The frequency of HLA-DR alleles in patients with tick-borne disease from Latvia

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Abstract

Background: The level of incidence of Tick-borne disease in Latvia still is one of the highest in Europe. There are some similarities between the viral agents, and HLA molecules, because in organism develops one way or another immune response to infection. Clarifying the polymorphisms of HLA molecules will allow to identify regularities of pathological process and to develop a new approach to treating these diseases.

The purpose: Of this study was to determine HLA-DR alleles in two groups Latvian patients: in patients with Lyme borreliosis (LB) and patients with Tick-borne encephalitis (TBE). The study included 38 patients with clinical stage – erythema migrans, 60 patients with TBE and 100 control (healthy) persons. All patients and healthy persons are residents of Latvia. HLA genotyping was performed by PCR with sequence-specific primers.

Results: The frequency of HLA-DRB1*17(03) (odds ratio, 4.06; pc=0.003), HLA-DRB1*04 (odds ratio, 3.22; pc=0.162), and HLA-DRB1*13 (odds ratio, 2.37; pc=0.055), were higher in patients with LB. And the HLA-DRB1*10 (odds ratio, 0.16; pc=0.044) was smaller in LB patients and significantly higher in controls. Among TBE patients the HLA-DRB1*04 (11 percent vs. 5 percent; odds ratio, 2.58; pc=0.386) and DRB1*17(03) (10 percent vs. 4 percent; odds ratio, 2.67; pc=0.396) alleles were increased, but the HLA-DRB1*01 (2 percent vs. 6 percent; odds ratio, 0.13; pc=0.240) was lower in patients, these differences were not significant after Bonferroni correction.

Conclusions: These data suggest the positive association of HLA-DRB1*17(03) allele with Lyme borreliosis in Latvian patients, and HLA-DRB1*10 allele could be associated with a potential protective effect. Among TBE patients statistically significant associations of HLA-DRB1 not detected.

Keywords: Tick-borne diseases, HLA alleles, marker, PCR

Background

Today ticks inhabit almost every continent, with the number of species worldwide topping 850 [1-4]. The recognized number of important diseases transmitted by ticks has been growing over the past 30 years [4,10,11].

Lyme disease is a debilitating infection transmitted via the bite of ticks infected with Borrelia burgdorferi (Bb). One of the most prominent clinical manifestations of Lyme disease is the development of chronic Lyme arthritis [12-15]. Some patients continue to experience persistent joint inflammation despite antibiotic treatment, a condition referred to as antibiotic-refractory Lyme arthritis [13-15]. This inflammatory response is characterized by proliferative synovitis, and it may persist for months or even several years. One of the factors that confer susceptibility to antibiotic-refractory Lyme arthritis is the presence of certain HLA–DR alleles [16,19,20]. Patients presenting with joint inflammation after antibiotic therapy have a higher frequency of HLA–DRB1*0401 (DR4) [16,17].
While the idea of HLA-related genes being involved in the control of the clinical progression of Lyme arthritis is well documented [17], the possible role of the HLA region in susceptibility to disease per se has also been suggested [18,21]. Some results have already been found for class I HLA alleles [19], however a greater number of studies have reported increased frequencies of class II alleles in Lyme arthritis patients in several populations [16,17,20].

Tick-borne encephalitis is an infection caused by viruses, and the diseases mainly affects the central nervous system of the man. Damage to the central nervous system may have different symptoms in each specific case: from moderate meningitis to very severe cases of meningoencephalitis, meningoencephalitis. The incidence of Tick-borne encephalitis in Latvia is one of the highest in Europe [10,22]. The prevalence of Tick-borne encephalitis virus in 2012 exceeded 10%, while in 2011 it was 5.7% and 4.1% in 2010 [10].

In the present study, we investigate the HLA DR alleles in two group’s patients: patients with Lyme borreliosis and patients with tick-borne encephalitis. The aim of the investigation was to identify risk alleles and protective alleles in Latvian patients. For this examinations, MHc classes II alleles was performed by PCR Low-resolution HLA-DR typing. The obtained data were compared with the control group of healthy individuals. The results of comparisons were assessed by Chi square test, Bonferroni test, and Fisher’s Exact Test (when necessary).

