foam cell formation, a key initial step in atherogenesis. Both homo- and heterozygous LPL deficiency have been demonstrated to predispose to premature CAD and increased progression of coronary atherosclerosis. In addition, low LPL activity has been associated with markers of decreased vascular compliance such as elevated systolic blood pressure, decreased nitric oxide production, and decreased forearm bloodflow.

One amino acid substitution in the LPL protein, D9N, underlies heterozygosity for LPL deficiency in approximately 2 to 5% of Caucasians and is therefore a very common variant in the general population. This D9N mutation leads to increased TG and decreased HDL cholesterol levels, and promotes the progression of angiographically assessed coronary atherosclerosis. A recent meta-analysis reported that this variant carried a summary odds ratio of 1.59, representing a 59% increase in CAD risk. A number of studies assessing the D9N mutation, however, have indicated that full expression of the associated atherogenic lipoprotein profile requires the presence of additional environmental or genetic factors.

Individuals with FH have a significantly increased predisposition to premature CVD, although there is generally unexplained variability with respect to biochemical and clinical phenotype. Recently we demonstrated that another common variant of the LPL gene, the N291S mutation, has a significant effect on cardiovascular risk in patients with FH and could explain part of the variation in clinical manifestations of CVD. Therefore, we wished to determine whether another frequent variant in the LPL gene, the D9N mutation, had a similar effect on lipid and lipoprotein levels and whether this mutated allele constituted an additional risk factor for CVD in patients heterozygous for FH. If this were the case, the combined frequency these 2 LPL mutations in the FH population could represent a significant cause of the variability in lipid phenotype and predisposition to CVD. Here we have assessed the consequences of heterozygosity for the D9N variant in a large cohort of patients with FH.
Materials and Methods

Study Population
A total of 2091 unrelated FH patients of Dutch white origin were included in the study. All subjects were ascertained at lipid clinics throughout the Netherlands and had a diagnosis of molecular or definite clinical FH. The diagnosis of FH was based on either the presence of a mutation in the LDL receptor gene or if the patient met the following clinical criteria: an LDL cholesterol level above the 95th percentile for age and sex, the presence of typical tendon xanthomas in the patient or in a first-degree relative, or in combination with a paediatric relative with an LDL cholesterol above the 95th percentile for age and sex. Secondary causes of hypercholesterolemia, including renal and hepatic disease, alcohol abuse, diabetes mellitus and hypothyroidism were excluded in all subjects. At baseline, when blood was collected for chemistry and lipid profile, none of the subjects was taking lipid-lowering medication for at least 8 weeks. Cases were FH patients who carried the D9N mutation, and in whom the common N291S and S447X LPL variants were excluded. Controls were FH patients selected from the remaining FH cohort, who did not carry any LPL mutation, including D9N, N291S and S447X amino acid substitutions. These individuals were randomly selected as nested controls, and were matched for age, sex and body mass index (BMI). Every control-subject with the same age ± 2 years, gender and BMI as each case-subject was included. Furthermore, control FH patients were selected in a blinded fashion for blood pressure, smoking, alcohol intake, the presence of CVD, or lipid and lipoprotein levels, and other biochemical values. The study was approved by the Institutional Review Board and informed consent was obtained from all participants.

DNA-Analysis
Genomic DNA was isolated from leucocytes as previously described. The D9N mutation was ascertained by amplifying LPL exon 2 by means of polymerase chain reaction methods, as described previously. After amplification, the polymerase chain reaction product was digested with TaqI, using a 40-nucleotide Guanine, Cytosine clamp (Eurogentec) in the forward primer. Subsequently, fragments were separated on a 4% agarose gel.

Biochemical Analysis
Total plasma cholesterol was determined by an enzymatic colometric procedure using cholesterase and cholesterol oxidase (CHOD-PAP, Boehringer Mannheim).
HDL cholesterol was determined after precipitation of chylomicrons, VLDL and LDL, using phosphotungstic acid and magnesium ions. LDL cholesterol was calculated by use of the Friedewald formula.

