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Association between Human Leukocyte Antigen Class II Alleles and Genotype of *Borrelia burgdorferi* in Patients with Early Lyme Disease

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Abstract

Background—On the basis of a polymerase chain reaction–restriction fragment–length polymorphism analysis of the 16S–23S ribosomal DNA intergenic spacer, clinical isolates of *Borrelia burgdorferi* can be classified into 3 genotypes designated as RST1, RST2, and RST3. RST1 strains are the most pathogenic, and RST3 strains are the least pathogenic.

Methods—Human leukocyte antigen (HLA) class II alleles were determined for a group of culture-positive patients with Lyme disease–associated erythema migrans and were evaluated for an association with the genotype of the infecting *B. burgdorferi* strain.

Results—The DRB1*0101 allele carriage rate was higher in patients infected with RST3 strains (9/25 [36.0%]) than in patients infected with RST1 strains (2/28 [7.1%]) or RST2 strains (7/36 [19.4%]) (P = .010). The same relationship was found for carriage of the DRB1*0101-DQB1*0501 haplotype (P= .018), because of tight linkage disequilibrium. Similar associations could not be demonstrated for any of the other *DRB1* and *DQB1* alleles or haplotypes that were assessed.

Conclusion—The DRB1*0101 allele and the DRB1*0101-DQB1*0501 haplotype may be relevant to the development of infection with strains from the least invasive genotypes of *B. burgdorferi.*

Lyme disease, which is caused by the spirochete *Borrelia burgdorferi*, is the most common vectorborne disease in North America [1,2]. Patients with *B. burgdorferi* infection may have no symptoms or may present with a wide range of clinical manifestations involving the skin, joints, nervous system, or heart [3].

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There is increasing evidence that genotypic variation of *B. burgdorferi* accounts for the variability in the microorganism's pathogenicity [4–9]. On the basis of a polymerase chain reaction–restriction fragment–length polymorphism analysis (PCR-RFLP) of the 16S–23S ribosomal DNA intergenic spacer, clinical isolates of *B. burgdorferi* from the United States can be classified genetically into 3 distinct genotypes designated as RST1, RST2, and RST3 [10,11]. In clinical studies of patients with Lyme disease–associated erythema migrans, RST1 was the most pathogenic, and RST3 was the least pathogenic. Compared with infection with RST2 or RST3 strains, infection with RST1 strains has been associated with a greater number of spirochetes in the erythema migrans skin lesion [6] and a higher rate of both spirochetemia and development of secondary skin lesions [4].

Whether human host factors contribute to the risk of infection or affect the clinical presentation of infection with strains from particular genotypes of *B. burgdorferi* is unknown. To explore this possibility, we studied the HLA class II alleles in patients with Lyme disease–associated erythema migrans and in relation to the genotype of the infecting *B. burgdorferi* strain. Our hypothesis was that HLA class II alleles might either influence susceptibility to infection with strains from the various genotypes of *B. burgdorferi* or affect the clinical manifestations. More specifically, we tested the possibility that either (1) genotype RST1 strains appear to be more invasive because they more commonly infect patients whose carriage of certain HLA class II alleles makes them less able to control RST1 infection or (2) infection with the least invasive RST3 strains is restricted to patients with certain HLA class II alleles.

Patients, materials, and methods

Patients who had been previously diagnosed with Lyme disease–associated erythema migrans at least 12 months before study entry were eligible for participation. Eligible patients were participants in other prospective studies at New York Medical College, for whom the diagnosis of Lyme disease was based on the growth of *B. burgdorferi* from a 2-mm skin-biopsy culture and/or blood culture by use of methods described elsewhere [4,12]. Patients returning for their annual follow-up visits were invited to participate in the present study, if the inclusion criteria were satisfied. Inclusion criteria were treatment with antibiotics at the time of the diagnosis of Lyme disease–associated erythema migrans and, on the basis of clinical assessment, resolution of the infection. Specifically, patients were not eligible if they fulfilled the criteria for posttreatment chronic Lyme disease (PTCLD) [13], which were the onset of symptoms within 6 months after the initial infection with *B. burgdorferi* and the persistence of these symptoms for at least 6 months after the initial infection. Symptoms attributed to PTCLD included 1 or more of the following: widespread musculoskeletal pain and fatigue that interfered with usual function; symptoms of memory impairment that interfered with usual function; and symptoms of radicular pain, paresthesias, and/or dysesthesias that interfered with usual function.

