Lack of association between HFE gene mutations and hepatocellular carcinoma in patients with cirrhosis

V Boige, L Castéra, N de Roux, N Ganne-Carrié, B Ducot, G Pelletier, M Beauagrand, C Buffet

Background: Liver cirrhosis may lead to hepatocellular carcinoma (HCC), regardless of its cause. Genetic and/or environmental factors may modulate the risk of HCC. Mutations in the HFE gene are responsible for genetic haemochromatosis, a condition known to be associated with liver cirrhosis, HCC, or both. It has recently been suggested that the C282Y HFE gene mutation may be more frequent in patients with HCC that have developed in the non-cirrhotic liver than in the general population. Whether or not HFE gene mutations are associated with an increased risk of HCC in patients with cirrhosis is unknown.

Aim: To assess the prevalence of HFE gene mutations in cirrhotic patients with and without HCC.

Patients and methods: A total of 133 consecutive cirrhotic patients with HCC were prospectively studied for the presence of C282Y and H63D mutations. The control group consisted of 100 cirrhotic patients without HCC. We used restriction enzyme digestion of polymerase chain reaction amplified genomic DNA for determination of HFE genotypes. Iron loading was assessed on non-tumoral liver biopsy samples from 89 patients with HCC and 73 patients without HCC.

Results: The prevalence of C282Y heterozygotes was similar in patients with and without HCC (5% vs 4%, respectively; p=0.65) and did not differ from that expected in the general population. None of the HCC patients was found to be homozygous for C282Y or H63D, nor compound heterozygous. The prevalence of H63D heterozygotes was similar in patients with and without HCC (31% vs 38%, respectively; p=0.25). No relation was detected between HFE genotypes and hepatic iron loading in patients with or without HCC.

Conclusion: C282Y and H63D mutations do not appear to be associated with an increased risk of HCC in patients with cirrhosis.
Liver iron loading was assessed in a semiquantitative fashion using Perl's Prussian blue staining on 162 available non-tumoral liver biopsy samples (89 with and 73 without HCC) as follows: 0, no staining; 1, minimal to moderate iron overload (<50% stained hepatocytes); and 2, massive iron overload (>50% stained hepatocytes).

**Statistics**

The two groups of patients (with or without HCC) were compared for sex, aetiology of cirrhosis, liver iron loading, and HFE genotype distribution in 133 cirrhotic patients with HCC and 100 cirrhotic patients without HCC (table 1). Except for age and sex, the two groups were comparable, particularly for aetiology of cirrhosis.

**RESULTS**

Patient characteristics and the distribution of HFE genotypes, according to the presence or the absence of HCC, are given in table 1. Except for age and sex, the two groups were comparable, particularly for aetiology of cirrhosis.

In all, the C282Y mutation was present on 2.6% of chromosomes in patients with HCC compared with 3.0% of chromosomes expected in the normal French population (3.6%). The frequency of the H63D mutation was 15.4% of chromosomes from patients with HCC compared with 20.5% in those without (p=0.12). The prevalence of H63D heterozygotes was similar in patients with and without HCC (31% v 38%, respectively; p=0.25) and slightly higher than that of 23.7% expected in the normal French population. None of the HCC patients was found to be a C282Y homozygote, H63D homozygote, or compound heterozygote.

Overall, no significant difference for the prevalence of C282Y and H63D mutations was observed between the two groups, even after adjustment for age and sex. When patients were studied according to aetiology of cirrhosis, no significant difference for the prevalence of the C282Y and H63D mutations was observed between the two groups of patients (table 2). Similarly, when considering patients with and without HCC together, the distribution of HFE genotypes did not differ according to the aetiology of cirrhosis.

Patients with available non-tumoral liver tissue samples did not differ from those without for most characteristics (age, sex, aetiology of cirrhosis, HFE genotypes). Hepatic iron loading did not differ between patients with and without HCC (p=0.8). Finally, no significant correlation between HFE genotype and hepatic iron loading was observed in patients with or without HCC (table 3).

**DISCUSSION**

The main result of this large prospective multicentre study was that the prevalence of C282Y and H63D HFE gene mutations did not differ between cirrhotic patients with and without HCC.

Several studies have previously suggested that the prevalence of HFE gene mutations was higher in cirrhotic patients without HCC (5% v 4%, respectively; p=0.65) and did not differ from that expected in the normal French population (3.6%).

Liver iron loading was similar in patients with and without HCC (5% v 4%, respectively; p=0.65) and did not differ from that expected in the normal French population (3.6%).

