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ORIGINAL ARTICLE

Human leucocyte antigen (HLA) class I and II typing in Belgian multiple sclerosis patients

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Abstract This is one of the first studies to compare the frequencies of different human leucocyte antigen (HLA) class I and II alleles and haplotype HLA-DRB1*15-DQB1*06 in a cohort of 119 patients with multiple sclerosis (MS) and a cohort of 124 healthy controls in Belgium. An association with MS was found for the HLA-DRB1*15 (odds ratio [OR] 2.60 [95% confidence interval (CI) 1.51–4.50]) and HLA-DQB1*06 (OR 1.97 [95% CI 1.18–3.29]) alleles, and for haplotype DRB1*15-DQB1*06 (OR 2.63 [95% CI 1.52–4.56]). The HLA-B*07 allele also tended to be more frequent in MS patients (OR 1.46 [95% CI 0.80–2.65]) and more frequent among MS patients with than in those without the HLA-DRB1*15 allele (26/54 [48.1%] versus 6/65 [9.2%]; p value <0.0001). Other alleles were underrepresented in MS patients, such as the HLA-DRB1*07 (OR 0.39 [95% CI 0.21–0.73]) and HLA-A*02 (OR 0.56 [95% CI 0.34–0.94]), showing a protective role against the disease. The HLA-B*44 (OR 0.58 [95% CI 0.31–1.09]) and HLA-DRB1*04 (OR 0.75 [95% CI 0.42–1.34]) alleles tended to be less frequent in MS patients. Altogether, the significant results observed in this population are in line with those from other countries and confirm that propensity to MS can be due to a complex presence of various HLA class I and class II alleles.

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Introduction

Multiple sclerosis (MS) is a common autoimmune neurological chronic disease, mostly affecting young adults [1]. The causative agents for MS are still unclear, but it is well established that genetic predispositions combined with environmental factors play a central role in the development of the disease [1–6]. Even though a recent study analyzing samples from almost 30,000 MS patients has identified 110 MS risk variants at 103 discrete loci outside the major histocompatibility complex (MHC) [7], the genetic susceptibility to MS is mainly determined by human leucocyte antigens (HLA), a cluster of genes located within the MHC on the short arm of chromosome 6 at p21.3 [3, 8]. In almost all populations studied, MS was found to be associated with HLA class II risk alleles [3, 8–16]: mainly, the DR15 specificity and its individual alleles (DRB1*15:01-DQA1*01:02-DQB1*06:02) [3, 16–19], but also other class II risk alleles (HLA-DRB1*13:03, HLA-DRB1*03:01, HLA-DRB1*08:01 and HLA-DQB1*03:02) as shown by the high-resolution map of HLA genetic risk that was recently built from the data of 17,465 MS cases and 30,385 controls [16]. Although considered as secondary to DR15 contribution, HLA class I alleles could also be associated with reduced (HLA-A*02:01, HLA-B*44:02, HLA-B*38:01 and HLA-B*55:01) or increased (HLA-A*03, HLA-B*07) susceptibility to MS [16, 20, 21]. Among class II risk alleles and class I protective alleles, the recent refinement study has identified two interactions that modulated the risk of MS: HLA-DQA1*01:01–HLA-DRB1*15:01 and HLA-

DQB1*03:01–HLA-DQB1*03:02 [16]. Here, we present the results of a study that compared the incidence of specific HLA alleles and haplotypes in a cohort of MS patients and a cohort of healthy controls in Belgium, where the disease affects about 10,000 people.

Methods

Study population

This study included 119 consecutive patients with MS who were followed at the Hôpital Erasme, Faculty of Medicine, Université Libre de Bruxelles, Belgium. All patients were diagnosed with MS according to the criteria proposed by McDonald et al. [22]. Patients with relapsing/remitting MS (RRMS), primary progressive MS (PPMS) or secondary progressive MS (SPMS) were included in the study. As control population, we used data from 124 anonymized consecutive healthy organ donors at the Hôpital Erasme for whom the HLA typing of studied loci was available. The study was approved by the local ethics committee (Approval No.: P2013/098/B406201316929).