On the basis of a review of the research study records, 106 patients were invited to participate in the present study, and 104 provided written, informed consent for HLA class II typing. The HLA test results from the study patients were used for 2 purposes. The primary purpose was to serve as a control group of patients who had recovered from Lyme disease in an evaluation of whether the HLA class II haplotype was associated with the development of PTCLD. The results of that investigation were described elsewhere [14]. The secondary purpose was to determine whether HLA class II alleles are associated with infection with strains from specific genotypes of *B. burgdorferi*. For this substudy, the 6 patients for whom *B. burgdorferi* genotyping had not been performed and 9 additional patients who were infected with strains from a single genotype were excluded, leaving a study group of 89 patients. This study was approved by the institutional review board at New York Medical College.

Genotyping of *B. burgdorferi* was performed by a PCR-RFLP method described elsewhere [11]. For HLA genotyping, high-molecular-weight genomic DNA was extracted from blood samples by use of the QIAamp Blood Kit (Qiagen) and protocols recommended by the manufacturer. The 4-digit alleles at the *HLA-DQB1* locus were resolved by PCR with sequence-specific primers (Pel-Freez Clinical Systems). Sequencing-based typing of *HLA-DRB1* was facilitated by SequiTyper software (version 2.0) and the DRβ plus kit, which are designed for use with the ALFexpress automated sequencer (all from Amersham Pharmacia Biotech) [15]. After individual alleles were resolved at each locus, *DRB1-DQB1* haplotypes were assigned manually in accordance with known linkage disequilibria observed in white individuals from the United States [16].

The allele frequency was defined as the frequency of a particular allele among all the alleles present at that locus in a group of patients. Because there are 2 alleles at each locus, the total number of alleles, or the denominator, equals 2*n*, where *n* is the number of subjects. The allele carriage rate was defined as the proportion of a group of patients who carry a particular allele, with the denominator being *n*. For the haplotype frequency and the haplotype carriage rate, each *DRB1-DQB1* haplotype was treated in a fashion analogous to that described above for an allele—that is, as a proportion of *2n* haplotypes or *n* subjects, respectively.

The relationships among the 3 *B. burgdorferi* genotypes and the frequencies of the HLA class II alleles were evaluated in a sequential 2-step approach. *DQB1* and *DRB1* allele frequencies and carriage rates were determined for patients infected with RST1, RST2, or RST3 strains of *B. burgdorferi*. In the first step of the analysis, a global test was performed using a likelihood-ratio χ^2 test to determine, for *DQB1* and *DRB1* alleles separately, if the allele frequencies in patients infected with strains from any of the 3 genotypes differed from those in the general white population in the United States, as defined by Klitz et al. [16].

If the allele frequencies differed from those in the general white population, then a second analysis was performed. In this analysis, genotype was treated as an ordinal variable and an extended Mantel-Haenzel 1-degree-of-freedom χ^2 test was used to determine if there was a difference in the allele carriage rates associated with the 3 *B. burgdorferi* genotypes. As per the study hypothesis, this analysis was restricted to those alleles in which the carriage rate in patients infected with RST2 strains was between that in patients infected with RST1 strains and that in patients infected with RST3 strains. Common *DRB1-DQB1* haplotypes were analyzed in the same way. For all analyses,$P < .05$ was considered to be statistically significant.

Results

In the present study, all 89 patients (51 men and 38 women) had culture-confirmed erythema migrans. The mean ± SD age was 55 ± 11 years, with a range of 25–88 years. All but 8 patients (9%) were white.

Of the 89 patients, 28 were infected with RST1 strains (25 whites, 1 Hispanic, and 2 patients of other/unknown ethnicity/race), 36 were infected with RST2 strains (33 whites, 2 blacks, and 1 Hispanic), and 23 were infected with RST3 strains (23 whites, 1 Hispanic, and 1 Asian).

Table 1 and Table 2 display the frequencies and carriage rates of 18 (4-digit) *DQB1* and 38 (4-digit) *DRB1* alleles, respectively, in patients infected with strains from any of the 3 *B. burgdorferi* genotypes. Also displayed are the allele frequencies found in nearly 1900 US white bone-marrow donors whose history of Lyme disease was unknown [16]. On the basis of the global test, the overall distributions of the *DQB1* and *DRB1* alleles differed between those in the general white population of the United States and those in at least 1 of the 3 groups of infected patients ($P = .024$ for *DQB1* and $P < .0001$ for *DRB1*); the overall distribution of the frequency of *DRB1-DQB1* haplotypes (table 3) also differed between that in the general white

population of the United States and that in at least 1 of the 3 groups of infected patients ($P < .0001$).

