Association of Symptomatic Acute Human Parvovirus B19 Infection with Human Leukocyte Antigen Class I and II Alleles

Jonathan R. Kerr,1 Derek. L. Mattey,2 Wendy Thomson,3 Kay V. Poulton,4 and William E. R. Ollier4

To determine the effect of the major histocompatibility complex on the development of symptoms during acute human parvovirus B19 infection, we compared human leukocyte antigen (HLA) class I and II alleles in 36 patients with symptomatic acute B19 infection with those in >900 control subjects from northwestern England. The frequency of each of HLA-DRB1*01 (P = .016), DRB1*04 (P = .007), and DRB1*07 (P < .0001) alleles was significantly higher in parvovirus B19 patients than in control subjects. In the parvovirus group, 63.9% carried the rheumatoid arthritis–associated shared epitope sequence, compared with 45% of control subjects (odds ratio [OR], 2.2; 95% confidence interval [CI], 0.97–4.8; P = .04), and carriage was associated with fatigue during the acute phase (OR, 4.2; 95% CI, 0.8–23.9; P = .047). All symptomatic parvovirus-associated HLA-DRB1 molecules carry a neutrally charged glutamine at position 10 and a positively charged lysine at position 12 of the first hypervariable region. HLA-B49 was associated with parvovirus infection independently of HLA-DRB1*01, DRB1*04, and DRB1*07.

Human parvovirus B19, which was discovered in 1975 [1], has been associated with an extremely wide variety of clinical manifestations. However, apart from predispositions, such as shortened red blood cell survival and immunosuppression, the factors that determine whether an infected person develops symptoms remain unknown. Although P antigen, or globoside, is the cellular receptor for parvovirus B19 [2] and its distribution may reflect the possible spectrum of symptoms of B19 infection [3], the prevalence of patients with the “p” phenotype who lack this antigen (1 in 200,000) [4] is too low to be a major factor determining the presence or absence of symptoms in an infection that has a seroprevalence as high as 60%–70% of the general population.

The immune system has been implicated in the mediation of a number of clinical manifestations of parvovirus B19 infection, including rash and arthralgia [5], fatigue [6], and glomerulonephritis [7], and autoantibody production is increasingly associated with B19 infection [8, 9]. Specific antiviral antibody production is thought to be the major defense against B19 virus, because normal human immunoglobulin frequently clears the virus from peripheral blood, resulting in clinical improvement in immunosuppressed persons [10, 11] and because specific antibody protects against infection both in vivo and in vitro. In addition, lymphoproliferative responses have recently been demonstrated against VP1/2 antigens in persons with past B19 infection [12]. The particular progression of these events in an individual may be mediated by the type of CD4+ T cell response [13, 14] that has been shown for other viruses [15, 16].

Therefore, we hypothesized that HLA may have a bearing on whether patients with acute B19 infection develop symptoms. To address this question, we compared HLA class I and II alleles in 36 patients with symptomatic acute B19 infection with those in control subjects from the same region of England.

Subjects, Materials, and Methods

Patients with symptomatic acute parvovirus B19 infection. Thirty-six patients with acute parvovirus B19 infection were identified by detection of serum anti-B19 IgM in response to suggestive symptoms as part of routine clinical practice. No markers of acute infection with other agents were found on testing. All patients were white and from northwestern England except for 1 Italian woman (patient 8) and 1 Jewish woman (patient 17). Blood samples were obtained from all patients at the time of or shortly after the onset

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Informed consent was obtained from the parvovirus B19–infected patients. The human experimentation guidelines of the US Department of Health and Human Services and those of the authors’ institutions were followed.

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of new symptoms, and all patients were well and healthy by their own assessment prior to the onset of these symptoms. Follow-up and the sampling, processing, and storage of blood were as described elsewhere [17]. Clinical symptoms and levels of circulating cytokines for these patients have been reported elsewhere [6, 17].

Control subjects. Control subjects, who also were from northwestern England, were typed for HLA class I and II alleles: HLA-DRB1 (n = 952), HLA-DQB1 (n = 931), HLA-DP (n = 966), and HLA-B (n = 965). Analysis of the proportions of those possessing the shared epitope in case patients and control subjects was performed using data from a different set of 180 control subjects from northwestern England [18].

Detection of parvovirus B19 markers and autoantibodies. Parvovirus B19 markers (antibodies and DNA) and autoantibodies (rheumatoid factor and anti-nuclear antibody) were detected as described elsewhere [17].