HLA typing

HLA typing was performed on DNA extracted from peripheral blood mononuclear cells, by low- to intermediate-resolution polymerase chain reaction using sequence-specific oligonucleotides (PCR-SSO). Reverse dot blotting was carried out on a nylon membrane containing immobilized sequence-specific oligonucleotide probes used for the typing of HLA class I (HLA-A*02, HLA-B*07, HLA-B*44) and HLA class II (HLA-DRB1*15, HLA-DRB1*04, HLA-DRB1*07, HLA-DQB1*06) alleles (INNO-LiPA®, Fujirebio).

Statistical methods

The allele carrier frequencies were determined by direct counting and calculated as the number of participants carrying the specific allele (either at homozygous or heterozygous status) divided by the total number of participants. Comparisons of frequencies for the HLA-DRB1*15, HLA-DRB1*04, HLA-DRB1*07, HLA-A*02, HLA-B*44, HLA-B*07 and HLA-DQB1*06 alleles, and the DRB1*15-DQB1*06 haplotype between the MS patients and the controls were carried out using Chi-square test. Associations of particular alleles with MS were expressed as odds ratios (ORs) with 95% confidence intervals (95% CIs). For every comparison, p values <0.05 were considered to be statistically significant. All p values were based on two-tailed tests. Bonferroni's method was used for correction by multiplying the p value obtained by the total number of alleles considered at each locus. Statistical analysis was performed using STATA 12.

Results

Characteristics of participants

The demographic characteristics of the 119 MS patients and 124 healthy controls were comparable. This study included 79 women and 40 men with MS. Among these patients, 105 had RRMS, 8 had SPMS, and 6 had PPMS. The mean age of the MS patients was 44 years.

Frequency of HLA alleles

The frequencies of HLA class I and class II alleles in patients with MS and in the control population are shown in Table 1. The HLA-DRB1*15 allele (OR 2.60 [95% CI 1.51–4.50]), the HLA-DQB1*06 allele (OR 1.97 [95% CI 1.18–3.29]) and the haplotype DRB1*15-DQB1*06 (OR 2.63 [95% CI 1.52–4.56]) were more frequent in patients with MS. Although not statistically significant, the HLA-B*07 allele also tended to be more frequent in MS patients (OR 1.46 [95% CI 0.80–2.65]). Moreover, the HLA-B*07 allele was more frequent among MS patients with the HLA-DRB1*15 allele than in patients without the HLA-DRB1*15 allele (26/54 [48.1%] versus 6/65 [9.2%]; p value <0.0001).

Other alleles were found to be underrepresented in MS patients, like the HLA-DRB1*07 (OR 0.39 [95% CI 0.21–0.73]) and HLA-A*02 (OR 0.56 [95% CI 0.34–0.94]) alleles. Although no statistically significant effect of the HLA-B*44 (OR 0.58 [95% CI 0.31–1.09]) and HLA-DRB1*04 (OR 0.75 [95% CI 0.42–1.34]) alleles was observed, both alleles tended to be less frequent in MS patients when compared with the control group. Within the cohort of MS patients, no statistically significant difference was detected in terms of frequencies of HLA-A*02 (20/54 [37.0%] versus 22/65 [33.8%]; p value $= 0.72$) and HLA-B*44 (6/54 [11.1%] versus 14/65 [21.5%]; p value $= 0.13$) alleles between MS patients with and without the HLA-DRB1*15 allele.