<table>
<thead>
<tr>
<th>Age (y) (mean (SD))</th>
<th>64 (10)</th>
<th>58 (13)</th>
<th>0.0003</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>113/20</td>
<td>45/55</td>
<td>0.0001</td>
</tr>
<tr>
<td>Aetiology of cirrhosis (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>76 (57)</td>
<td>57 (57)</td>
<td>NS</td>
</tr>
<tr>
<td>HCV</td>
<td>30 (22)</td>
<td>26 (26)</td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td>19 (7)</td>
<td>4 (4)</td>
<td></td>
</tr>
<tr>
<td>Mixed*</td>
<td>17 (13)</td>
<td>9 (9)</td>
<td></td>
</tr>
<tr>
<td>Other†</td>
<td>1(1)</td>
<td>4 (4)</td>
<td></td>
</tr>
<tr>
<td>HFE genotype (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C282Y/C282Y</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>NS</td>
</tr>
<tr>
<td>C282Y/H63D</td>
<td>0 (0)</td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td>H63D/H63D</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>C282Y/WT†</td>
<td>7 (5)</td>
<td>4 (4)</td>
<td></td>
</tr>
<tr>
<td>H63D/WT†</td>
<td>41 (31)</td>
<td>38 (38)</td>
<td></td>
</tr>
<tr>
<td>WT/WT †</td>
<td>85 (64)</td>
<td>54 (54)</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Clinical characteristics and HFE genotype distribution in 133 cirrhotic patients with HCC and 100 cirrhotic patients without HCC.

<table>
<thead>
<tr>
<th>HCC+ (n=133)</th>
<th>No HCC (n=100)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>37</td>
<td>64</td>
</tr>
<tr>
<td>Grade 1</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Grade 2</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>p Value</td>
<td>0.13</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C282Y and/or H63D*</th>
<th>No mutation†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>37</td>
</tr>
<tr>
<td>Grade 1</td>
<td>18</td>
</tr>
<tr>
<td>Grade 2</td>
<td>14</td>
</tr>
<tr>
<td>p Value</td>
<td>0.13</td>
</tr>
</tbody>
</table>

* C282Y heterozygotes, H63D heterozygotes, and compound heterozygotes were considered together.
† No mutation=wild-type/wild-type.

Table 3: Liver iron loading in 162 cirrhotic patients with and without HFE gene mutations.

| HCC−, without hepatocellular carcinoma; HCC+, with hepatocellular carcinoma. 
| WT, wild type. 
| The p value was obtained by comparing the distribution of HCC genotype according to either the presence or absence of HCC in alcoholic, viral, and mixed/other cirrhosis.
with HCC compared with those without HCC.\textsuperscript{14,15} Willis and colleagues\textsuperscript{26} reported a 7% prevalence of the C282Y homozygous mutation in patients with HCC, significantly higher than that of 0.7% expected in the normal population. It must be stressed however that this study was performed retrospectively on a limited number of patients (n=28) by extracting DNA from archived tissue samples from a population of 181 patients with alcoholic cirrhosis. Lauret and colleagues\textsuperscript{27} found that the prevalence of the C282Y heterozygous mutation was significantly higher in 43 patients with HCC than in 136 without HCC (20.9% and 4.4%, respectively; p=0.002). This result was not observed in another group of 98 patients with viral cirrhosis of whom 34 had HCC. In the present study, the prevalence of the C282Y heterozygous mutation in patients with HCC was lower (5%) and did not differ between patients with alcoholic and viral cirrhosis (6.6% and 2.6%, respectively). Aldersley and colleagues\textsuperscript{28} found a 6.3% prevalence of the C282Y homozygous mutation in 32 patients with HCC compared with 0% in a group of 82 chronic cholestatic liver disease controls, and a 25% prevalence of the C282Y heterozygotes. This prevalence was considered to be higher than that expected in the normal population.\textsuperscript{29} However, liver iron loading did not differ between cirrhotic patients with and without HCC in the present study, a finding in keeping with our previous work where we did not find a significant relationship between hepatic iron content and the occurrence of HCC in patients with alcoholic or hepatitis C virus related cirrhosis.\textsuperscript{30} Thus the role of liver iron overload in the development in cirrhotic patients without GH remains to be elucidated.

In conclusion, the similar prevalence of C282Y and H63D mutations in cirrhotic patients with or without HCC suggests a lack of association between HFE gene mutations and HCC in patients with cirrhosis. These mutations do not appear to be associated with an increased risk of HCC in patients with cirrhosis without iron overload.

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