Autoimmunity Reviews 18 (2019) 558–560

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Influence of HLA-DRB1 susceptibility alleles on the autoantibodies spectrum of systemic lupus erythematosus in European part of Russia

ARTICLE INFO

Keywords:
HLA-DRB1
Systemic lupus erythematosus

Both systemic lupus erythematosus (SLE) and APS (antiphospholipid syndrome) are associated with HLA-DRB1 polymorphisms [1]. Our objective was to investigate whether these or other genetic variants in the HLA-DRB1 region are associated with specific autoantibody production in SLE and secondary APS in the European part of Russia.

We collected the clinical data and sera samples from patients with systemic lupus erythematosus and healthy donors. The mean age of 115 SLE patients (105 females and 10 males) and 1940 healthy controls (1315 females and 625 males) was 43 and 31 years, respectively. In SLE group 42% of patients had deep vein thrombosis (DVT) or/and arterial thrombosis (AT). Genotyping of HLA-DRB1 was performed by a polymerase chain reaction technique using the sequence-specific primer method (DNA Technology Research&Production, LLC, Moscow, Russia) according to the manufacturer's instructions.

Analysis of the healthy population frequency of HLA-DRB1 genes in European Part of Russia showed that the allelic genes HLA-DRB * 15, HLA-DRB * 07, HLA-DRB * 13, HLA-DRB * 11, HLA-DRB1 * 01 were more common. In group of patients with SLE HLA-DRB1 * 15 occur in 17,39% (n = 40) patients, of which 2,2% were homozygotes (n = 5), and DRB1 * 03 – in 16,52% (n = 38), of which 0.4% - homozygotes (n = 1), DRB1 * 07 - in 13,47% (n = 31), of which 0,8% (n = 2) homozygotes, DRB * 11 - in 12,6% (n = 29). According to our data, only DRB1 * 03 showed a statistically significant association with SLE morbidity in comparison with the control group (p < 0,0001, OR 2172) (Table 1).

Then, we analyzed the differences in the profile of autoantibodies in patients with SLE with different allelic variants. The allelic variants DRB1*03 (*03/*03 or *03/*X) and DRB1*15 (*15/*15 or *15/*X) associated with antibodies to Ro52 and SSa60. The genotype DRB1 * 07 (* 07/* 07 or * 07/X) showed an increased risk for the synthesis of antibodies to double-stranded DNA (p = .0027), antibodies to histones (p = .01), antibodies to nucleosomes (p = .005). Then an association between aPL and the HLA-DRB1 alleles was investigated. Patients with SLE and positive antiphospholipid antibodies were associated with HLA-DRB1*04 (p = 0,0364, OR = 2821). HLA-DRB1*15 was more frequent in aPLs negative patients (p = 0,0106, OR = 3654). In our cohort, HLA-DRB1*04 was associated with most of aPLs specificities (aB2GP1 IgG, aCL IgG and IgM) but not with positive test for LAC. HLA-DRB1*13 was associated with IgG and IgM antibodies against β2GP-1 (Table 2).

We have studied the contribution of HLA-DRB1 alleles to disease susceptibility using a collection of SLE patients (N = 115) and a large control cohort (N = 1940). In European/Caucasian SLE patients, the HLA-DR3 serotype (or HLA-DRB1*03:01 for genotype) and DR2 (DRB1*15:01) have been associated with disease risk [2]. In our cohort, only DRB1 * 03, but not DRB1*15 showed a statistically significant association with SLE in comparison with the control group.

One hundred and eighty autoantibodies were so far described in SLE patients [3]. Josef S. Smolen and all. in 1987 published one of the first papers dedicated to association of antinuclear autoantibodies and HLA-DR antigens [4]. They showed that HLA-DR3 was related to the presence of anti-Ro/SSA or anti-La/SSB, and anti-Sm or antiRNP, or both were associated with HLA-DR4. The association of anti-Ro and/or anti-La antibodies with HLA-DR3 and/or HLA-DR2 was found in several studies [5,6]. In our study we also found a link between the allelic variants DRB1*03 (*03/*03 or *03/*X) and DRB1*15 (*15/*15 or *15/*X) with antibodies to Ro52 and SSa60.