For 7 *DQB1* alleles and for 16 *DRB1* alleles (shown in bold-face in table 1 and table 2, respectively), the carriage rates differed between patients infected with RST1 strains and patients infected with RST3 strains, and the carriage rate in patients infected with RST2 strains was between these rates; these alleles were suitable for testing our study hypothesis. For these alleles, only the carriage rate of the DRB1*0101 allele differed across the 3 groups of infected patients ($P = .010$). In the 28 patients infected with RST1 strains, the carriage rate of the DRB1*0101 allele was 7.1% (2/28), compared with 19.4% (7/36) in the patients infected with RST2 strains (odds ratio [OR], 3.1 [95% confidence interval {CI}, 0.6–16.5]) and 36.0% (9/25) in the patients infected with RST3 strains (OR, 7.3 [95% CI, 1.4–38.2]). The frequency of the DRB1*0101 allele in the general white population of the United States is 9.1% [16], a value that differed significantly from the frequency of 20% (10/50) that we observed in patients infected with RST3 strains ($P = .022$) but did not differ significantly from the frequency of 3.6% (2/56) that we observed in patients infected with RST1 strains ($P = .235$). Furthermore, extending the analysis to all 56 of the HLA class II alleles that we assessed did not reveal any other 4-digit *DQB1* or *DRB1* alleles whose carriage rates differed significantly across the 3 groups of infected patients when the Mantel-Haenzel 1-degree-of-freedom χ^2 test was used (table 1 and table 2). For the *DRB1-DQB1* haplotypes evaluated (table 3), only the carriage rate of the DRB1*0101-DQB1*0501 haplotype differed across the 3 groups of infected patients ($P = .018$). Indeed, the DRB1*0101 allele was found in almost exclusive linkage disequilibrium with the DQB1*0501 allele.

Identical types of sequential analyses were also performed for 2-digit *DQB1* and *DRB1* alleles. None of the carriage rates of the 2-digit alleles differed significantly across the 3 groups of infected patients (data not shown).

Discussion

The association between the DRB1*0101 allele, as well as the DRB1*0101-DQB1*0501 haplotype, and infection with RST3 strains is consistent with the hypothesis that host factors would be least important for the development of infection with the most pathogenic genotype (RST1) of *B. burgdorferi* and increasingly important for the development of infection with the least pathogenic genotypes, especially RST3 [4,6]. The relatively small sample size of our population, plus the low frequencies of some individual 4-digit alleles in the general population [16], limited the power of the present study to find an association between the infecting genotype and rare HLA class II variants.

The immunologic event that might account for an association between carriage of the DRB1*0101 allele and infection with certain genotypes of *B. burgdorferi* is unclear. The observation that all but 1 of the patients infected with RST3 strains who carried the DRB1*0101 allele were heterozygous for this allele makes alteration in antigen presentation by this molecule an unlikely explanation. Rather, the association between the DRB1*0101 allele and infection with certain genotypes may be a marker for other genetic factors (e.g., polymorphisms in HLA class III genes) relevant to the host defense against *B. burgdorferi*. The critical role that complement plays in the innate immune response to *B. burgdorferi* [17] suggests the potential relevance of variants in major histocompatibility complex–encoded complement genes (complotype) in linkage disequilibrium with *DRB1* alleles [18].

Our reliance on confirmation of *B. burgdorferi* infection by culture may have introduced a selection bias toward patients with higher numbers of spirochetes in skin tissue, because a culture is more likely to have a positive result under these circumstances [6]. Also, a culture

may underestimate the frequency of coinfections with multiple genotypes [19]. Therefore, patients carrying the DRB1*0101 allele may be less able to defend against the growth of RST3 strains to high numbers in skin tissue. Follow-up studies in which the infecting genotype of *B. burgdorferi* is identified directly in skin tissue by PCR [19] will be necessary to understand whether carriage of the DRB1*0101 allele is a risk factor per se for infection with RST3 strains.

