Lipoprotein(a) levels in patients with homozygous familial hypercholesterolaemia*

Familial hypercholesterolaemia (FH) is a clinical syndrome that results from mutations in the low-density lipoprotein receptor (LDLR) gene. The worldwide prevalence of homozygosity is about 1/1 000 000. Patients with homozygous FH have markedly elevated low-density lipoprotein (LDL) cholesterol levels that are refractory to commonly used hypolipidemic drugs [1].

It has been previously suggested that mutations in the LDLR gene affect lipoprotein(a) (Lp(a)) plasma level [2]. Interestingly, Krafí et al. have recently stated that FH heterozygotes have significantly higher Lp(a) levels than non FH individuals from the same population, while FH homozygotes have about two-fold higher Lp(a) than FH heterozygotes (median value 36.6 vs 14.4 mg/dl) and this increase could not be explained by differences in apo(a) allele frequencies [3]. The underlying mechanisms are not clear enough but may be related to a delayed Lp(a) catabolism through the LDLR but also to other poorly understood metabolic changes in FH, which may include the metabolism of fatty acids which is known to affect lipoprotein synthesis or to direct synthesis of LDL (and Lp(a)) [1,4,5]. However, the increase in Lp(a) levels observed in patients with homozygous FH may be related to the underlying genetic defect.

There are no data concerning Lp(a) levels in homozygous patients sharing a class V mutation of the LDLR. In class V mutations the LDLR retains the ability to bind and internalise its ligand but fails to release it in the endosome and thus the receptor does not recycle to the cell surface. Patients with this class of mutations tend to have relatively low-plasma cholesterol levels and less severe clinical features compared to patients carrying other classes of mutations [6]. Taking these data into account, we evaluated the serum lipid profile in unrelated patients with homozygous (n = 7) and heterozygous (n = 22) FH sharing a class V mutation of the LDLR (the 1775G > A mutation), and in 42 unrelated normolipidemic individuals from the same population (control group). Lp(a) levels of the homozygous patients were higher than those found in heterozygotes sharing the same mutation (median value 16.15 mg/dl, range 10.7–70 mg/dl vs median value 10.9 mg/dl, range 1.7–30.7 mg/dl, respectively, \( P < 0.01 \) by Mann–Whitney U-test), whereas normal controls had significantly lower Lp(a) levels compared to heterozygous patients (median value 6 mg/dl, range 0.8–24 mg/dl, \( P < 0.05 \) by Mann–Whitney U-test). As shown in Table 1, Lp(a) levels in our homozygous FH patients were substantially lower compared to those previously mentioned [3,7]. However, none of the patients in the previous studies were homozygous for a class V mutation, probably accounting for the higher Lp(a) levels. In the first report [3], most of the homozygotes shared at least one class II mutation (FH Afrikaner-1, FH Gujerat). In class II mutations the LDLR is not transferred to the cell membrane and patients tend to have higher plasma cholesterol levels than patients carrying class V mutation [6]. Guo et al. also reported higher plasma Lp(a) levels in homozygous FH patients (Table 1), but the responsible mutations were not mentioned. Instead, most of their patients were essentially devoid of cellular LDLR activity in fibroblast assays, a fact that strongly excluded the possibility of a class V mutation [7]. Our data suggest that the underlying genetic defect may affect not only the classic lipid profile of patients with homozygous FH but also Lp(a) levels.

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Table 1

Lp(a) and total cholesterol (T CHOL) levels (mg/dl) in homozygous FH

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<tr>
<td>Patients with a Class V mutation (1775G &gt; A)</td>
<td>36.6 (not shown)</td>
<td>39.0 (21–116)</td>
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<tr>
<td>Lp(a) median (range)</td>
<td>16.15 (10.7–70)</td>
<td>799 ± 205</td>
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<td>T CHOL (mean ± SD)</td>
<td>440 ± 80</td>
<td>Not shown</td>
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References


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