Discussion

Different risk and protective alleles as well as combination of alleles modulating the risk for MS have been identified in MS patients across the world, stressing the importance of the genetic background in this disease. The present study was one of the first to investigate HLA class I and class II

Table 1 Phenotypic frequencies of HLA alleles in patients with MS and controls

Allele	MS group		Control group		OR (95% CI)	*p* value	*p* value$_{corr}$
	N	*n* (%)	*N*	*n* (%)			
A*02	119	42 (35.3)	124	61 (49.2)	0.56 (0.34–0.94)	**0.03**	**0.03**
B*07	119	32 (26.9)	124	25 (20.2)	1.46 (0.80–2.65)	0.22	
B*044	119	20 (16.8)	124	32 (28.8)	0.58 (0.31–1.09)	0.09	
DRB1*15	119	54 (45.4)	124	30 (24.2)	2.60 (1.51–4.50)	**0.001**	**0.003**
DRB1*04	119	28 (23.5)	124	36 (29.0)	0.75 (0.42–1.34)	0.33	
DRB1*07	119	18 (15.1)	124	39 (31.5)	0.39 (0.21–0.73)	**0.003**	**0.009**
DQB1*06	119	73 (61.3)	121	54 (44.6)	1.97 (1.18–3.29)	**0.009**	**0.009**
DRB1*15-DQB1*06	119	53 (44.54)	124	29 (23.39)	2.63 (1.52–4.56)	**0.001**	

Bonferroni's method was used for correction for multiple comparisons (*p* value$_{corr}$)

HLA human leucocyte antigen, *MS* multiple sclerosis, *N* number of participants tested in each group, *n (%)* number (percentage) of participants expressing the allele, *OR* odds ratio, *CI* confidence interval

Bold indicates that there is a statistically significant difference at the $p < 0.05$ level

alleles and their effect on MS susceptibility in Belgium. Two previous studies conducted in the 1990s showed that the DR2 haplotype (now preferentially covered by HLA-DR15 and HLA-DR16 serotype group, primarily recognizing gene products of the HLA-DRB1*15 and HLA-DRB1*16 allele groups) (relative risk [RR] = 3.71), the HLA-DRBl*1501 allele (RR = 2.47; *p* value = 0.0035), and the DRBl*1501-DQA1*0102 haplotype (RR = 2.65; *p* value = 0.0013) were positively associated with MS in Belgium [23, 24]. A more recent study conducted in 468 Belgian patients with MS and 482 controls confirmed the association of the HLA-DRB1*1501 allele with MS (OR 2.67 [95% CI 2.11–3.38]; p value $= 5 \times 10^{-21}$) [25]. Moreover, 313 cases and 1705 controls from Belgium were included in the recent refinement study, which has built a high-resolution map of HLA genetic risk and has assessed interactions involving classical HLA alleles [16]. The significant results observed in the present study are in line with these previous findings and with other studies conducted in other countries, and confirm the complex role of HLA class I and II genes.

Our results confirmed that HLA class II alleles are associated with MS risk. The HLA-DRB1*15 allele and the DRB1*15-DQB1*06 haplotype were clearly associated with the disease, which is in line with the results of broader studies conducted in Europe, and especially in Caucasian populations [3, 11, 12, 14, 16, 23, 25–30]. The recently published fine-mapping study confirmed that MS risk was dominated by the HLA-DRB1*15:01 (OR 3.92, p value $= 2 \times 10^{-686}$) allele and suggested that the HLA-DQB*06:02–HLA-DRB1*15:01 haplotype was associated with younger age of disease onset [16]. A positive association was also found for the HLA-DQB1*06 allele, in accordance with previous studies conducted in 282 patients with MS in Slovakia (OR 1.99 [95% CI 1.38–2.87]) [12], in 94 MS patients compared with 98 healthy patients in Italy (DQB1*06:02; RR = 3.32) [31] and in 149 patients with MS in Spain (DQB1*06:02; OR 3.1 [95% CI 1.9–5.2]) [32]. Previous association studies performed in African Americans to better localize the HLA gene responsible for MS susceptibility showed that the DRB1*1501 disease associations were independent of DQB1*0602, indicating a primary role for the DRB1 locus in MS and a potential modulating influence of the DQB1 locus on clinical outcome [19]. In our study, the frequency of HLA-B*07 allele tended to be higher in MS patients, although the association was not significant, and this allele was more frequent among MS patients with the HLA-DRB1*15 allele than in patients without the HLA-DRB1*15 allele. This observation is in line with a previous study that found an increased frequencies of HLA-B*0702 in MS patients (secondary to DRB1*15, DQB1*06) [33]. The association of MHC class I alleles with susceptibility to MS supports a possible role of certain immune cell types, such as $CD8^+$ T cells, in the onset of MS [20]. In a previous study, $CD8^+$ T cells recognizing Epstein Barr virus-derived peptides (in the context of HLA-A*02 or HLA-B*07) tended to be more frequently observed in MS patients than in controls [34].