Inclusion of only those subjects who did not develop PTCLD after antibiotic treatment might have introduced some selection bias. Our study population, however, may be considered to be representative of the vast majority of patients with erythema migrans, because antibiotic therapy at this stage of Lyme disease is usually highly successful [20,21].

The precedent for a genotype-specific response in infection with another microorganism has been demonstrated for human papilloma virus (HPV). An association between certain HLA class II haplotypes and risk of cervical cancer was found to be specific to infection with HPV-16 [22].

Intriguingly, DRB1*0101 is also a principal allele associated with antibiotic treatment–resistant Lyme arthritis [23]. Whether the identical associations in infections with RST3 strains and antibiotic treatment–resistant Lyme arthritis can be linked biologically or are mere coincidences will need to be determined through further research.

The frequency of the DRB1*0101 allele was found to differ between patients infected with RST3 strains (20.0%) and the general white population of the United States (9.1%) ($P = .022$) [16]. The inclusion of a single Hispanic and a single Asian in the group of patients infected with RST3 strains is unlikely to have contributed to this difference, because the reported frequency of the DRB1*0101 allele in Hispanics is significantly less than that in whites, whereas the frequency in Asians appears to be similar to that in whites [24]. Other evidence also points to a notably high carriage rate of the DRB1*0101 allele in patients infected with RST3 strains in the present study. In the 95 patients with Lyme disease who were recruited from the northeastern United States by Klempner et al. [14], the carriage rate of the DRB1*0101 allele was 12.6%. The genotypes of the infecting strains of *B. burgdorferi* were unknown in the Klempner et al. study, but, presumably, some of the patients were infected with RST3 strains. Nevertheless, the carriage rate of the DRB1*0101 allele was significantly greater in the patients infected with RST3 strains in the present study, compared with that in patients with Lyme disease in the study by Klempner et al. (9/25 vs. 12/95; $P = .015$) [14].

A statistical adjustment for multiple comparisons is controversial in studies evaluating associations between infectious diseases and HLA haplotypes and alleles [25,26], and no adjustment was performed in the present study. Because the strength of the observed genetic associations may be relatively modest (OR usually <2) [27], if an adjustment is made, researchers run the risk of overlooking true associations. Consequently, our results should be interpreted cautiously in the absence of confirmation by other investigations.

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Table 1

DQB1 allele frequencies and carriage rates.

DQB1 allele[a]	Allele frequency in control population,[a] %	Allele frequency in patients, %			Allele carriage rate in patients, %			*P*[b]
		RST1 infection	RST2 infection	RST3 infection	RST1 infection	RST2 infection	RST3 infection	
0201	**13.2**	**7.1**	**12.5**	**14.0**	**10.7**	**22.2**	**24.0**	**.214**
0202	**11.2**	**7.1**	**11.1**	**12.0**	**14.3**	**19.4**	**24.0**	**.371**
0301	**17.9**	**12.5**	**15.3**	**18.0**	**21.4**	**30.6**	**36.0**	**.244**
0302	10.5	10.7	11.1	4.0	17.9	22.2	8.0	.362
0303	4.5	5.4	1.4	2.0	10.7	2.8	4.0	.277
0304	0.2	0.0	0.0	0.0	…	…	…	…
0305	**0.2**	**0.0**	**1.4**	**2.0**	**0.0**	**2.8**	**4.0**	**.325**
0401	0.0	1.8	0.0	0.0	3.6	0.0	0.0	.210
0402	2.4	3.6	4.2	0.0	7.1	8.3	0.0	.277
0501	11.6	16.1	15.3	20.0	32.1	30.6	36.0	.776
0502	**1.3**	**5.4**	**2.8**	**0.0**	**10.7**	**5.6**	**0.0**	**.093**
0503	2.1	5.4	2.8	2.0	10.7	2.8	4.0	.277
0504	0.1	0.0	2.8	2.0	0.0	5.6	4.0	.404
0601	0.7	0.0	1.4	0.0	0.0	2.8	0.0	.965
0602	**14.3**	**10.7**	**8.3**	**6.0**	**21.4**	**13.9**	**12.0**	**.343**
0603	5.9	10.7	5.6	10.0	17.9	11.1	20.0	.859
0604	**3.4**	**1.8**	**2.8**	**6.0**	**3.6**	**5.6**	**12.0**	**.230**
0609	0.7	1.8	1.4	2.0	3.6	2.8	4.0	.939

NOTE. Boldface indicates that the allele carriage rate associated with RST2 infection was between that associated with RST1 infection and that associated with RST3 infection.