**Cardiovascular Disease**

To determine the significance of the D9N mutation for cardiovascular risk we calculated the number of patients with definite clinical manifestations of cardiovascular disease in the FH patients with and without the D9N mutation. Patients were classified as having clinically manifest cardiovascular disease if their history revealed one or more of the following: a myocardial infarction documented by electrocardiogram abnormalities and enzyme changes; an ischemic stroke proven by CT-scan; stable angina pectoris assessed by the ROSE questionnaire and requiring anti-anginal medication; intermittent claudication, or an intervention when either peripheral or coronary balloon angioplasty or bypass surgery had been performed. FH patients were classified as free of cardiovascular disease, when they did not meet any of the above mentioned criteria.

**Statistical Analysis**

FH patients with the D9N mutation were compared with FH patients without this mutation with respect to baseline characteristics, lipids and lipoproteins. Mean values of the various parameters of both FH cohorts were compared using Student's t-tests. Triglyceride data were log transformed before statistical tests, but untransformed levels are reported in the tables. Chi-square analysis was used to compare the frequency of FH heterozygotes with and without the D9N mutation in TG, HDL and BMI tertiles. The odds ratio for cardiovascular disease was calculated using Fisher's exact test. To assess the impact of this mutation on lipid abnormalities, environmental factors and cardiovascular risk, we used the logistic regression model. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS 7.5 Benelux B.V.). A probability of <0.05 was used to indicate statistical significance.

**Results**

**Frequency of the D9N mutation**

In our cohort of 2091 unrelated FH patients, 94 D9N carriers were identified, yielding a carrier frequency of 4.5%. Subsequently, fourteen patients were excluded...
from further analyses, since they also carried the N291S mutation (n=7), the S447X mutation (n=6) or were homozygous for the D9N mutation (n=1). The remaining FH patients with the D9N mutation were matched in a case-control manner with regard to age, gender and BMI, with 203 FH control subjects, not carrying any of the common LPL variants.

Baseline Characteristics
Consequently, a total of 80 FH heterozygotes (36 male and 44 females) with the D9N mutation (cases) and 203 FH heterozygotes (87 males and 116 females) without the D9N mutation (controls) were studied in greater detail. The baseline characteristics of both cohorts are shown in Table 1. Both groups were appropriately matched for age, gender and BMI. In addition, both groups were comparable with respect to blood pressure, smoking habits, alcohol intake and plasma glucose levels.

Table 1. Baseline Characteristics of FH patients carrying the LPL D9N mutation and matched FH control subjects

<table>
<thead>
<tr>
<th></th>
<th>FH with D9N n=80</th>
<th>FH without D9N n=203</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>39±19 (5-78)</td>
<td>41±16 (6-67)</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>24±4 (14-34)</td>
<td>24±4 (14-32)</td>
</tr>
<tr>
<td>M/F</td>
<td>36/44</td>
<td>87/116</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>130±18</td>
<td>130±17</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>81±10</td>
<td>81±12</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>62%</td>
<td>64%</td>
</tr>
<tr>
<td>Current</td>
<td>38%</td>
<td>36%</td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>31%</td>
<td>27%</td>
</tr>
<tr>
<td>&lt;3 u/day</td>
<td>59%</td>
<td>64%</td>
</tr>
<tr>
<td>≥3 u/day</td>
<td>10%</td>
<td>9%</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>4.9±0.8</td>
<td>4.9±0.6</td>
</tr>
</tbody>
</table>

M/F denotes male/female ratio; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure. Values are given as means ± standard deviation, with ranges in parentheses for age and BMI. All baseline characteristics did not statistically.
Table 2. Lipid, lipoprotein, and apolipoprotein levels in FH patients carrying the D9N mutation and in matched FH control patients