Table 1. Demographic data, clinical symptoms at acute infection and follow-up, duration of follow-up, B19 markers, and autoantibodies for 36 patients from northwestern England with symptomatic parvovirus B19 infection.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at onset, years</th>
<th>Sex</th>
<th>Clinical symptom(s)</th>
<th>Serum B19 DNA</th>
<th>NS1 IgG</th>
<th>RF</th>
<th>ANA</th>
<th>Duration, months</th>
<th>Follow-up data</th>
<th>Serum B19 DNA</th>
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<td>M</td>
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<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4</td>
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</tr>
<tr>
<td>3</td>
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<td>F</td>
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<td>33</td>
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<td>F</td>
<td>Arthralgia, fatigue</td>
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<td>30</td>
<td>Arthralgia</td>
<td>-</td>
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<tr>
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<td>41</td>
<td>F</td>
<td>Arthralgia</td>
<td>+</td>
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<td>37</td>
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<tr>
<td>35</td>
<td>34</td>
<td>F</td>
<td>Rash, arthralgia, fatigue</td>
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<td>27</td>
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<td>-</td>
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<tr>
<td>36</td>
<td>40</td>
<td>F</td>
<td>Rash, arthralgia, lymphadenopathy</td>
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<td>38</td>
<td>32</td>
<td>F</td>
<td>IUD-R</td>
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<td>26</td>
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</table>

NOTE. ANA, anti-nuclear antibody; CFS, chronic fatigue syndrome; IUD, intrauterine death without preceding maternal symptoms; IUD-R, intrauterine death with preceding maternal rash; NS1, nonstructural protein 1; RF, rheumatoid factor; TAC, transient aplastic crisis.

a +, Positive; −, negative.

b (−) denotes absence of symptoms.

HLA allele determination. HLA alleles were determined by hybridization of sequence-specific oligonucleotide probes to human genomic DNA extracted from whole blood.

Statistical analysis. The frequency distribution of alleles for HLA-DRB1, HLA-DQB1, HLA-DP, and HLA-B in the parvovirus B19–infected group initially was compared with that of control subjects by χ² tests for homogeneity. Each allele in the disease group that demonstrated significant differences to control subjects was then further examined by either χ² test or Fisher’s exact analysis of 2 × 2 contingency tables. The strength of the association between parvovirus B19 infection and HLA alleles and phenotypes was estimated using odds ratios (ORs) and 95% confidence intervals (CIs). Where appropriate, P values were corrected for multiple comparisons, according to the procedure of Holm [19]. Multivariate logistic regression analysis was used to determine whether different HLA phenotypes were independently associated with par-
Thirty-six patients with acute B19 infection (serum anti-B19 IgM positive) were studied both during the acute phase and again during convalescence. Details of clinical symptoms, B19 markers, autoantibodies, and duration of follow-up are shown in table 1. At follow-up, 4 of these patients fulfilled Centers for Disease Control and Prevention criteria for chronic fatigue syndrome, as described elsewhere [17] (table 1).

**Results**

**Patients with symptomatic parvovirus B19 infection.** Thirty-six patients with acute B19 infection (serum anti-B19 IgM positive) were studied both during the acute phase and again during convalescence. Details of clinical symptoms, B19 markers, autoantibodies, and duration of follow-up are shown in table 1. At follow-up, 4 of these patients fulfilled Centers for Disease Control and Prevention criteria for chronic fatigue syndrome, as described elsewhere [17] (table 1).