[a] See [16] for definition.

[b] χ^2 test (1 *df*) for a difference in carriage rates among the ordinal *Borrelia burgdorferi* genotype categories.

Table 2

DRB1 allele frequencies and carriage rates.

DQB1 allele[a]	Allele frequency in control population,[a] %	Allele frequency in patients, %			Allele carriage rate in patients, %			*P*[b]
		RST1 infection	RST2 infection	RST3 infection	RST1 infection	RST2 infection	RST3 infection	
0101	**9.1**	**3.6**	**9.7**	**20.0**	**7.1**	**19.4**	**36.0**	**.010**
0102	**1.4**	**5.4**	**2.8**	**2.0**	**10.7**	**5.6**	**4.0**	**.327**
0103	0.6	1.8	4.2	2.0	3.6	8.3	4.0	.920
0301	**13.2**	**5.4**	**11.1**	**12.0**	**7.1**	**19.4**	**24.0**	**.100**
0313	0.0	1.8	0.0	0.0	3.6	0.0	0.0	.210
0401	**10.3**	**7.1**	**2.8**	**2.0**	**10.7**	**5.6**	**4.0**	**.327**
0402	**1.0**	**1.8**	**1.4**	**0.0**	**3.6**	**2.8**	**0.0**	**.390**
0403	**0.7**	**0.0**	**5.6**	**6.0**	**0.0**	**11.1**	**12.0**	**.100**
0404	4.0	0.0	4.2	0.0	0.0	8.3	0.0	.939
0405	**0.3**	**3.6**	**2.8**	**0.0**	**7.1**	**5.6**	**0.0**	**.218**
0406	0.1	0.0	0.0	0.0	…	…	…	…
0407	1.0	0.0	0.0	0.0	…	…	…	…
0408	0.3	0.0	0.0	0.0	…	…	…	…
0701	**14.9**	**10.7**	**12.5**	**14.0**	**17.9**	**22.2**	**28.0**	**.381**
0801	**2.3**	**3.6**	**2.8**	**2.0**	**7.1**	**5.6**	**4.0**	**.622**
0802	0.03	0.0	0.0	0.0	…	…	…	…
0803	0.1	0.0	0.0	0.0	…	…	…	…
0804	0.03	0.0	0.0	0.0	…	…	…	…
0901	**0.8**	**1.8**	**1.4**	**0.0**	**3.6**	**2.8**	**0.0**	**.390**
1001	**0.7**	**1.8**	**1.4**	**0.0**	**3.6**	**2.8**	**0.0**	**.390**
1101	5.7	5.4	6.9	2.0	10.7	13.9	4.0	.442
1102	0.2	0.0	0.0	0.0	…	…	…	…
1103	**0.3**	**0.0**	**1.4**	**2.0**	**0.0**	**2.8**	**4.0**	**.325**
1104	2.8	1.8	1.4	6.0	3.6	2.8	12.0	.198
1108	0.0	0.0	1.4	0.0	0.0	2.8	0.0	.965
1201	1.1	5.4	0.0	4.0	10.7	0.0	8.0	.622
1301	5.7	10.7	4.2	6.0	21.4	8.3	12.0	.299
1302	4.2	5.4	4.2	8.0	10.7	8.3	16.0	.563
1303	0.7	0.0	0.0	0.0	…	…	…	…
1305	**0.3**	**0.0**	**2.8**	**4.0**	**0.0**	**5.6**	**8.0**	**.159**
1401	2.0	3.6	2.8	2.0	7.1	2.8	4.0	.568
1404	0.03	0.0	0.0	0.0	…	…	…	…
1407	0.0	1.8	0.0	0.0	3.6	0.0	0.0	.210
1501	**14.5**	**10.7**	**9.7**	**6.0**	**21.4**	**13.9**	**12.0**	**.343**
1502	**0.7**	**1.8**	**1.4**	**0.0**	**3.6**	**2.8**	**0.0**	**.390**
1503	0.03	0.0	0.0	0.0	…	…	…	…
1601	**1.0**	**5.4**	**1.4**	**0.0**	**10.7**	**2.8**	**0.0**	**.059**
1602	0.2	0.0	0.0	0.0	…	…	…	…

NOTE. Boldface indicates that the allele carriage rate associated with RST2 infection was between that associated with RST1 infection and that associated with RST3 infection.