In our study, other alleles were underrepresented in MS patients compared with healthy controls. The HLA-DRB1*07 allele had a protective role against MS development, confirming the results of previous studies conducted in 282 patients with MS in Slovakia (OR 0.53 [95% CI 0.34–0.83]) [12], in 1784 patients from Scandinavia [9], and a previous meta-analysis in Caucasians [11]. The HLA class I HLA-A*02 allele was also underrepresented in patients with MS; these results are in line with the recently published fine-mapping study (OR 0.67, p value $= 7.8 \times 10^{-70}$) [16] and remind of previous studies conducted in 532 patients with MS in the USA (OR

0.67 [95% CI 0.55–0.81) [20], 1273 Italian MS patients (OR 0.61 [95% CI 0.51–0.72]) [35], Portuguese MS patients [36], 1084 Swedish patients (OR 0.63; p value $= 7 \times 10^{-12}$) [37] and 200 Swedish patients (OR 0.52; p value $= 0.0015$) [33]. Although the effect was not significant, the HLA-B*44 allele tended to be less frequent in MS patients, which is in line with the results of the recent fine-mapping study (OR 0.78, p value $= 4.7 \times 10^{-17}$) [16] and a previous study showing that this HLA class I allele reduced the susceptibility to MS (OR 0.62 [95% CI 0.48–0.80]) [20]. Finally, the HLA-DRB1*04 allele also tended to be less frequent in MS patients when compared with controls, which confirmed the results of a study previously conducted in Spain [32].

Altogether, these results confirm that the propensity to MS can be due to a complex presence of various HLA class I and class II alleles. The frequency of different HLA alleles playing a role in MS observed in this study conducted in Belgian patients shows that while some HLA class I and class II alleles are associated with MS risk, especially the HLA-DRB1*15 and HLA-DQB1*06 alleles and the haplotype DRB1*15-DQB1*06, others confer protection against MS, especially the HLA-A*02 and HLA-DRB1*07 alleles.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

Ethical approval The study was approved by the local ethics committee (Approval No.: P2013/098/B406201316929).

