Author's response to reviews

Title: The importance of HLA DRB1 gene allele to clinical features and disability in patients with multiple sclerosis in Lithuania

Authors:

Renata Balnyte (rbalnyte@yahoo.com)
Daiva Rastenyte (daiva.rastenyte@lsmuni.lt)
Antanas Vaitkus (antanasyaitkus@lsmuni.lt)
Dalia Mickeviciene (daliaamickeviciene@gmail.com)
Erika Skrodeniene (erikas@takas.lt)
Astra Vitkauskiene (astra.vitkauskiene@lsmuni.lt)
Ingrida Uloziene (ingrida.uloziene@lsmuni.lt)

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Author's response to reviews: see over
Dear Reviewers,

Thank's for your remarks and comments.

My revisions:

1. “According to the studies held in the regions with a high prevalence of HLA DRB1*15 allele, it was related to an earlier course of the disease.” – we mean “According to the studies held in the regions with a high prevalence of HLA DRB1*15 allele, it was related to the earlier onset of the disease”.

2. We describe patients group in ‘Enrolment of the patients’- The clinical course was the relapsing - remitting (RR) in 60 patients, secondary-progressive (SP) – 48 and primary-progressive (PP) in 12 patients.

3. (44 (36.7%) men and 76 (63.3%) women).

4. Results: Present the separately Mean duration of symptoms for the RR and SP form “a half (50.0%) had the relapsing - remitting disease course”. What about other half? It should be noted in the text. – we corrected: Of 120 MS patients, 50.0% had the relapsing - remitting disease course, 40.0% - secondary-progressive, 10.0% - primary-progressive.

5. Associations of HLA DRB1 alleles with clinical features and disability of MS Patients

   It looks like the authors compared the age at onset between different alleles by pooling all the patients together. It should be written which patients they included in the comparison. The PP patients could have later disease onset compared to RR. – we corrected: The first symptoms of MS in patients with RR and PP courses of the disease and who had HLA DRB1*15 allele and HLA DRB1*13 allele, manifested at younger age (28.32 ± 5.49 yrs and 28.64 ± 6.24 yrs, respectively) than in those without these alleles (vs. 30.94 ± 8.43 yrs and 33.94 ± 9.25, respectively, p<0.05).

6. From the Table 2 is not clear what for is the chi square and p, for the comparison between RR and SP+PP? It should be clear, both in the text and the Table. We corrected- HLA DRB1*08 allele was more frequently found among the RR MS patients than among the patients with progressive forms (SP+PP) of MS (p=0.014), while HLA DRB1*15 allele was more prevalent among the patients with progressive MS forms (p<0.001).

7. “The lowest EDSS score during the last visit” doesn’t mean much, since someone has disease duration of 5 years and someone 15 years. The EDSS should be corrected for the disease duration. We corrected – we used „Two factors dispersion analysis” for this correction: The lowest EDSS score during the last visit was among the patients with HLA DRB1*08 allele compared with patients without this allele (EDSS score 3.15 ± 1.95 vs. 4.49 ± 1.96, p=0.006) and the highest ones among those with HLA DRB1*15 allele (EDSS score 4.60 ± 2.10 vs. 4.05 ± 1.94, p=0.047), but interactions between this alleles and disease duration to disability last visit revealed no significant.
8. Try also the same calculation with MSSS.- we don’t use this scale, therefore did not calculate.

9. Is EDSS in normal distribution? Why did you performed both parametric and nonparametric test (Table 3)? It usually isn’t, especially if you look it in whole patient group (with RR and SP). The table 3 does not explain much, since there is no disease duration for the period between diagnosis and last visit. –

We corrected and used cox regression models: Cox regression models were used to analyse impact of gender, age, disease duration and HLA DRB1 alleles for reaching and EDSS of 6, we included 82 patients, because 38 reached this outcome. Duration of the disease were independent and significant factors for disability to reach EDSS of 6 in all models with each newly added HLA DRB1 allele (excluding models with *03, *04 alleles, where disease duration had only marginal significance), but HLA DRB1*08 allele (OR = 0.18, 95%CI 0.039-0.8, p= 0.029) was demonstrated to be independent factor to take a longer time to reach an EDSS of 6, while HLA DRB1*01 allele (OR = 5.92, 95%CI 1.30-26.8, p=0.021) was related in a shorter time to reach and EDSS of 6.

10. The number of participants should be present, for the groups compared and presented in Figure (in the legend below the figure)

We corrected - HLA DRB1*15 allele frequencies were determined for MS patients in the cerebrospinal fluid was found in OGJ than those who are not found OGBs in the cerebrospinal fluid (80.6% vs. 64.2%, OR 2.3, CI 95% 1.017–5.301; p=0.043).

11. “We have previously shown that HLA-DRB1*15 and *08 alleles are strongly associated not only with disease risk in our population (13), but also HLA DRB1 alleles can influence disease course and disability.”

When previously with course and disability?

We corrected - We have previously shown that HLA-DRB1*15 and *08 alleles are strongly associated with disease risk in our population (13).

12. “Results of our study indicate that MS patients with HLA DRB1*15 allele had a higher frequency of progressive forms and disability,”, but, not significantly different

“...especially HLA DRB1*15 allele’s, role in MS.”

Not in MS, but in association with disease onset, progression or severity.

We corrected: Results of our study indicate that MS patients with progressive forms have more often HLA DRB1*15 allele, also this allele was related to younger age of the first symptoms and a higher disability, while in patients with relapsing-remitting form of MS HLA DRB1*08 allele was determined more frequently and these patients had lower disability.

13. There is no need for citing all the names of authors of the papers cited in the discussion. Try to make discussion more coherent, there are too many enumerations of different study, and is a bit hard to follow. The authors should add something about limitations of the study. The number of patients is relatively small.

The conclusion is too pretentious for study of this size. Try to stay within the significant results, and to suggest the replication in a bigger study, since it should be done.

We have revised the discussion and conclusions of the context of your comments. Language was corrected.