<table>
<thead>
<tr>
<th></th>
<th>FH with D9N n=80</th>
<th>FH without D9N n=203</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>8.6±2.1 (4-16)</td>
<td>8.6±1.6 (5-14)</td>
<td>ns</td>
</tr>
<tr>
<td>LDL-C</td>
<td>6.6±2.0 (2-13)</td>
<td>6.6±1.7 (3-12)</td>
<td>ns</td>
</tr>
<tr>
<td>HDL-C</td>
<td>1.17±0.37 (0.73-2.8)</td>
<td>1.32±0.37 (0.65-2.77)</td>
<td>0.002</td>
</tr>
<tr>
<td>TG</td>
<td>1.83±1.39 (0.56-8.72)</td>
<td>1.43±0.65 (0.29-3.75)</td>
<td>0.01</td>
</tr>
<tr>
<td>ApoA1</td>
<td>1.37±0.27* (0.83-2.10)</td>
<td>1.53±0.32‡ (0.84-2.48)</td>
<td>0.0001</td>
</tr>
<tr>
<td>ApoB100</td>
<td>2.04±0.54* (0.70-3.02)</td>
<td>2.15±0.60‡ (1.04-4.04)</td>
<td>ns</td>
</tr>
<tr>
<td>TC/HDL</td>
<td>8.04±3.16 (2.86-18.91)</td>
<td>7.01±2.51 (3.25-16.84)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

TC indicates total cholesterol; TG, triglyceride level (values in mmol/l); and ApoA1 and ApoB100, indicated apolipoprotein-A1 and B100 (values in g/l); P values were calculated using the student’s t test. All values are given as mean levels ± standard deviation, with ranges in parentheses. *D9N carriers: ApoA1 and B100, n= 61. ‡Non-D9N carriers: ApoA1 and B100, n=172.

Lipids and Lipoproteins

Mean lipid and lipoprotein levels are given in Table 2. No significant differences were found for total cholesterol or LDL-cholesterol levels. However, FH patients carrying the D9N variant exhibited significantly higher TG (1.83 ± 1.39 vs 1.43 ± 0.65 mmol/l, p=0.01) and lower HDL cholesterol; (1.17 ± 0.37 vs 1.32 ± 0.37 mmol/l, p =0.002) and apo A1 levels (1.37 ± 0.27 vs 1.53 ± 0.32 g/l, p=0.0001). Conversely, TC/HDL ratio’s (8.04 ± 3.16 vs 7.01 ± 2.51, p =0.01) were significantly higher in FH heterozygotes carrying the D9N mutation. When all subjects with an age < 18 years old were excluded, the observed differences with respect to TG and TC/HDL ratio became more prominent, as was the case for TG levels (2.12 ± 1.46 vs 1.49 ± 0.64, p =0.001) and the TC/HDL ratio (8.76 ± 3.16 vs 7.12 ± 2.52, p =0.0001) (Table 3).

Table 3. Association between the D9N mutation and the low HDL/High TG phenotype

<table>
<thead>
<tr>
<th></th>
<th>Prevalence (%)</th>
<th>D9N</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With D9N</td>
<td>Without D9N</td>
</tr>
<tr>
<td>HDL&lt;0.91</td>
<td>21 (26)</td>
<td>25 (12)</td>
</tr>
<tr>
<td>TG&gt;2.8</td>
<td>12 (15)</td>
<td>10 (15)</td>
</tr>
<tr>
<td>HDL&lt;0.91 and TG&gt;2.8</td>
<td>6 (8)</td>
<td>3 (1)</td>
</tr>
</tbody>
</table>

Values of TG and HDL are in mmol/l. OR and CI indicate odds ratio and confidence intervall, respectively.
Frequency of D9N mutation by TG and HDL tertile

Both FH cohorts were further analysed by HDL and TG tertiles. Fifty percent (40/80) of the subjects carrying the D9N mutation were found in the lowest HDL tertile versus 26% of FH patients not carrying this mutation (53/203) (p=0.0002). In addition, there were significantly more non-D9N mutation carriers in the upper HDL tertile when compared to those carrying the D9N mutation (39% vs 21%, p=0.005). In addition, a significant enrichment of FH patients carrying the D9N mutation became evident in the upper tertile for triglyceride levels (FH with D9N; 35/80 (44%) vs FH without D9N; 60/203,(30%), p=0.03).