References

1. Pugliatti M, Rosati G, Carton H, Riise T, Drulovic J, Vecsei L, Milanov I (2006) The epidemiology of multiple sclerosis in Europe. Eur J Neurol 13:700–722. doi:10.1111/j.1468-1331.2006.01342.x
2. Evans C, Beland SG, Kulaga S, Wolfson C, Kingwell E, Marriott J, Koch M, Makhani N, Morrow S, Fisk J, Dykeman J, Jette N, Pringsheim T, Marrie RA (2013) Incidence and prevalence of multiple sclerosis in the Americas: a systematic review. Neuroepidemiology 40:195–210. doi:10.1159/000342779
3. International Multiple Sclerosis Genetics Consortium, Wellcome Trust Case Control Consortium, Sawcer S, Hellenthal G, Pirinen M, Spencer CC, Patsopoulos NA, Moutsianas L, Dilthey A, Su Z, Freeman C, Hunt SE, Edkins S, Gray E, Booth DR, Potter SC, Goris A, Band G, Oturai AB et al (2011) Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. Nature 476:214–219. doi:10.1038/nature10251
4. Koch-Henriksen N, Sorensen PS (2010) The changing demographic pattern of multiple sclerosis epidemiology. Lancet Neurol 9:520–532. doi:10.1016/S1474-4422(10)70064-8
5. Oksenberg JR, Baranzini SE, Sawcer S, Hauser SL (2008) The genetics of multiple sclerosis: SNPs to pathways to pathogenesis. Nat Rev Genet 9:516–526. doi:10.1038/nrg2395
6. Kamm CP, Uitdehaag BM, Polman CH (2014) Multiple sclerosis: current knowledge and future outlook. Eur Neurol 72:132–141. doi:10.1159/000360528
7. Beecham AH, Patsopoulos NA, Xifara DK, Davis MF, Kemppinen A, Cotsapas C, Shah TS, Spencer C, Booth D, Goris A, Oturai A, Saarela J, Fontaine B, Hemmer B, Martin C, Zipp F, D'Alfonso S, Martinelli-Boneschi F, Taylor B et al (2013) Analysis of immune-related loci identifies 48 new susceptibility variants for multiple sclerosis. Nat Genet 45:1353–1360. doi:10.1038/ng.2770
8. Dyment DA, Herrera BM, Cader MZ, Willer CJ, Lincoln MR, Sadovnick AD, Risch N, Ebers GC (2005) Complex interactions among MHC haplotypes in multiple sclerosis: susceptibility and resistance. Hum Mol Genet 14:2019–2026. doi:10.1093/hmg/ddi206
9. Link J, Kockum I, Lorentzen AR, Lie BA, Celius EG, Westerlind H, Schaffer M, Alfredsson L, Olsson T, Brynedal B, Harbo HF, Hillert J (2012) Importance of human leukocyte antigen (HLA) class I and II alleles on the risk of multiple sclerosis. PLoS One 7:e36779. doi:10.1371/journal.pone.0036779
10. Ramagopalan SV, Morris AP, Dyment DA, Herrera BM, DeLuca GC, Lincoln MR, Orton SM, Chao MJ, Sadovnick AD, Ebers GC (2007) The inheritance of resistance alleles in multiple sclerosis. PLoS Genet 3:1607–1613. doi:10.1371/journal.pgen.0030150
11. Zhang Q, Lin CY, Dong Q, Wang J, Wang W (2011) Relationship between HLA-DRB1 polymorphism and susceptibility or resistance to multiple sclerosis in Caucasians: a meta-analysis of non-family-based studies. Autoimmun Rev 10:474–481. doi:10.1016/j.autrev.2011.03.003
12. Michalik J, Cierny D, Kantorova E, Kantorova D, Juraj J, Parnicka Z, Kurca E, Dobrota D, Lehotsky J (2015) The association of HLA-DRB1 and HLA-DQB1 alleles with genetic susceptibility to multiple sclerosis in the Slovak population. Neurol Res 37:1060–1067
13. Hauser SL, Oksenberg JR, Lincoln R, Garovoy J, Beck RW, Cole SR, Moke PS, Kip KE, Gal RL, Long DT (2000) Interaction between HLA-DR2 and abnormal brain MRI in optic neuritis and early MS. Optic Neuritis Study Group. Neurology 54:1859–1861
14. Zivadinov R, Uxa L, Zacchi T, Nasuelli D, Ukmar M, Furlan C, Pozzi-Mucelli R, Tommasi MA, Locatelli L, Ulivi S, Bratina A, Bosco A, Grop A, Cazzato G, Zorzon M (2003) HLA genotypes and disease severity assessed by magnetic resonance imaging findings in patients with multiple sclerosis. J Neurol 250:1099–1106. doi:10.1007/s00415-003-0164-7
15. Cocco E, Murru R, Costa G, Kumar A, Pieroni E, Melis C, Barberini L, Sardu C, Lorefice L, Fenu G, Frau J, Coghe G, Carboni N, Marrosu MG (2013) Interaction between HLA-DRB1-DQB1 haplotypes in Sardinian multiple sclerosis population. PLoS One 8:e59790. doi:10.1371/journal.pone.0059790
16. Moutsianas L, Jostins L, Beecham AH, Dilthey AT, Xifara DK, Ban M, Shah TS, Patsopoulos NA, Alfredsson L, Anderson CA, Attfield KE, Baranzini SE, Barrett J, Binder TM, Booth D, Buck D, Celius EG, Cotsapas C, D'Alfonso S et al (2015) Class II HLA interactions modulate genetic risk for multiple sclerosis. Nat Genet 47:1107–1113. doi:10.1038/ng.3395
17. Miretti MM, Walsh EC, Ke X, Delgado M, Griffiths M, Hunt S, Morrison J, Whittaker P, Lander ES, Cardon LR, Bentley DR, Rioux JD, Beck S, Deloukas P (2005) A high-resolution linkage-disequilibrium map of the human major histocompatibility

