Association between Genes of the Major Histocompatibility Complex Class II and the Outcome of Hepatitis C Virus Infection

To the Editor—We would like to thank E. J. Minton and colleagues [1] for their recent paper confirming that DRB1*11 and DQB1*0301 alleles were associated with clearance of circulating hepatitis C virus (HCV) [1]. They confirmed the results of a study that we published 1 year ago [2]. We showed that the frequency of DQB1*0301 and DRB1*1101 alleles was higher among a group of French patients with transient infection than in those with persistent infection (84% vs. 30.8%, 40% vs. 9.8%, respectively); these findings are remarkably similar to those of Minton et al. among British patients [1].

In our study, the association between HCV clearance and major histocompatibility complex (MHC) class II alleles was stronger with DQB1*0301 than with DRB1*1101. It was the opposite in the study by Minton et al. Our results argued in favor of a stronger association of HCV clearance with DQB1*0301 than with DRB1*11, because the P value was lower for DQB1*0301 than for DRB1*1101. On the other hand, a linkage disequilibrium between DQB1*0301 and DRB1*1101 or DRB1*04 is well known. In our healthy control population consisting of 800 healthy unrelated subjects, DQB1*0301 was closely linked with DRB1*1101 (>90%) and in a lesser way with DRB1*04 (~60%). In accordance with this linkage disequilibrium in our controls, there was a significant increase of DRB1*1101 frequency in subjects with transient HCV infection compared with patients with persistent infection (40% vs. 9.8%, respectively), whereas no statistical difference was observed for DRB1*04 (32% vs. 15.7%, respectively).

In the study by Minton et al. [1], the absence of data concerning the reference population, especially on DRB1*04 haplotypes, does not allow the authors to conclude in favor of DRB1*11 rather than DQB1*0301 susceptibility. On the other hand, the possibility that the DQB1*0301 and DRB1*11 alleles described in both studies could be markers for tightly linked genes involved in HCV protection cannot be ruled out. New data from various populations with different haplotypic DRB1* and DQB1* combinations would be of great interest.

In the study by Minton et al. [1], only host response through HLA genotyping was studied, without taking into account virologic parameters, such as viral genotype. Because, as reported by the authors, virologic factors could influence virus clearance, it is crucial to make sure that there is no difference in virus genotype between subjects with transient or persistent infection. By definition, serum HCV RNA cannot be detected in subjects with transient infection; therefore, virus serotyping must be used [3]. In our study, virus serotypes could be determined in 68% of patients with transient infection. In this group, 32% of the serologic assay was unreactive, because the level of antibodies against HCV was probably low, as reported by Lechmann et al [4]. For the serotyped subjects, no differences were observed in the distribution of HCV serotypes between subjects with transient infection and those with persistent HCV infection. These data suggest that host- rather than virus-related factors are probably involved in the spontaneous clearance of HCV. To test this hypothesis, it would be interesting to perform virus serotyping in the population studied by Minton et al. [1].

Many other studies have reported that MHC class II alleles could play a role in the natural history of HCV infection [5–9]. In all these works, the involvement of MHC class II genes in the outcome of HCV infection could be related to the ability of HLA molecules to modulate the activation of T lymphocytes [10]. Differences in binding affinities of antigenic peptides to HLA molecules might modify the degree of T cell activation. Taking into account the remarkable similarities between our studies among French patients and those of Minton et al. among British patients, further studies in different populations are required to determine whether DQB1*0301 and DRB1*11 alleles modulate immune response, leading to spontaneous clearance of HCV.

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References
Reply

To the Editor—We thank Alric et al. [1] for their comments concerning our study of major histocompatibility complex class II polymorphisms and association with outcome in hepatitis C virus (HCV) infection [2]. We were also reassured to see essentially similar conclusions reached by British (our) and French (their) groups, although the frequency of DRB1*11 in the local population is much higher in Toulouse, France (25.2%), than in Trent, United Kingdom (14.1%); linkage with DQB1*0301 is similar in both local populations (>90% and 98%, respectively). We find that the frequency with which DQB1*0301 is normally associated with DRB1*04 is comparable in the British (57%) and French (60%) populations. In our population, logistic regression analysis suggests that DRB1*11 is more strongly associated with transient HCV infection than is DQB1*0301.

Alric et al. [1] discuss the frequency of these polymorphisms in HCV patients compared with the frequency in the healthy local population. We found that the frequencies of DRB1*11 were similar in patients with persistent infection and in a control population of bone marrow panel volunteers (table 1). However, the frequency of DQB1*0301 in the normal population was closer to that in patients with transient infection than with persistent infection. DRB1*04 was more common in the normal population than in either group of HCV patients.

We have since analyzed the frequencies of DRB1*11 subtypes in relation to outcome in HCV infection in a larger group of patients. There was no significant difference in DRB1*11 subtype frequencies between groups of patients determined to be HCV positive or negative by use of polymerase chain reaction.

These authors comment on the importance of virus strain on outcome in hepatitis C virus infection. We fully agree with this and are in the process of serotyping patients as part of a larger study of immune resistance polymorphisms. Unfortunately, as Alric et al. mention [1], up to one-third of serum samples may be impossible to type, so the data are limited.

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References

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Table 1. Frequency (%) of major histocompatibility class II alleles in healthy controls in region of Trent, United Kingdom, and in patients with hepatitis C virus (HCV).

<table>
<thead>
<tr>
<th>Allele</th>
<th>Local controls (n = 547)</th>
<th>Transient HCV (n = 35)</th>
<th>Persistent HCV (n = 135)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRB1*11</td>
<td>14.1</td>
<td>31.4</td>
<td>8.2</td>
</tr>
<tr>
<td>DRB1*04</td>
<td>38.9</td>
<td>22.9</td>
<td>28.9</td>
</tr>
<tr>
<td>DQB1*0301</td>
<td>44.6</td>
<td>51.4</td>
<td>24.4</td>
</tr>
</tbody>
</table>

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CCR5 Genotype and Human Immunodeficiency Virus (HIV)–Specific Mucosal Antibody in Seronegative Women at High Risk for HIV Infection

To the Editor—In a recent report, Wilkinson et al. [1] concluded that homozygosity for the 32-bp deleted form of the CCR5 chemokine receptor (CCR5-D32) conferred resistance against human immunodeficiency virus type 1 (HIV-1) infection in parenterally exposed individuals. The prevalence of CCR5-D32 homozygosity was 9% in exposed hemophiliacs and 11% in exposed transfusion recipients. In addition, Hoffman et al. [2] recently examined potentially protective effects of CCR5-D32 heterozygosity in HIV-1-discordant couples. To contribute to these findings, we report results of CCR5 genotype testing and HIV-specific mucosal antibody titers in persistently seronegative women with a self-reported history of parenteral or sexual exposure to HIV.

A subset of 31 subjects enrolled in a longitudinal study of HIV-1 infection in women (the HIV Epidemiology Research Study) were identified as persistently seronegative despite (1) self-reported vaginal or anal sex with an HIV-positive man without use of a condom or (2) use of a needle after use by an HIV-positive person and without first using bleach to disinfect the needle. Of the 31 high-risk women identified, 68% had ex-