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IMMUNOGENETIC MANIFESTATIONS OF LYME BORRELIOSIS

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In this study, we sought to identify human leukocyte antigen (HLA) DRB1 *alleles that might be associated with Lyme borreliosis in Latvian patients. Case patients and control subjects were similar in age, sex, and ethnic heritage and differed only in the presence of* Borrelia burgdorferi *infection. The frequency of* HLA-DRB1*07 *(OR 3.52; p = 0.001),* HLA-DRB1*15 *(OR 3.02; p = 0.001) and HLA-DRB1 *17 (03) (OR 2.63; p = 0.001) were significantly increased in the Lyme disease patients compared with the control groups. The frequency of the alleles* -DRB1*11*(OR 0.37; p = 0.005) and* -DRB1*13 *(OR 0.34; p = 0.002) was smaller in* Borreliosis *patients and significantly higher in the control group.*

Key words: *Lyme borreliosis, HLA alleles, PCR-SSP.*

INTRODUCTION

Lyme borreliosis is a tick-borne infection caused by the spirochete *Borrelia burgdorferi* (Nadelman, 2001; Wormser, 2006). At least three species of *Borrelia burgdorferi* sensu lato (*Borrelia burgdorferi* sensu stricto, *Borrelia garinii*, and *Borrelia afzelii*) can cause the disease.

Lyme disease is the most common vector-borne disease in the United States and Europe, and its incidence is also high in Latvia (Piacentino, 2002; Anonymous, 2014). During the last five years (2010–2014), morbidity of Lyme borreliosis in Latvia varied from 39.5 to 23.5 per 100 000 inhabitants (829 to 469 people per year) (Table 1). The largest number of cases of Lyme borreliosis was recorded in 2011 — 866 infected persons (Table 1). Latvia is considered to be an endemic territory for diseases, but people may become affected in other countries of the world.

In Europe, Lyme disease is caused by infection by one or more pathogenic European genospecies of the spirochaete *B. burgdorferi* sensu lato, mainly transmitted by the tick *Ixodes ricinus* (Piacentino, 2002; Anonymous, 2014). Cases of *B. burgdorferi* sensu lato-infected ticks are found predominantly in central Europe, particularly in Slovenia and Austria, but have been isolated in almost every country on the continent (Piacentino, 2002; Anonymous, 2014). Incidence in southern Europe, Italy and Portugal, for example, is much lower (Piacentino, 2002; Anonymous, 2014). The incidence in children was shown to be higher than in adults in European studies (Piacentino, 2002).

Table 1

NUMBER OF BORRELIOSIS CASES (PER 100 000 INHABITANTS AND ABSOLUTE COUNT) IN LATVIA AS REPORTED TO THE CENTER OF DISEASE PREVENTION AND CONTROL (CDPC) OF LATVIA

Years	2010	2011	2012	2013	2014
Latvia, absolute count	829	866	724	454	469
Latvia, per 100 000 inhabitants	39.5	42.0	35.6	22.6	23.5

The disease usually begins with erythema migrans accompanied by viral-like or meningitis-like symptoms. A week later, meningitis, facial palsy, atrioventricular nodal block, or migratory musculoskeletal pain may develop, followed months to years later by episodes of frank arthritis, encephalopathy, polyneuropathy, or acrodermatitis (Abramowicz, 2000; Auwaerter, 2004; Fleming, 2004; Auwaerter, 2007).

Musculoskeletal and neurologic sequelae may occur from Lyme disease. Some of the late consequences of Lyme disease, such as oligoarticular arthritis, axonal polyneuropathy, or active encephalopathy, are thought to be caused by persistent spirochetal infection and are amenable to antibiotic treatment (Halperin, 2003; Wormser, 2003; Coulter *et al.*, 2004; Halperin, 2004). Other syndromes such as persistent arthritis, fibromyalgia, subtle joint pain, or mild encephalopathy do not improve with antibiotic treatment, suggesting a mechanism other than active infection (Fleming, 2004; Feder, 2007; Halperin, 2007).

The majority of individuals with treatment-resistant Lyme disease have the *HLA-DRB1*0401* or *HLA-DRB1*0101* allele, alleles which also occur more frequently in patients with rheumatoid arthritis (Philipp, 2005; Feder, 2007; Oksi, 2007). Furthermore, while *Borrelia burgdorferi* DNA can be detected in joint fluid of Lyme disease patients by PCR prior to treatment with antibiotics, it is unusual to detect such DNA in synovium or synovial fluid after antibiotic treatment (Bateman, 2000; Qureshi, 2002). These findings suggest that the pathogenesis of joint disease in chronic Lyme arthritis may be a result of antibody directed against a component of the B. burgdorferi spirochete that cross-reacts with synovial tissue.