Materials and methods
Characteristic of the studied patients
The study included 38 patients with clinical stage–erythema migrans, 60 patients with tick-borne encephalitis and 100 control (healthy) persons. The included patients’ ages ranged from 18 to 45 years of age, representing 60.4% of the total studied. All patients and healthy persons are residents of Latvia. The clinical diagnosis was confirmed at Infectology Center of Stradiņš University, laboratory of Clinical Immunology and Immunogenetics. The prevalence of Tick-borne encephalitis in Latvia is one of the highest in Europe [10,22]. The frequency of allele DRB1* alleles of the TBE patients and control group are shown in Table 1. There were differences between patients and controls was performed using the Chi square test, with the Bonferroni correction or Fisher’s Exact Test when necessary [26]. Data were considered statistically significant when the P value was less than or equal to 0.05. However, to account for multiple comparisons, the observed P values were corrected (pc) for the number of alleles when one locus was considered alone. The odds ratios (OR), with 95% confidence intervals (95% CI), were calculated using SISA statistics online http://home.clara.net/sisa/, to evaluate the risk of the individual developing the disease while having a particular HLA type.

Results
The frequency of DRB1* alleles of the LB patients and control group are shown in Table 1. There were differences between LB patients and the control group for HLA-DRB1*17(03) (15 percent vs. 4 percent; odds ratio, 4.06; p=0.002) and HLA-DRB1*04 (13 percent vs. 5 percent; odds ratio, 2.67; p=0.001), which appeared with greater frequency in the patients. We also detected a difference for HLA-DR*13. The frequency of allele DRB1*13 (13 percent vs. 6 percent; odds ratio, 2.37; p=0.049) was higher in Borreliosis patients and lower in controls (Table 1). In contrast, HLA-DRB1*10 (2 percent vs. 8 percent; odds ratio, 0.16; p=0.036) frequencies were lower in LB patients (Table 1).

The frequency of DRB1* alleles of the TBE patients and control group are shown in Table 2. Among TBE patients the DRB1*04 (11 percent vs. 5 percent; odds ratio, 2.58; p=0.03) and DRB1*17(03) (10 percent vs. 4 percent; odds ratio, 2.67; p=0.031) alleles, had the greatest frequency. While DRB1*01 frequency was lower (1 percent vs.6 percent; odds ratio, 0.13; p=0.017) in these patients (Table 2).

Of interest, all 10 patients with Lyme borreliosis who had HLA-DRB1*04 were heterozygous at the DR locus. Four had HLA-DRB1*04 and HLA-DRB1*17(03), two had HLA-DRB1*04 and HLA-DRB1*15, one had HLA-DRB1*04 and HLA-DRB1*18(03), and one HLA-DRB1*04 and HLA-DRB1*11.
Table 1. The frequency of DRB1* alleles studied in-patients with LB and healthy controls from Latvia.

| Allele DRB1 Patient (n=38) | Controls (n=100) | OR (95% CI) | p-value | pc-value |
|---------------------------|------------------|-------------|---------|----------|
| DRB1*01                   |                  |             |         |          |
| 12 (6%)                   | 2 (3%)           | 2 (3%)      | 0.42 (0.06-2.07) | 0.207 -- |
| DRB1*02                   |                  |             |         |          |
| 15 (8%)                   | 12 (6%)          | 12 (6%)     | 0.42 (0.06-2.07) | 0.207 -- |
| DRB1*03                   |                  |             |         |          |
| 9 (5%)                    | 3 (4%)           | 3 (4%)      | 0.87 (0.18-3.65) | 0.569 -- |
| DRB1*04                   |                  |             |         |          |
| 9 (5%)                    | 10 (13%)         | 10 (13%)    | 3.22 (1.15-9.07) | 0.011 0.162 |
| DRB1*07                   |                  |             |         |          |
| 15 (8%)                   | 3 (4%)           | 3 (4%)      | 0.51 (0.11-1.94) | 0.217 -- |
| DRB1*08                   |                  |             |         |          |
| 10 (5%)                   | 2 (3%)           | 2 (3%)      | 0.51 (0.08-2.58) | 0.311 -- |
| DRB1*09                   |                  |             |         |          |
| 16 (8%)                   | 2 (3%)           | 2 (3%)      | 0.31 (0.05-1.46) | 0.083 -- |
| DRB1*10                   |                  |             |         |          |
| 15 (8%)                   | 1 (2%)           | 1 (2%)      | 0.16 (0.01-1.22) | 0.036 0.044 |
| DRB1*11                   |                  |             |         |          |
| 21 (11%)                  | 8 (11%)          | 8 (11%)     | 1.00 (0.39-2.53) | 0.831 -- |
| DRB1*12                   |                  |             |         |          |
| 17 (9%)                   | 4 (6%)           | 4 (6%)      | 0.60 (0.16-1.98) | 0.364 -- |
| DRB1*13                   |                  |             |         |          |
| 12 (6%)                   | 10 (13%)         | 10 (13%)    | 2.37 (0.90-6.23) | 0.049 0.055 |
| DRB1*14                   |                  |             |         |          |
| 13 (7%)                   | 6 (8%)           | 6 (8%)      | 1.23 (0.40-3.66) | 0.682 -- |
| DRB1*15                   |                  |             |         |          |
| 12 (6%)                   | 4 (6%)           | 4 (6%)      | 1.87 (0.23-3.04) | 0.537 -- |
| DRB1*16                   |                  |             |         |          |
| 11 (6%)                   | 2 (3%)           | 2 (3%)      | 0.46 (0.07-2.30) | 0.255 -- |
| **DRB1*17 (03)**          |                  |             |         |          |
| 8 (4%)                    | 11 (15%)         | 11 (15%)    | 4.06 (1.44-11.65) | 0.002 0.003 |
| DRB1*18 (03)              |                  |             |         |          |
| 8 (4%)                    | 6 (8%)           | 6 (8%)      | 2.06 (0.61-6.83) | 0.155 -- |