[a] See [16] for definition.

[b] χ^2 test (1 *df*) for a difference in carriage rates among the ordinal *Borrelia burgdorferi* genotype categories.

Table 3

DRB1-DQB1 haplotype frequencies and carriage rates.

Haplotype[a]		Haplotype frequency in control population,[a] %	Haplotype frequency in patients, %			Haplotype carriage rate in patients, %			P^b
DRB1 allele	*DRB1* allele		RST1 infection	RST2 infection	RST3 infection	RST1 infection	RST2 infection	RST3 infection	
0101	**0501**	**9.1**	**3.6**	**6.9**	**18.0**	**7.1**	**13.9**	**32.0**	**.018**
0101	0504	0.1	0.0	2.8	2.0	0.0	5.6	4.0	.404
0102	**0501**	**1.4**	**5.4**	**2.8**	**2.0**	**10.7**	**5.6**	**4.0**	**.327**
0102	0504	0.03	0.0	0.0	0.0	…	…	…	…
0103	0301	0.2	0.0	0.0	2.0	0.0	0.0	4.0	.180
0103	0501	0.5	1.8	4.2	0.0	3.6	8.3	0.0	.568
0301	**0201**	**13.1**	**5.4**	**11.1**	**12.0**	**7.1**	**19.4**	**24.0**	**.100**
0301	0301	0.03	0.0	0.0	0.0	…	…	…	…
0301	0602	0.03	0.0	0.0	0.0	…	…	…	…
0313	0201	0.0	1.8	0.0	0.0	3.6	0.0	0.0	.210
0401	0301	5.4	0.0	1.4	0.0	0.0	2.8	0.0	.965
0401	0302	4.9	7.1	1.4	2.0	10.7	2.8	4.0	.277
0401	0401	0.03	0.0	0.0	0.0	…	…	…	…
0402	**0302**	**1.0**	**1.8**	**1.4**	**0.0**	**3.6**	**2.8**	**0.0**	**.390**
0403	0302	0.4	0.0	2.8	2.0	0.0	5.6	4.0	.404
0403	0304	0.1	0.0	0.0	0.0	…	…	…	…
0403	**0305**	**0.2**	**0.0**	**1.4**	**2.0**	**0.0**	**2.8**	**4.0**	**.325**
0403	0402	0.0	0.0	1.4	0.0	0.0	2.8	0.0	.965
0404	0301	0.03	0.0	0.0	0.0	…	…	…	…
0404	0302	3.9	0.0	4.2	0.0	0.0	8.3	0.0	.939
0404	0402	0.03	0.0	0.0	0.0	…	…	…	…
0405	0202	0.1	0.0	1.4	0.0	0.0	2.8	0.0	.965
0405	**0302**	**0.3**	**1.8**	**1.4**	**0.0**	**3.6**	**2.8**	**0.0**	**.390**
0405	0401	0.0	1.8	0.0	0.0	3.6	0.0	0.0	.210
0406	0402	0.1	0.0	0.0	0.0	…	…	…	…
0407	0301	0.9	0.0	0.0	2.0	0.0	0.0	4.0	.180
0407	0302	0.1	0.0	0.0	0.0	…	…	…	…
0408	0301	0.2	0.0	0.0	0.0	…	…	…	…
0408	0304	0.1	0.0	0.0	0.0	…	…	…	…
0701	**0202**	**11.1**	**7.1**	**9.7**	**12.0**	**14.3**	**16.7**	**24.0**	**.366**
0701	0301	0.1	0.0	1.4	0.0	0.0	2.8	0.0	.965
0701	0303	3.7	3.6	1.4	2.0	7.1	2.8	4.0	.568
0801	0201	0.0	0.0	0.0	2.0	0.0	0.0	4.0	.180
0801	0301	0.03	0.0	0.0	0.0	…	…	…	…
0801	0302	0.03	0.0	0.0	0.0	…	…	…	…
0801	**0402**	**2.2**	**3.6**	**2.8**	**0.0**	**7.1**	**5.6**	**0.0**	**.218**
0802	0402	0.03	0.0	0.0	0.0	…	…	…	…
0803	0301	0.1	0.0	0.0	0.0	…	…	…	…
0804	0402	0.03	0.0	0.0	0.0	…	…	…	…
0901	0201	0.0	0.0	1.4	0.0	0.0	2.8	0.0	.965
0901	0202	0.03	0.0	0.0	0.0	…	…	…	…
0901	0303	0.8	1.8	0.0	0.0	3.6	0.0	0.0	.210
1001	**0501**	**0.7**	**1.8**	**1.4**	**0.0**	**3.6**	**2.8**	**0.0**	**.390**
1101	0301	5.6	5.4	5.6	2.0	10.7	11.1	4.0	.408
1101	0302	0.03	0.0	0.0	0.0	…	…	…	…
1101	0304	0.03	0.0	0.0	0.0	…	…	…	…
1101	0502	0.0	0.0	1.4	0.0	0.0	2.8	0.0	.965
1101	0602	0.1	0.0	0.0	0.0	…	…	…	…
1102	0301	0.2	0.0	0.0	0.0	…	…	…	…