B. burgdorferi sensu lato is a Gram-negative spirochete. The molecular typing of *B. burgdorferi* has been recently reviewed in detail (Bunikis, 2002). While all three species occur in Europe, only *B. burgdorferi* sensu stricto occurs in the United States. It has been suggested that the different clinical manifestations were caused by distinct species of *B. burgdorferi* sensu lato. Based on DNA amplification, the late dermatologic manifestation acrodermatitis chronica atrophicans (ACA), which is observed in Europe but rarely in the United States, was mostly associated with *B. afzelii* (Nadelman, 2001; Wormser, 2000). Neuroborreliosis is frequently but not exclusively caused by *B. garinii* (Halperin, 2003; Halperin, 2005), and all three species have been detected in synovial fluid samples from patients with Lyme arthritis (Steere, 2001; Steere, 2003; Steere, 2006; Stricker, 2007). The first suggestion that antibiotic-refractory Lyme arthritis might have an autoimmune component was the demonstration of its association with the *HLA–DR4* and *HLA–DR2* alleles (Steere, 2003). Patients who have *HLA–DR4* and *HLA–DR2* molecules, which bind an epitope of *B. burgdorferi* outer surface protein A (OspA163–175), are more likely to have antibiotic-refractory arthritis than the patients with other *DRB* molecules (Sikand, 2001). Molecular techniques have identified the OspA163–175-binding molecules as the rheumatoid arthritis alleles (*DRB1*0401, 0404, 0405, 0101, 0102*) (Steere, 2006; Wormser, 2006) and the *DRB5*0101* allele linked to *DRB1*1501* (the former *DR2* allele) (Steere, 2006). Moreover, patients with antibiotic-refractory arthritis often have T cell recognition of OspA163–175 (Steere, 2006; Wormser, 2006). Many autoimmune diseases are linked to variants of *HLA* genes such as those encoding the MHC class II complex. Antibiotic-refractory Lyme arthritis is associated with MHC class II variants that are able to bind to fragments of the *B. burgdorferi* protein OspA (outer surface protein A) encompassing amino acid residues 165 through 173 (Schoen, 2000). Antigen-presenting cells whose MHC class II molecules display OspA163–175 peptides on their surface stimulate T cells that recognize the OspA peptide. How OspA163–175-reactive T cells cause autoimmunity has been an area of intensive research, yet no clear answer has emerged (Schoen, 2000).

The purpose of this study was to identify immunogenetic markers of *HLA DRB1* in patients with clinical, epidemiological and laboratory approved Lyme borreliosis.

MATERIALS AND METHODS

DNA samples were obtained from 145 patients (58 males and 87 females; aged between 35 and 74 years) with the clinical stage of *erythema migrans* and 200 control (healthy) persons (92 males and 108 females; aged between 21 and 57 years). The clinical diagnosis was confirmed at the Infectology Centre of Latvia. Immunogenetic examinations were performed at the Rīga Stradiņš University Clinical Immunology and Immunogenetic Laboratory. Approval of the Rīga Stradiņš University Ethics Committee was obtained to perform this study, each participant signed an informed consent to participation in this study.

Genomic DNA was extracted from proteinase-K-treated peripheral blood leukocytes using the routine "salting-out" method (Halperin, 2005; Halperin *et al.,* 2007). The DNA was stored in TE buffer (10 ml Tris–HCl, pH 7.5, and 2 ml 0.5M Na^2 EDTA per litre of distilled water). The DNA concentration (about 100–200 μg/ml in most samples), was determined using a fluorospectrometer NanoDrop 3300 (USA).

***HLA*-typing.** *HLA-DR* genotyping for *DRB1* 01* to **18*, was performed by PCR with sequence-specific primers (PCR–SSP) (Klitz, 2003). The reaction mixture (15 μl) included 1.0 μl DNA, 1.5 μl PCR buffer [50 mM KCl, 1.5 mM MgCl2, 10 mM Tris-HCl (pH 8.3)], 0.6 μl dNTPs (25 mmol/l), 1.0 μl specific primers (0.2 mmol/l), and 0.5 U of the *Taq* DNA polymerase (Promega). The reaction mixture was subjected to 35 amplification cycles, each consisting of one denaturation cycle at 94°C (60 s), seven annealing cycles at 94 °C (40 s) and 67 °C (15 s), and final 28 extension cycles at 93 °C (10 s) and 65 °C (9 s). PCR products were visualised by agarose-gel electrophoresis (Olerup, 1993; Klitz, 2003). After addition of 2 M loading buffer, the PCR reaction mixtures were loaded in agarose gels pre-stained with ethidium bromide (0.5 μk/ml). Gels were run for 15 min at 10 V/cm gel in 0.5 mM TBE (0.89 M Tris, 0.89 M boric acid and 0.02 M EDTA in aqueous solution) buffer and then examined under UV illumination and recorded (Olerup, 1993; Klitz, 2003).