Abbreviations: OR: Odds ratio; CI: Confidence interval; p-value: Probability; pc-value (after Bonferroni adjustment)

Table 2. The frequency of DRB1* alleles studied in-patients with TBE and healthy controls from Latvia.

| Allele DRB1 Patient (n=60) | Controls (n=100) | OR (95% CI) | p-value | pc-value |
|---------------------------|------------------|-------------|---------|----------|
| DRB1*01                   |                  |             |         |          |
| 12 (6%)                   | 1 (2%)           | 1 (2%)      | 0.13 (0.01-0.99) | 0.017 0.240 |
| DRB1*02                   |                  |             |         |          |
| 12 (6%)                   | 8 (7%)           | 8 (7%)      | 1.12 (0.40-3.05) | 0.811 -- |
| DRB1*03                   |                  |             |         |          |
| 9 (5%)                    | 5 (4%)           | 5 (4%)      | 0.92 (0.26-3.11) | 0.887 -- |
| DRB1*04                   |                  |             |         |          |
| 9 (5%)                    | 13 (11%)         | 13 (11%)    | 2.58 (0.99-6.80) | 0.030 0.386 |
| DRB1*07                   |                  |             |         |          |
| 15 (8%)                   | 7 (6%)           | 7 (6%)      | 0.76 (0.27-2.07) | 0.568 -- |
| DRB1*08                   |                  |             |         |          |
| 10 (5%)                   | 4 (4%)           | 4 (4%)      | 0.66 (0.17-2.34) | 0.480 -- |
| DRB1*09                   |                  |             |         |          |
| 16 (8%)                   | 9 (8%)           | 9 (8%)      | 0.93 (0.37-2.33) | 0.871 -- |
| DRB1*10                   |                  |             |         |          |
| 15 (8%)                   | 8 (7%)           | 8 (7%)      | 0.88 (0.33-2.30) | 0.779 -- |
| DRB1*11                   |                  |             |         |          |
| 21 (11%)                  | 8 (7%)           | 8 (7%)      | 0.61 (0.24-1.51) | 0.247 -- |
| DRB1*12                   |                  |             |         |          |
| 17 (9%)                   | 9 (8%)           | 9 (8%)      | 0.87 (0.35-2.16) | 0.751 -- |
| DRB1*13                   |                  |             |         |          |
| 12 (6%)                   | 6 (5%)           | 6 (5%)      | 0.82 (0.27-2.45) | 0.707 -- |
| DRB1*14                   |                  |             |         |          |
| 13 (7%)                   | 9 (8%)           | 9 (8%)      | 1.17 (0.44-3.03) | 0.732 -- |
| DRB1*15                   |                  |             |         |          |
| 12 (6%)                   | 2 (2%)           | 2 (2%)      | 0.27 (0.04-1.28) | 0.066 -- |
| DRB1*16                   |                  |             |         |          |
| 11 (6%)                   | 8 (7%)           | 8 (7%)      | 1.23 (0.44-3.41) | 0.668 -- |
| **DRB1*17 (03)**          |                  |             |         |          |
| 8 (4%)                    | 12 (10%)         | 12 (10%)    | 2.67 (0.98-7.40) | 0.031 0.396 |
| DRB1*18 (03)              |                  |             |         |          |
| 8 (4%)                    | 11 (9%)          | 11 (9%)     | 2.42 (0.87-6.83) | 0.058 -- |