Anti-dsDNA antibodies have been included in the 1982 American College of Rheumatology (ACR) revised criteria for the classification of SLE and in the 1997 update of the criteria for the classification of SLE. Since 1998, Podrebarac and all. in 1998 described the association between anti-dsDNA production and the presence of HLA-DRB1*1501 (DR2) allele [7]. In recent times, the link between HLA-DRB1*1501 and HLA-DRB1*03 with the presence of anti-dsDNA has been established by several studies. In the present study, we found that the genotype DRB1*07 (*07/*07 or *07/X) showed an increased risk for the synthesis of antibodies to double-stranded DNA (p = .0027), antibodies to histones, antibodies to nucleosomes. DRB1*07 allele is significantly associated with South Indian, Mexican, Hungarian, Egyptian and Korean SLE patients [8,9]. But none of the studies described the same autoantibodies associations. In the Hungarian SLE and in the Egyptian study patients the *07 allele was detected more frequently in the patients with one or more severe renal manifestations. In the Koreans HLA-DRB1 *07:01 were strongly associated with the risk of anti-Sm antibody production.

In SLE and in the primary antiphospholipid syndrome (PAPS), aPL occurrence has previously been associated with HLA-DRB1 genotypes, in particular with HLA-DRB1*04 and HLA-DRB1*13 and in a few studies with HLA-DRB1*07 [10,11]. It has been suggested that HLA-DRB1*04 and HLA-DRB1*13 is protect allele from development of SLE [12,13]. Despite that fact, it was strongly associated with vascular

https://doi.org/10.1016/j.autrev.2019.03.013
Received 8 January 2019; Accepted 12 January 2019
Available online 04 March 2019

Table 1
Number of positive HLA-DRB1 allele carriers in systemic lupus erythematosus (SLE) patients from the SLE groups versus controls.

Allelic genes HLA-DRB1	SLE (n = 115)	Control (n = 1940)	P-value	OR [95% CI]
*01	21 (9,13%)	488 (12,58%)	0,1502	0,6984 [0,4415 to 1105]
*03	38 (16,52%)	324 (8,35%)	< 0,0001	2172 [1506 to 3133]
*04	24 (10,43%)	405 (10,43%)	0,9129	0,9996 [0,6469 to 1545]
*07	31 (13,47%)	535 (13,78%)	0,9727	0,9740 [0,6598 to 1438]
*08	10 (4,34%)	147 (3,78%)	0,8004	1154 [0,5996 to 2222]
*09	1 (0,43%)	74 (1,9%)	0,1715	0,2246 [0,03107 to 1624]
*10	0	44 (1,13%)	0,1957	0,187 [0,01147 to 3048]
*11	29 (12,6%)	472 (12,16%)	0,9234	1042 [0,6975 to 1556]
*12	4 (1,73%)	93 (2,4%)	0,6782	0,7207 [0,2625 to 1979]
*13	22 (9,56%)	494 (12,73%)	0,1916	0,725 [0,4625 to 1136]
*14	0	66 (1,7%)	0,0847	0,1244 [0,007673 to 2018]
*15	40 (17,39%)	602 (15,52%)	0,5042	1146 [0,8062 to 1630]
*16	6 (2,61%)	152 (3,92%)	0,4085	0,6570 [0,2873 to 1502]

Notes: HLA: human leukocyte antigen; SLE: systemic lupus erythematosus; OR: odds ratio; CI: confidence interval; $p < .05$ was considered to be statistically significant.

Table 2
Associations between antinuclear and antiphospholipid antibodies antibodies and HLA-DRB1*03, HLA-DRB1*04, HLA-DRB1*07, HLA-DRB1*13, HLA-DRB1*15 among patients with systemic lupus erythematosus.