The association between the D9N mutation and the high TG/low HDL phenotype is illustrated in Table 3. The odds for having this trait when carrying the D9N mutation is 5.4 (p=0.02). As expected, an increased likelihood became apparent for the presence of either low HDL (odds ratio (OR)=2.53; 95% CI, 1.32 to 4.86; p=0.007) or high TG (OR=3.41; 95% CI, 1.41 to 8.24, p=0.01) for carriers of this mutation.

Figure 1. Triglyceride levels in FH patients with and without the D9N mutation by BMI tertile

Number of patients +D9N/-D9N; tertile 1: n=27/66, tertile 2: n=23/72, tertile 3: n=30/65.
Influence of BMI
Subsequently, the FH cohort (n=283) was divided into tertiles for BMI. The first tertile contained all subjects with a BMI of < 22.6 kg/m². This tertile contained 27 D9N carriers (34%) and 66 noncarriers (33%). In the second tertile contained all subjects with a BMI > 22.6 but < 25 kg/m². This tertile contained 23 D9N (29%) carriers and 72 noncarriers (35%) were present. The third tertile contained all subjects with a BMI over 25 kg/m². In this tertile, 30 D9N (38%) carriers and 65 noncarriers (32%) were found. Within each tertile, TG (Figure 1) and HDL cholesterol levels were then calculated. In all three BMI tertiles mean HDL levels were lower in D9N carriers, whereas TG levels were higher. However, the largest differences in HDL and TG levels between carriers and noncarriers became evident in the upper tertile. The FH heterozygotes carrying the D9N had significantly higher TG levels; (2.19 ± 1.18 vs 1.61 ± 0.70, p=0.02), and a trend towards lower HDL levels (1.19 ± 0.46 vs 1.38 ± 0.36, p=0.06).

In the lowest BMI tertile, mean TG levels were similar between the 2 FH groups, whereas the HDL concentration was lower, but not significantly, in FH heterozygotes with the D9N mutation, (1.18 ± 0.28 vs 1.32 ± 0.32, p=0.06).

D9N and Cardiovascular Disease
For this analysis, only adults (age > 18) were included. In the FH cohort carrying the D9N mutation (n=62), 21 patients had definite clinical manifestations of CVD (33.9%) whereas in the FH cohort not carrying the mutation (n=185), 29 cases of CVD were present (15.7%). This difference resulted in an OR for CVD in D9N carriers of 2.8 (Table 4). There was no difference between the age of onset of CVD between the FH heterozygotes with the D9N mutation (48.8 ± 12.5 vs 46.7 ± 8.8, p=0.6) and

<table>
<thead>
<tr>
<th>Table 4. Frequency of and odds ratio for CVD in FH patients carrying the LPL D9N mutation and matched FH control patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency (%)</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>FH with D9N</td>
</tr>
<tr>
<td>FH without D9N</td>
</tr>
</tbody>
</table>

CVD denotes cardiovascular disease, defined as myocardial infarction, definite angina pectoris, documented stroke, and surgery for peripheral arterial disease. FH indicates familial hypercholesterolemia.

*p=0.002 (Fisher exact test)
those not carrying the D9N mutation. When further analyzing the type of CVD, no differences could be observed. In both groups more than half of the FH heterozygotes had clinical manifestations of cardiac disease. In addition, the prevalence of combined vascular disease was similar in both groups (data not shown).

**Logistic Regression Analysis**

Logistic regression analysis revealed a significant influence of the D9N mutation on the likelihood of developing CVD in the FH cohort. In this model, in which we included age, BMI, blood pressure, alcohol intake, HDL and TG, the effect of the D9N mutation for developing CVD remained significant. Age was the most significant predictor (OR=1.3, CI, 1.0-1.1, p<0.0001), followed by BMI (OR=1.3; 95% CI, 1.0-1.3, p=0.02) and the presence of the D9N mutation (OR=2.2, 95% CI, 1.0-4.8, p=0.04) (Table 5).