Abbreviations: OR: Odds ratio; CI: Confidence interval; p-value: Probability; pc-value (after Bonferroni adjustment)

two were homozygous and had severe meningoencephalitis. The other 11 patients were heterozygous at the DR locus. Four had HLA-DRB1*04 and HLA-DRB1*18(03), three had HLA-DRB1*04 and HLA-DRB1*17(03) and remaining had HLA-DRB1*04 in association with a different DR alleles. A secondary association was noted with the HLA-DRB1*17(03) allele. This allele was found in 15 percent of the patients with Lyme borreliosis and in 10 percent of the patients with TBE, but in only
4 percent in controls group (Tables 1 and 2). The frequency of HLA-DRB1*17(03) allele was significantly higher among LB patients compared with the control group, than among TBE (odds ratio, 4.06; p=0.002 and odds ratio, 2.67; p=0.031, respectively) (Tables 1 and 2).

Also, the frequency of HLA-DRB1*18(03) tended to be higher among Lyme borreliosis and TBE patients (8 and 9 percent vs. 4 percent; odds ratio, 2.06 and 2.42, respectively) but this difference was not statistically significant (Tables 1 and 2).

In contrast, the allele DRB1*10 (odds ratio, 0.16; p=0.036) was smaller in Lyme borreliosis patients and significantly higher in controls (Table 1). And a different allele - DRB1*01 (odds ratio, 0.13; p=0.017) was smaller in TBE patients and significantly higher in controls (Table 2).

The second step, p values of all detected alleles were exposed to Bonferroni correction (pc), and only frequency of HLA-DRB1*17(03) allele was significantly higher in Latvian patients with Lyme borreliosis, and HLA-DRB1*10 allele was significantly lower in LB patients (Table 1). Among TBE patients all detected HLA-DRB1 differences were not significant after Bonferroni correction (Table 2).

Discussion

Many studies have tried to identify genetic markers for infectious diseases; some of them have focused on HLA [4-6,27,28]. The products of HLA genes interact with surface-specific receptors of T lymphocytes, resulting in activation of the host’s immune response. Association of TBD infections with the host’s HLA has been partially investigated [29,30]. The type and strength of this association differs among distinct populations, as well as among racial and/or ethnic groups [31].

In our HLA study, a strong association was confirmed between Lyme borreliosis and the HLA-DRB1*17(03) (part of the older HLA-DR3). Although, the frequency of HLA-DRB1*04 allele was increased in patients with Lyme borreliosis and Tick-borne encephalitis, but after applying the Bonferroni correction these differences were not significant. Interestingly, the association between Lyme and HLA-DRB1*17(03) was found only in the Latvian population, while the association of HLA-DRB1*04 was confirmed by many authors, in particular Steere A.C. and co-authors [12,13].

One more statistically significant difference was found in patients with Lyme borreliosis. In our study, the frequency of HLA-DRB1*10 allele was significantly lower in Borreliosis patients compared with the control group. Although, many authors have noted HLA-DRB1*11 allele as a possible protective allele [6,12,17].

These results suggest that the high risk for Tick-borne Disease in Latvian associated with the HLA-DRB1*17(03), and perhaps, HLA-DRB1*04 alleles. But, the HLA-DRB1*10 allele seems to have a protective effect in Latvian patients with Lyme borreliosis.

Although this series of 60 patients with Tick-borne encephalitis is the largest tested to date, the number of patients was not large enough to show significant differences between TBE patients and control group in the frequencies of individual alleles.

There are several hypotheses about the HLA/disease association mechanism, and it is possible that this mechanism varies for different diseases. One of the hypotheses attributes a greater or less affinity of HLA for the disease-causing peptide [6,12,36]. Thus, the HLA antigens function as receptors for some etiological agents, by facilitating their entry into the cell or by making such entry difficult. Another possibility would be the early intervention of HLA in the thymic selection of lymphocytes, by determining which antigens will be presented to the T lymphocytes [20,33,37,38]. There is also the hypothesis that there may be a mechanism of tolerance of T cells to these pathogens, through molecular mimicking between antigens of the infectious microorganisms and antigens of the host, thus providing susceptibility or protection against these diseases [32,33]. We reviewed the main associations of the HLA-DR alleles with Lyme borreliosis and Tick-borne encephalitis.