**HLA-DRB1 allele associations in parvovirus patients versus control subjects.** Allele frequencies of HLA-DRB1 in the case patient group are presented in table 2. Initial χ² analysis revealed that the frequency distribution of HLA-DRB1 alleles was significantly different between the parvovirus B19 group and control subjects (Pearson χ², 26.7; df, 12; P = .008). Examination of adjusted residuals indicated that the frequencies of the HLA-DRB1*01, DRB1*04, and DRB1*07 alleles were significantly different among patients than among control subjects, and they made the largest contribution to the χ² value. Using 2 × 2 contingency tables, we found each of these alleles to be significantly more frequent among parvovirus B19 patients, compared with control subjects (table 3). Logistic regression analysis revealed that each of the HLA-DRB1*01, DRB1*04, and DRB1*07 phenotypes were independently associated with symptomatic acute parvovirus B19 infection. The strongest association was with HLA-DRB1*07 (P < .0001), although the associations with DRB1*01 (P = .016) and DRB1*04 (P = .007) were still significant. Overall, parvovirus-infected patients were significantly more likely to carry an HLA-DRB1*01, DRB1*04, or DRB1*07 allele than were control subjects. At least 1 of these alleles was found in 34 (94.4%) of 36 parvovirus-infected patients, compared with 22 (61.1%) of 36 control subjects. The strongest association was with HLA-DRB1*07 (P < .0001), although the associations with DRB1*01 (P = .016) and DRB1*04 (P = .007) were still significant. Overall, parvovirus-infected patients were significantly more likely to carry an HLA-DRB1*01, DRB1*04, or DRB1*07 allele than were control subjects. At least 1 of these alleles was found in 34 (94.4%) of 36 parvovirus-infected patients, compared with 22 (61.1%) of 36 control subjects.
with 574 (60.3%) of 952 control subjects (OR, 11.5; 95% CI, 2.7–69.6; \( P < .0001 \)).

Many subtypes of HLA-DRB1*01 and DRB1*04 carry a conserved amino acid sequence (QKRAA, QRRAA, or RRRAA) at position 70–74 in the third hypervariable region of the DRβ chain. This so-called shared epitope is associated with both development and severity of rheumatoid arthritis [21]. In the symptomatic parvovirus group, 63.8% possessed the shared epitope, compared with 45% of control subjects (OR, 2.2; 95% CI, 0.97–4.8; \( P = .04 \)) [18]. Furthermore, the carriage of 2 shared epitope alleles was 19.4% in the parvovirus group, compared with only 6.7% in the control subjects (OR, 3.4; 95% CI, 1.1–10.3; \( P = .01 \)).

Although HLA-DRB1 alleles are in strong linkage disequilibrium with HLA-B, -DQB1 and -DP alleles, the association of symptomatic parvovirus B19 infection with DRB1*01, DRB1*04, and DRB1*07 alleles was independent of these other loci (data not shown).

**HLA-DRB1, HLA-DP, and HLA-B associations in parvovirus patients versus control subjects.** The overall frequency distribution of HLA-DRB1, -DP, and -B alleles in the parvovirus-infected group was not significantly different from that for control subjects. However, the frequency of both HLA-DRB1*06 (12.5% vs. 23.4%; OR, 0.47; 95% CI, 0.22–0.98; \( P = .032 \)) and DP*0401 (29.2% vs. 43.0%; OR, 0.59; 95% CI, 0.31–0.95; \( P = .05 \)) was lower in the symptomatic parvovirus B19-infected group than in control subjects. In addition, the frequency HLA-B49 was higher in the parvovirus group compared with control subjects (5.6% vs. 1.0%; OR, 4.2; 95% CI, 0.8–23.9; \( P = .001 \)). The latter association was still significant (\( P = .001 \)) in a multivariate regression model that included HLA–DRB1*01, DRB1*04, and DRB1*07 (data not shown).

**HLA allele associations with particular symptoms or markers within the parvovirus group.** We examined the parvovirus group for possible associations between the shared epitope and particular clinical manifestations, B19 markers, and autoantibodies at the acute infection stage and at follow-up. We found an association only in the case of fatigue. During acute B19 infection, only 4 (30.8%) of 13 shared epitope-negative patients had fatigue, compared with 15 (65.2%) of 23 shared epitope–positive patients (OR, 4.2; 95% CI, 0.8–23.9; \( P = .047 \)). At follow-up, there was also an association, but it did not reach significance (OR, 2.13; 95% CI, 0.77–5.91; \( P = .14 \)). Homozygous versus heterozygous carriage of the shared epitope did not alter the significance of this association (data not shown).

**Sequence alignment of parvovirus-associated HLA-DRB1 alleles.** Sequence alignment of HLA-DRB1*01, DRB1*04, and DRB1*07 alleles using the IMGT/HLA database (international Immunogenetics project; available online at http://www.ebi.ac.uk/imgt/hla/index.html) focused on the hypervariable regions of P1, P4, P6, P7, and P9 binding pockets [20] revealed a sequence and charge similarity within the first hypervariable region of DRB1*01, DRB1*04, and DRB1*07 that is different from that of most non-associated molecules. Thus, all parvovirus-associated molecules carry a neutrally charged glutamine at position 10 and a positively charged lysine at position 12 (table 4).