**Discussion**

We have investigated the influence of the D9N mutation in the LPL gene on lipid and lipoprotein levels and the impact of this mutation on cardiovascular risk in a large cohort of FH patients. We show that patients who carry a mutation both in the LPL and the LDL receptor gene exhibit significantly lower HDL and apoAl levels, higher TG levels and a higher TC/HDL ratio. This was particularly apparent when FH patients were divided into tertiles and a significant enrichment of D9N carriers in the lowest HDL tertile and the upper TG tertile was apparent. In addition, we show that heterozygosity for the D9N mutation is strongly associated with the high TG/low HDL trait. Several studies in other patient groups than FH have shown

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>OR</th>
<th>CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>2.2</td>
<td>1.0-4.8</td>
<td>0.04</td>
</tr>
<tr>
<td>Age</td>
<td>1.3</td>
<td>1.0-1.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI</td>
<td>1.3</td>
<td>1.0-1.3</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* additional factors included the model where, alcohol, blood pressure, and TG and HDL cholesterol.

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previously that the D9N mutation in the LPL gene is associated with a decreased LPL activity and with both higher fasting TG and VLDL levels and lower HDL levels.\textsuperscript{12,25,26} In addition, it has been postulated that heterozygosity for this mutation may promote the progression of atherosclerosis. However, because not all D9N mutation carriers have elevated TG levels and/or decreased HDL levels, environmental as well as other genetic factors most likely contribute to the expression of the clinical phenotype in subjects carrying this LPL variant. Possibly the most significant environmental factor that can enhance the expression of the D9N mutation is increased body mass. This gene/environment interaction in subjects carrying the D9N mutation has previously been described.\textsuperscript{12,26} In line with these observations we demonstrate here that the effects of the D9N mutation are most apparent in subjects with increased body mass. We reported similar results for FH heterozygotes carrying another common variant in the LPL gene, the N291S mutation.\textsuperscript{19} This may have a particular clinical relevance in terms of patient management. FH patients with LPL variants should clearly be encouraged to attain normal body mass and to participate in weight-reduction programs. The mechanism of this interaction is not entirely clear. In a previous study on chylomicronemia in pregnancy, it was postulated that carriers of either the D9N or the N291S mutation are able to maintain low TG levels in the fasting state, but when body mass increases, augmented VLDL secretion from the liver overcomes the capacity of the lipolytic cascade and hypertriglyceridemia ensues.\textsuperscript{27} In another study, it was hypothesized that the D9N mutation could cause a delay in the secretion of the LPL protein in the postprandial state.\textsuperscript{13}

With respect to apoB/apoAl ratio, as well as apoB levels of carriers and noncarriers, no differences could be detected. Higher levels of apoB would be expected in the D9N carriers reflecting the more atherogenic "small dense LDL" phenotype, commonly associated with elevated levels of TGs; we have no explanation for our findings in this respect.

We also report here that in addition to the detrimental lipid profile, FH heterozygotes carrying the D9N variant have an odds ratio of 2.8 for CVD. The overall incidence of CVD in our study population was 17.6%, which is in line with the reported CVD incidence for FH heterozygotes of this age.\textsuperscript{15} The increased incidence of CVD in FH patients carrying the D9N mutation can in part be explained by their lipid and lipoprotein abnormalities, such as impaired hydrolysis of TG-rich lipoproteins, low HDL cholesterol, increased levels of both remnant particles and small dense LDL particles, all favouring the progression of atherosclerosis.

However, in our logistic regression model we demonstrate that the D9N is also
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independently associated with CVD risk. This finding, also reported for the N291S variant, may be related to altered proteoglycan binding or lipid particle uptake at the level of the vessel wall or to the associated endothelial dysfunction or other proatherogenic changes in these cells.

In conclusion, the common D9N LPL mutation leads to increased TG levels and decreased HDL levels in patients with FH. This effect is exponentially increased when increased body mass is present.\textsuperscript{1,2,26,28} Frequent variants of the LPL gene, such as the D9N and the N291S mutations, are apparently present in 10% of FH heterozygotes and are a major additional risk factor for the development of premature coronary disease in these subjects, who are already exposed to a very high a priori risk of CVD.

References