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Haplotype[a]		Haplotype frequency in control population,[a] %	Haplotype frequency in patients, %			Haplotype carriage rate in patients, %			
DRB1 allele	*DRB1* allele		RST1 infection	RST2 infection	RST3 infection	RST1 infection	RST2 infection	RST3 infection	*P*[b]
1103	**0301**	**0.3**	**0.0**	**1.4**	**2.0**	**0.0**	**2.8**	**4.0**	**.965**
1104	0301	2.7	1.8	1.4	4.0	3.6	2.8	8.0	.454
1104	0502	0.03	0.0	0.0	0.0	…	…	…	…
1104	0603	0.1	0.0	0.0	2.0	0.0	0.0	0.0	.180
1108	0301	0.0	0.0	1.4	0.0	0.0	2.8	2.8	.965
1201	0301	1.1	5.4	0.0	4.0	10.7	0.0	0.0	.622
1301	0501	0.03	1.8	0.0	0.0	3.6	0.0	0.0	.210
1301	0503	0.1	0.0	0.0	0.0	…	…	…	…
1301	0603	5.6	8.9	4.2	6.0	17.9	8.3	8.3	.499
1302	0501	0.0	1.8	0.0	0.0	3.6	0.0	0.0	.210
1302	0602	0.03	0.0	0.0	0.0	…	…	…	…
1302	0603	0.03	0.0	0.0	0.0	…	…	…	…
1302	**0604**	**3.4**	**1.8**	**2.8**	**6.0**	**3.6**	**5.6**	**5.6**	**.230**
1302	0609	0.7	1.8	1.4	2.0	3.6	2.8	2.8	.939
1303	0301	0.7	0.0	0.0	0.0	…	…	…	…
1305	0301	0.3	0.0	2.8	2.0	0.0	5.6	5.6	.404
1305	0603	0.0	0.0	0.0	2.0	0.0	0.0	0.0	.180
1401	0503	2.0	3.6	2.8	2.0	7.1	2.8	2.8	.568
1401	0602	0.03	0.0	0.0	0.0	…	…	…	…
1404	0503	0.03	0.0	0.0	0.0	…	…	…	…
1407	0503	0.0	1.8	0.0	0.0	3.6	0.0	0.0	.210
1501	0501	0.03	0.0	0.0	0.0	…	…	…	…
1501	0502	0.1	0.0	0.0	0.0	…	…	…	…
1501	**0602**	**14.2**	**8.9**	**8.3**	**6.0**	**17.9**	**13.9**	**13.9**	**.546**
1501	**0603**	**0.2**	**1.8**	**1.4**	**0.0**	**3.6**	**2.8**	**2.8**	**.390**
1502	0601	0.7	0.0	1.4	0.0	0.0	2.8	2.8	.965
1502	0602	0.03	1.8	0.0	0.0	3.6	0.0	0.0	.210
1503	0602	0.03	0.0	0.0	0.0	…	…	…	…
1601	**0502**	**1.0**	**5.4**	**1.4**	**0.0**	**10.7**	**2.8**	**2.8**	**.059**
1602	0301	0.03	0.0	0.0	0.0	…	…	…	…
1602	0502	0.2	0.0	0.0	0.0	…	…	…	…

NOTE. Boldface indicates that the allele carriage rate associated with RST2 infection was between that associated with RST1 infection and that associated with RST3 infection.

[a] See [16] for definition.

[b] χ^2 test (1 *df*) for a difference in carriage rates among the ordinal *Borrelia burgdorferi* genotype categories.