complex and first generation of tag single-nucleotide polymorphisms. Am J Hum Genet 76:634–646. doi:10.1086/429393
18. Hauser SL, Oksenberg JR (2006) The neurobiology of multiple sclerosis: genes, inflammation, and neurodegeneration. Neuron 52:61–76. doi:10.1016/j.neuron.2006.09.011
19. Oksenberg JR, Barcellos LF, Cree BA, Baranzini SE, Bugawan TL, Khan O, Lincoln RR, Swerdlin A, Mignot E, Lin L, Goodin D, Erlich HA, Schmidt S, Thomson G, Reich DE, Pericak-Vance MA, Haines JL, Hauser SL (2004) Mapping multiple sclerosis susceptibility to the HLA-DR locus in African Americans. Am J Hum Genet 74:160–167. doi:10.1086/380997
20. Healy BC, Liguori M, Tran D, Chitnis T, Glanz B, Wolfish C, Gauthier S, Buckle G, Houtchens M, Stazzone L, Khoury S, Hartzmann R, Fernandez-Vina M, Hafler DA, Weiner HL, Guttmann CR, De Jager PL (2010) HLA B*44: protective effects in MS susceptibility and MRI outcome measures. Neurology 75:634–640. doi:10.1212/WNL.0b013e3181ed9c9c
21. Hollsberg P, Hansen HJ, Haahr S (2003) Altered CD8+ T cell responses to selected Epstein–Barr virus immunodominant epitopes in patients with multiple sclerosis. Clin Exp Immunol 132:137–143
22. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, Fujihara K, Havrdova E, Hutchinson M, Kappos L, Lublin FD, Montalban X, O'Connor P, Sandberg-Wollheim M, Thompson AJ, Waubant E, Weinshenker B, Wolinsky JS (2011) Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 69:292–302. doi:10.1002/ana.22366
23. Vandevyver C, Buyse I, Philippaerts L, Ghabanbasani Z, Medaer R, Carton H, Cassiman JJ, Raus J (1994) HLA and T-cell receptor polymorphisms in Belgian multiple sclerosis patients: no evidence for disease association with the T-cell receptor. J Neuroimmunol 52:25–32
24. Ghabanbasani MZ, Gu XX, Spaepen M, Vandevyver C, Raus J, Marynen P, Carton H, Cassiman JJ (1995) Importance of HLA-DRB1 and DQA1 genes and of the amino acid polymorphisms in the functional domain of DR beta 1 chain in multiple sclerosis. J Neuroimmunol 59:77–82
25. Goris A, Walton A, Ban M, Dubois B, Compston A, Sawcer S (2008) A Taqman assay for high-throughput genotyping of the multiple sclerosis-associated HLA-DRB1*1501 allele. Tissue Antigens 72:401–403. doi:10.1111/j.1399-0039.2008.01101.x
26. Masterman T, Ligers A, Olsson T, Andersson M, Olerup O, Hillert J (2000) HLA-DR15 is associated with lower age at onset in multiple sclerosis. Ann Neurol 48:211–219
27. Kouri I, Papakonstantinou S, Bempes V, Vasiliadis HS, Kyritsis AP, Pelidou SH (2011) HLA associations with multiple sclerosis in Greece. J Neurol Sci 308:28–31. doi:10.1016/j.jns.2011.06.037