Statistical analysis. The significance of differences in individual subtypes between patients and controls was assessed

by Mantel–Haenszel test and Fisher exact correction. Odds ratios (OR), and 95% confidence intervals (CI) were computed by standard methods (Anonymous, 2012).

RESULTS

Typing of all sixteen alleles *DRB1* was conducted (Table 2). Predisposition to Lyme disease_was associated with the *HLA-DRB1*07* (OR 3.52; $p = 0.001$), *HLA-DRB1*15*(OR 3.02; $p = 0.001$) and *HLA-DRB1 *17*(03) (OR 2.63; $p = 0.001$) alleles (Table 2). For the *DRB1 *02* and *DRB1 *04* alleles, the evidence is controversial. The presence of *DRB1 *02* and *DRB1 *04* alleles in healthy persons and borreliosis patients suggests lack of an association with Lyme disease. However, the number of studied individuals was very low. The distribution of alleles in the patients included in this study followed the global patterns: *HLA-DRB1 *04* and *DRB1 *17(03)* are the most frequent alleles in the Caucasian population. The *HLA-DRB1*01*, and *DRB1*18(03)* alleles were shown to be considerably increased in patients, although the difference was not significant when the p value was corrected for the number of alleles (Table 2). Moreover, the allele *-DRB1*11*(OR 0.37; $p = 0.005$) and *-DRB1*13* (OR 0.34; $p = 0.002$) was rarer in Borreliosis patients and significantly more frequent in controls.

This data suggest that *HLA-DRB1* alleles may have a considerable effect by susceptibility to Lyme borreliosis.

Table 2

THE FREQUENCY OF DRB1* ALLELES STUDIED IN PATIENTS WITH LYME BORRELIOSIS AND HEALTHY CONTROLS FROM LATVIA

Allele *DRB1*	Patients (n = 145); alleles 290	Controls (n = 200); alleles 400	OR (95% CI)	*p*
*01	28	31	1.27 [0.72–2.24]	0.377
*02	18	13	1.97 [0.90–4.34]	0.064
*03	19	29	0.90 [0.47–1.70]	0.721
*04	23	19	1.73 [0.88–3.38]	0.084
***07**	35	15	**3.52 [1.82–6.91]**	**0.001**
*08	11	28	0.52 [0.24–1.12]	0.071
*09	9	29	0.41 [0.18–0.92]	0.018
*10	14	26	0.51 [0.26–1.01]	0.056
***11**	10	35	**0.37 [0.17–0.88]**	**0.005**
*12	11	29	0.50 [0.23–1.07]	0.055
***13**	10	38	**0.34 [0.16–0.72]**	**0.002**
*14	16	37	0.57 [0.30–1.09]	0.069
***15**	38	19	**3.02 [1.65–5.58]**	**0.001**
*16	5	12	0.57 [0.17–1.76]	0.285
***17(03)**	32	18	**2.63 [1.40–5.00]**	**0.001**
*18(03)	11	12	1.27 [0.52–3.14]	0.566

ND, not defined; OR, odds ratio, p, probability, significant associations for $p < 0.05$. Bold-face type highlights statistically significant associations for patients vs controls.

DISCUSSION

Numerous studies have established an association of *HLA-DR* alleles with infectious and autoimmune diseases (Klitz, 2003). The various *HLA-DR* alleles, which are expressed on thymic epithelial cells, as well as on antigen presenting cells, have different peptide-binding requirements. The ability of the *HLA-DR* alleles to accommodate self- or disease-associated peptides depends on the properties of the respective peptide-binding groove (Smith, 2002). Therefore, the immune response against infectious agents, as well as susceptibility to autoimmune diseases, varies from one individual to another.

In our *HLA* study, an association was confirmed between Lyme borreliosis and the *HLA-DRB1 *07*, and *-DRB1 *17(03)* (part of the former *HLA-DR3*) alleles. Secondary association was noted with *HLA-DRB1 *15* (part of the former *HLA-DR2* and *DR5* serotype groups). The distribution of alleles in the patients included in this study follows the global pattern: *HLA-DRB1 *07* and DRB1 **17(03)* were the most frequent alleles in the Caucasian population (Kotsch, 1999).