	DRB1*03/DRB1*X (n = 38)		DRB1*04/DRB1*X (n = 24)		DRB1*07/DRB1*X (n = 31)		DRB1*13/DRB1*X (n = 22)		DRB1*15/DRB1*X (n = 40)	
	N (%)	P Value	N (%)	p Value	N (%)	p Value	N (%)	p Value	N (%)	p Value
aDsDNA	18(47%)	0,2061	5 (20%)	0,3339	17(54%)**	0,0027	12(54%)	0,0936	16(40%)	0,1157
aHistone	5(13%)	1000	2(8%)	0,7523	8(25%)*	0,01	6(27%)*	0,0293	4(10%)	10,000
aNucleosome	9(23%)	0,072	3(12,5%)	0,7745	10(32%)**	0,005	5(22%)	0,5464	9(22%)	0,1396
aRo 52	18(47%)*	0,0198	3 (12,5%)	0,3956	9(29%)	0,8246	7(31%)	0,6113	16(40%)*	0,0111
aSSa 60	18(47%)**	< 0,0001	2(8%)	0,2714	7(22%)	10,000	7(31%)	0,437	16(40%)**	0,0045
aRNP/Sm	6(15%)	1000	3 (12,5%)	0,9135	5(16%)	0,78	7(31%)*	0,025	7(17,5%)	0,3118
aβ2GP1 IgG	9 (23,6%)	0,841	11 (45%)*	0,0295	10 (32%)	0,157	12(54%)**	0,0039	6(15%)	0,0637
aβ2GP1 IgM	8 (21%)	0,6474	7 (29%)	0,163	4 (13%)	0,79	8 (36%)*	0,0437	7 (17,5%)	0,0637
aCL IgG	9(23,6%)	0,3606	10 (41%)*	0,0399	11 (35,4%)	0,02	9 (40%)	0,056	4(10%)	10,000
aCL IgM	7(18,4%)	1000	10 (41%)*	0,0164	7(22,5%)	1342	8 (36%)	0,09	5(12,5%)	0,5794
LAC	12(31,5%)	0.0368	10 (41%)	0,2384	9 (29%)	0,66	10 (45%)	0,13	6(15%)	0,2229

Notes: aDsDNA – antibodies to dsDNA, aHIstone – antibodies to histones, aNucleosome – antibodies to nucleosomes, aRo52 – antibodies to Ro-52, aSSa60 – antibodies to SSa60, aRNP/Sm – antibodies to RNP/Sm, aβ2GP1 – antibodies to beta2-glycoprotein 1, aCL – antibodies to cardiolipins, LAC – lupus anticoagulant, $p < .05$ was considered to be statistically significant.

events and with aPL among SLE patients in most of the studies [14,15]. HLA-DRB1*04 is associated with cardiovascular events both in rheumatoid arthritis and in SLE. The positive associations between HLA-DRB1*04/*13 and aPL suggest that aPL is one of tunderlying mechanisms, which contributes to vascular vulnerability among carriers of these genotypes. We confirm the association between the HLA-DRB1*04, HLA-DRB1*13 for aPL especially for aB2GP1 IgG. Also we analyzed patients with SLE and APS and patients with SLE – carriers of aPLs separately. Interestingly, for SLE-APS found association for HLA-DRB1*13, but not for HLA- DRB1*04. HLA-DRB*04 were associated with aPLs carriers.

To conclude, we demonstrate that SLE and secondary APS in European part of Russia has been associatedwith HLA-DRB1*03. We found a link between the allelic variants DRB1*03 (*03/*03 or *03/*X) and DRB1*15 (*15/*15 or *15/*X) with antibodies to Ro52 and SSa60, DRB1*07 - with antibodies to dsDNA, nucleosomes and histones. Presence of the risk alleles, HLA-DRB1*04 and HLA-DRB1*13, was associated with increased risk for synthesis of antiphospholipid antibodies and cardiovascular events.

Funding

This work is supported by the grant of the Government of the Russian Federation for the state support of scientific research carried out under the supervision of leading scientists, agreement 14.W03.31.0009.