28. Romero-Pinel L, Pujal JM, Martinez-Yelamos S, Gubieras L, Matas E, Bau L, Torrabadella M, Azqueta C, Arbizu T (2011) HLA-DRB1: genetic susceptibility and disability progression in a Spanish multiple sclerosis population. Eur J Neurol 18:337–342. doi:10.1111/j.1468-1331.2010.03148.x
29. Ballerini C, Guerini FR, Rombola G, Rosati E, Massacesi L, Ferrante P, Caputo D, Talamanca LF, Naldi P, Liguori M, Alizadeh M, Momigliano-Richiardi P, D'Alfonso S (2004) HLA-multiple sclerosis association in continental Italy and correlation with disease prevalence in Europe. J Neuroimmunol 150:178–185. doi:10.1016/j.jneuroim.2004.01.015
30. Allen M, Sandberg-Wollheim M, Sjogren K, Erlich HA, Petterson U, Gyllensten U (1994) Association of susceptibility to multiple sclerosis in Sweden with HLA class II DRB1 and DQB1 alleles. Hum Immunol 39:41–48
31. Ciusani E, Allen M, Sandberg-Wollheim M, Eoli M, Salmaggi A, Milanese C, Nespolo A, Gyllensten U (1995) Analysis of HLA-class II DQA1, DQB1, DRB1 and DPB1 in Italian multiple sclerosis patients. Eur J Immunogenet 22:171–178
32. Fernandez O, Fernandez V, Alonso A, Caballero A, Luque G, Bravo M, Leon A, Mayorga C, Leyva L, de Ramon E (2004) DQB1*0602 allele shows a strong association with multiple sclerosis in patients in Malaga, Spain. J Neurol 251:440–444. doi:10.1007/s00415-004-0350-2
33. Fogdell-Hahn A, Ligers A, Gronning M, Hillert J, Olerup O (2000) Multiple sclerosis: a modifying influence of HLA class I genes in an HLA class II associated autoimmune disease. Tissue Antigens 55:140–148
34. Zivadinov R, Weinstock-Guttman B, Zorzon M, Uxa L, Serafin M, Bosco A, Bratina A, Maggiore C, Grop A, Tommasi MA, Srinivasaraghavan B, Ramanathan M (2009) Gene-environment interactions between HLA B7/A2, EBV antibodies are associated with MRI injury in multiple sclerosis. J Neuroimmunol 209:123–130. doi:10.1016/j.jneuroim.2009.01.023
35. Bergamaschi L, Leone MA, Fasano ME, Guerini FR, Ferrante D, Bolognesi E, Barizzone N, Corrado L, Naldi P, Agliardi C, Dametto E, Salvetti M, Visconti A, Galimberti D, Scarpini E, Vercellino M, Bergamaschi R, Monaco F, Caputo D et al (2010) HLA-class I markers and multiple sclerosis susceptibility in the Italian population. Genes Immun 11:173–180. doi:10.1038/gene.2009.101
36. Silva AM, Bettencourt A, Pereira C, Santos E, Carvalho C, Mendonca D, Costa PP, Monteiro L, Martins B (2009) Protective role of the HLA–A*02 allele in Portuguese patients with multiple sclerosis. Mult Scler 15:771–774. doi:10.1177/1352458509104588
37. Brynedal B, Duvefelt K, Jonasdottir G, Roos IM, Akesson E, Palmgren J, Hillert J (2007) HLA-A confers an HLA-DRB1 independent influence on the risk of multiple sclerosis. PLoS One 2:e664. doi:10.1371/journal.pone.0000664