One potential pathway to autoimmunity is molecular mimicry, in which a cross-reactive host protein in the joint continues to stimulate OspA163–175-specific T cells even after the eradication of *B. burgdorferi* by antibiotics (Smith, 2002; Klitz, 2003; Steere, 2006). Although the simplicity of the molecular mimicry model is appealing, exhaustive efforts to find a cross-reactive autoantigen that stimulates OspA163–175-specific T cells have failed (Smith, 2002; Steere 2006). Moreover, levels of OspA163–175-reactive T cells decline soon after initiation of antibiotic therapy despite continuing arthritis following treatment.

Thus, chronic arthritis does not seem to involve molecular mimicry driven by a cross reaction between the OspA163–175 epitope and a self-antigen in the joint. It is possible that molecular mimicry involves another *B. burgdorferi* antigen that is able to bind the MHC class II variants found in genetically susceptible individuals.

Numerous studies from USA and our HLA studies have shown that *HLA-DRB1*15* and *-DRB1*0401* alleles are associated with chronic Lyme arthritis and lack of response to antibiotic therapy (Steere, 2003; Auwaerter, 2007). This allele is also associated with an increased risk of developing severe rheumatoid arthritis (Hu, 2005). In a study of antibody responses in patients throughout the course of Lyme disease, immunoglobulin G (IgG) responses to outer-surface protein A (OspA) and OspB of the spirochete often developed near the beginning of prolonged episodes of arthritis (Steere, 2003, 2006; Fallon, 2008). Arthritis lasted considerably longer after treatment in patients with *HLA-DR4* and OspA and OspB antibody reactivity than in those who lacked responses to these proteins (Seltzer, 2000; Nowakowski, 2003). Persons with treatment-resistant Lyme arthritis usually have T cells that react with many OspA epitopes, whereas treatment-responsive patients usually do not. A possible explanation for these findings is that the

T-cell response to OspA in patients with treatment-resistant Lyme arthritis may cross-react with a self antigen in the joint, and the response to this self antigen may continue to cause joint inflammation for months or even years after the eradication of the spirochete from the joint.

Treatment for patients with acute manifestations of Lyme disease is well established and effective. Understanding the pathophysiology of chronic neuroborreliosis and treatment-resistant Lyme arthritis are both major challenges and a prerequisite for the eventual development of effective treatments for these conditions.

The development of an effective vaccine against Lyme disease and the improved understanding of the long-term outcome of Lyme disease can be considered the most important advances in the field over the past several years.

CONCLUSIONS

In this study, we sought to identify *HLA DRB1* alleles that might be associated with Lyme borreliosis in Latvian patients. The inflammatory events of the subacute arthritis can set the stage for development of chronic disease in individuals possessing an *HLA* susceptibility allele. In particular, *HLA-DRB1*07* (OR 3.52; $p = 0.001$), *HLA-DRB1*15* (OR 3.02; $p = 0.001$) and *-DRB1 *17* (03) (OR 2.63; $p = 0.001$) contribute definitely to a genetic predisposition to *Borrelia burgdorferi* infection in the Latvian population, which may have implications in our understanding of pathogenesis of this disease. The frequency of *HLA-DRB1 *02* (OR 1.97; $p = 0.064$); and *HLA-DRB1 *04* (OR 1.73; $p = 0.084$) was increased in the Lyme disease patients compared with the control group. Moreover, the allele *-DRB1*11*(OR 0.37; $p = 0.005$) and *-DRB1*13* (OR 0.34; $p = 0.002$) was rarer in Borreliosis patients and significantly more frequent in controls.

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IMŪNĢENĒTISKĀS IZPAUSMES LAIMBORELIOZES GADĪJUMĀ

Šajā pētījumā mēs noteicām *HLA DRB1 Lyme borreliosis* (LB) pacientiem Latvijā. Pētījuma grupa un kontroles grupa tika atlasītas un sadalītas līdzīgi pēc vecuma, dzimuma, etniskās piederības un atšķīrās ar *Borrelia burgdorferi* klātbūtni. *HLA-DRB1*07* (OR 3.52; p = 0.001), *HLA-DRB1*15* (OR 3.02; p = 0.001) un *HLA-DRB1 *17* (03) (OR 2.63; p = 0.001) sastopamības biežums bija ievērojami lielāks LB pacientiem nekā kontroles grupai. Alēles *DRB1*11* (OR 0.37; p = 0.005) un *DRB1*13* (OR 0.34; p = 0.002) bija retāk LB pacientiem un ievērojami vairāk kontroles grupai.