**Discussion**

Parvovirus B19 infection is not uncommonly associated with clinical manifestations of a rheumatic nature or with diseases in which HLA molecules are known to be important in their pathogenesis [22]. For this reason, we hypothesized that particular HLA alleles may be associated with symptomatic as opposed to asymptomatic B19 infection. We found that HLA-DRB1*01, DRB1*04, and DRB1*07 were each independently associated with symptomatic parvovirus B19 infection. Many of the DRB1*01 and DRB1*04 subtypes encode the rheumatoid arthritis–associated “shared epitope” sequence [21]. However, DRB1*07 does not carry the shared epitope sequence, so this region is unlikely to fully explain the HLA-DR association with symptomatic parvovirus infection. Several other studies have examined the role of HLA-DR in the pathogenesis of parvovirus arthritis. The first of these examined a small number of patients (\( n = 18 \)) and found a positive association between HLA-DR4 antigen and acute B19 arthritis [23], but this was not borne out in further studies [24–26]. Early studies were done using serologic typing, and results were reported in terms of antigen frequency. However, methods using oligonucleotide probes that determine specific HLA-DR alleles are much more accurate and provide information on the particular genotype of each patient. To our knowledge, previous to our study, the only other study to do HLA-DR molecular typing was by Gendi et al. [26], whose case ascertainment was identical to our own (i.e., positivity for serum anti–B19 IgM). They typed HLA-DRB1 alleles in 34 patients and 297 control subjects; however, they reported only on phenotype frequencies. In contrast to our study, Gendi et al. [26] found no associations between HLA-DR and parvovirus infection, although they did find that

**Table 4.** Protein sequence alignments encoded by different HLA-DRB1 alleles, showing the charge at the first hypervariable region, amino acids 9–13.

<table>
<thead>
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<th>HLA-DRB1 allele</th>
<th>Amino acids at positions 9–13</th>
<th>Charge for each amino acid at positions 9–13</th>
<th>Net charge</th>
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<tr>
<td>*0901</td>
<td>QKDKF</td>
<td>+ n – + n</td>
<td>+</td>
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<tr>
<td>*1001</td>
<td>EEEKF</td>
<td>– n + n n</td>
<td>–</td>
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<tr>
<td>*1101</td>
<td>EYSTS</td>
<td>– n n n n</td>
<td>–</td>
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<tr>
<td>*1301</td>
<td>EYSTS</td>
<td>– n n n n</td>
<td>–</td>
</tr>
<tr>
<td>*1501</td>
<td>WQPKR</td>
<td>n n + +</td>
<td>+</td>
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<tr>
<td>*1601</td>
<td>WQPKR</td>
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**NOTE.** n, neutral.
symptoms of the joints persisted for >1 week in all HLA-
DR4–positive patients. A possible explanation is the ethnic
background of parvovirus-infected patients. Although this was
not documented in previous studies, the subjects in those studies
were from southern England, which is known to have greater
ethnic heterogeneity than does northwestern England, where
our study was performed.

We have shown that HLA-B49 was associated with sym-
tomatic parvovirus (P = .001). This was independent of the
association with HLA-DRB1*01, DRB1*04, and DRB1*07.
The role of the HLA-B locus in parvovirus B19 infection has
previously been examined by Woolf et al. [24], who found no
association when comparing patients with control subjects;
however, these authors used serologic methods in only 26 pa-
tients and 318 control subjects. Persistent B19 arthritus has been
linked previously with HLA-B27 [27], which is strongly
associated with spondyloarthropathy, but we found no association
with B27 in our study.

The association with DRB1*07 is particularly interesting,
because this allele has been associated (usually with DQB1*02)
with a variety of diseases and syndromes, including atopy [28,
29], antiphospholipid syndrome [30, 31], idiopathic nephrotic
syndrome [32, 33], coeliac disease [34], and immune cilia
syndrome [35]. Parvovirus B19 infection has been associated with
production of antiphospholipid antibodies and systemic lupus
erythematosus [8, 36, 37] and with nephrotic syndrome and
proteinuria [38].

HLA-DRB1*01, DRB1*04, and DRB1*07 alleles encode a
glutamine at position 10 and a lysine at position 12 of the first
hypervariable region. The significance of this is not entirely
clear, because these particular residues do not appear to con-
tribute directly to contact of the binding groove with bound
peptide [20, 39]. However they may influence the binding ability
of adjacent residues, such as the tryptophan at position 9. Poly-
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