The HLA alleles vary in ethnically different populations [2,8,9]. Studies suggest that the alleles that confer resistance to certain pathogens are prevalent in areas where they cause endemic diseases. Greater resistance to infectious diseases occurs in persons that are heterozygote for specific HLA alleles, because a heterozygous person would have a broader spectrum of peptides to link to the T lymphocytes [11,13,35]. These alleles also vary from one disease to another, due to the differences in their pathogenesis [34]. In our study, only two patients with TBE who had HLA-DRB1*04, were homozygous and had severe meningoencephalitis. The diversity of these results is probably due to environmental influences, in addition, possible differences among ethnic group’s populations [9].

Genetic studies of infectious diseases not only help us to gain a better understanding of the pathogenic mechanisms of diseases, they may also help with the development of vaccines.

One of the advantages of polymorphism of the HLA region, apparently to avoid deficiencies in efficient immune response to against a specific infectious agent [34]. Susceptibility to an infectious disease may be due to imperfections in some stages of this system. A person that has a certain combination of HLA alleles that do not link in an appropriate manner to the peptide, or whose HLA-peptide link does not elicit an adequate response from the lymphocytes, will be less apt to resist the invasion of the infectious agent than a person who does not have these deficiencies [34]. In patients in whom HLA provides protection, these genes probably select and stimulate T cells that multiply and eliminate the invading agent, through the production of inflammatory cytokines or by destroying the infected cells themselves [35].

Conclusions

HLA predisposition to Lyme borreliosis and Tick-borne encephalitis appears not to be limited to HLA-DR, but some alleles
also have a significant influence. In our study, the HLA-DRB1*17(03) (odds ratio, 4.06; pc=0.003), HLA-DRB1*04 (odds ratio, 3.22; pc=0.162), and HLA-DRB1*13 (odds ratio, 2.37; pc=0.055) alleles contribute significantly to a genetic predisposition Lyme borreliosis in Latvian population, but, the HLA-DRB1*10 allele (odds ratio, 0.16; pc=0.044) could be associated with a potential protective effect. Among TBE patients the HLA-DRB1*01 (odds ratio, 0.13; pc=0.240) was lower in patients, but these differences were not significant after Bonferroni correction.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions

| Authors’ contributions | LK | JE | MZ | IL1 | IL2 | GK | LV | AK |
|------------------------|----|----|----|-----|-----|----|----|----|
| Research concept and design | -- | -- | -- | -- | -- | -- | -- | ✓ |
| Collection and/or assembly of data | -- | -- | ✓ | ✓ | ✓ | -- | -- | -- |
| Data analysis and interpretation | ✓ | -- | -- | -- | -- | -- | -- | -- |
| Writing the article | ✓ | -- | -- | -- | -- | -- | -- | -- |
| Critical revision of the article | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | -- | -- |
| Final approval of article | -- | -- | -- | -- | -- | -- | -- | -- |
| Statistical analysis | -- | ✓ | -- | -- | -- | -- | -- | -- |

Acknowledgement and funding
This work was supported by Riga Stradiņš University grant 09.1604 and the European Social Fund (ESF) project “Support for doctoral study program and scientific degree receiving in Riga Stradiņš University, agreement No. 2009/0147/1DP/1.1.2.1.2/09/IPIA/VIAA/009”.

Publication history
Editors: Farzin Roohvand, Pasteur Institute of Iran, Iran. Gyanendra Singh, LSU Health Sciences Center, USA. EIC: IShitqia Qadri, King Abdul Aziz University, Saudi Arabia. Received: 15-Jun-2014 Final Revised: 29-Aug-2014 Accepted: 08-Oct-2014 Published: 15-Oct-2014

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Citation:
Kovalchuka L, Eglite J, Zalite M, Lucenko I, Logina I, 
Karelis G, Viksna I and Krumina A. The frequency of HLA-DR alleles in patients with tick-borne 
disease from Latvia. *Res J Infect Dis.* 2014; 2:4. 
http://dx.doi.org/10.7243/2052-5958-2-4