References

[1] Arango MT, Perricone C, Kivity S, et al. HLA-DRB1 the notorious gene in the mosaic of autoimmunity. Immunol Res 2017. https://doi.org/10.1007/s12026-016-8817-7.
[2] Graham RR, Ortmann W, Rodine P, et al. Specific combinations of HLA-DR2 and DR3 class II haplotypes contribute graded risk for disease susceptibility and autoantibodies in human SLE. Eur J Hum Genet 2007;15(8):823–30. https://doi.org/10.1038/sj.ejhg.5201827.
[3] Yaniv G, Twig G, Shor DBA, et al. A volcanic explosion of autoantibodies in systemic lupus erythematosus: a diversity of 180 different antibodies found in SLE patients. Autoimmun Rev 2015. https://doi.org/10.1016/j.autrev.2014.10.003.
[4] Smolen JS, Klippel JH, Penner E, et al. HLA-DR antigens in systemic lupus erythematosus: association with specificity of autoantibody responses to nuclear antigens. Ann Rheum Dis 1987;46(6):457–62. https://doi.org/10.1136/ard.46.6.457.
[5] Hamilton RG, Harley JB, Bias WB, et al. Two ro (ss-a) autoantibody responses in systemic lupus erythematosus. Arthritis Rheum 1988;31(4):496–505. https://doi.org/10.1002/art.1780310406.
[6] Gottenberg J-E, Busson M, Loiseau P, et al. In primary Sjögren's syndrome, HLA class II is associated exclusively with autoantibody production and spreading of the autoimmune response. Arthritis Rheum 2003;48(8):2240–5. https://doi.org/10.1002/art.11103.
[7] Podrebarac TA, Boisert DM, Goldstein R. Clinical correlates, serum autoantibodies and the role of the major histocompatibility complex in French Canadian and non-French Canadian Caucasians with SLE. Lupus 1998;7(3):183–91. https://doi.org/10.1191/096120398678919976.
[8] Bang SY, Choi JY, Park S, et al. Brief report: influence of HLA-DRB1 susceptibility alleles on the clinical subphenotypes of systemic lupus erythematosus in Koreans. Arthritis Rheumatol 2016;68(5):1190–6. https://doi.org/10.1002/art.39539.
[9] Granados J, Vargas-Alarcón G, Andrade F, Melin-Aldana H, Alcocer-Varela J, Alarcón-Segovia D. The role of HLA-DR alleles and complotypes through the ethnic barrier in systemic lupus erythematosus in Mexicans. Lupus. 1996;5(3):184–9. https://doi.org/10.1177/096120339600500304.
[10] Lundström E, Gustafsson JT, Jönsen A, et al. HLA-DRB1*04/*13 alleles are

associated with vascular disease and antiphospholipid antibodies in systemic lupus erythematosus. Ann Rheum Dis 2013;72(6):1018–25. https://doi.org/10.1136/annrheumdis-2012-201760.
[11] Shoenfeld Y, Twig G, Katz U, Sherer Y. Autoantibody explosion in antiphospholipid syndrome. J Autoimmun 2008. https://doi.org/10.1016/j.jaut.2007.11.011.
[12] E.D.R. G, A. F-N, J. S, et al. HLA class II DNA typing in a large series of European patients with systemic lupus erythematosus: correlations with clinical and autoantibody subsets. Medicine (Baltimore) 2002;81(3):169–78.
[13] Furukawa H, Oka S, Tsuchiya N, et al. The role of common protective alleles HLA-DRB1∗13 among systemic autoimmune diseases. Genes Immun 2017;18(1):1–7. https://doi.org/10.1038/gene.2016.40.
[14] Farragher TM, Goodson NJ, Naseem H, et al. Association of the HLA-DRB1 gene with premature death, particularly from cardiovascular disease, in patients with rheumatoid arthritis and inflammatory polyarthritis. Arthritis Rheum 2008;58(2):359–69. https://doi.org/10.1002/art.23149.
[15] Gonzalez-Gay MA, Gonzalez-Juanatey C, Lopez-Diaz MJ, et al. HLA-DRB1 and persistent chronic inflammation contribute to cardiovascular events and cardiovascular mortality in patients with rheumatoid arthritis. Arthritis Rheum 2007;57(1):125–32. https://doi.org/10.1002/art.22482.

Olga Tkachenko[a,*], Sergey Lapin[a], Alexey Maslyansky[b], Valentina Myachikova[b], Veronika Guseva[a], Elizaveta Belolipetskaia[c], Irina Belyaeva[c], Vladimir Mazurov[c], Nadezhda Ivanova[d], Liya Mikhailova[a,e], Boris Gilburd[e,f,g]

[a] *Center for Molecular Medicine, First Pavlov State Medical University of St. Peterburg, Saint Petersburg, Russia*
[b] *Rheumatology Department, V.A. Almazov North-West Federal Medical Research Center, Saint Petersburg, Russia*
[c] *North-Western State Medical University named after I. I. Mechnikov, Saint Petersburg, Russia*
[d] *Raisa Gorbacheva Memorial Research Institute for Pediatric Oncology, Hematology and Transplantation, First Pavlov State Medical University of St. Peterburg, Saint Petersburg, Russia*
[e] *Laboratory of the Mosaics of Autoimmunity, Saint-Petersburg University, Saint Petersburg, Russia*
[f] *Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, Israel*
[g] *Sackler Faculty in Medicine, Sheba Medical Center, Tel-Aviv University, Israel*
E-mail address: tkachenie@mail.ru (O. Tkachenko).

[*] Corresponding author at: Center for Molecular Medicine, First Pavlov State Medical University of St. Peterburg, L'va Tolstogo str. 6-8, Saint Petersburg 197022, Russia.