UDC 575
DOI: 10.2298/GENSR1103517V
Original scientific paper

HLA II CLASS ANTIGENS AND SUSCEPTIBILITY TO COELIAC DISEASE

Svetlana VOJVODIĆ, and Dušica ADEMOVIĆ-SAZDANIĆ

Institute for Blood Transfusion of Vojvodina, Department for laboratory testing, Tissue Typing Compartment, Novi Sad, Serbia

Vojvodić S. and D. Ademović - Sazdanić (2011): *HLA II class antigens and susceptibility to coeliac disease.* - Genetika, Vol 43, No. 3, 517-526.

Coeliac disease (CD) is a systemic autoimmune, complex and multifactorial disorder, which is caused by interactions between genetic and environmental factors. The only established genetic risk factors so far are the human leucocyte antigens. The aim of this study was to assess the distribution of II class human leukocyte antigens (HLA) in patients with coeliac disease and to investigate the susceptibility to coeliac disease in family members. We typed HLA DR and DQ antigens in 37 patients from Vojvodina with coeliac disease, 23 first-degree relatives, and 210 controls, serologically using standard lymphocytotoxicity technique. HLA DQ5(1), DQ6(1), DR11(5), DQ7(3), DQ2 and DR15(2) were the most common antigens in the control group. Frequency of HLA DQ2, DR3 and DR7 was higher in CD patients than in the control group. The relative risks for HLA

Corresponding author: Svetlana Vojvodić, Institute for Blood Transfusion of Vojvodina, Hajduk Veljkova 9a, 21000 Novi Sad, Tel.: +381 21 4877 963; fax: +381 21 4877 978, e-mail: ssvu@EUnet.rs

DQ2, DR3 and DR7 were 4.846, 6.986 and 2.106, respectively, while positive association was found between HLA DQ2 and DR3 and CD. Frequency of HLA DQ2, DR3 and DR16(2) was higher in first-degree relatives than in the control group while a positive association was found between HLA DQ2 and DR3. A negative association was found between HLA DQ5(1) and DQ6(1) in coeliac patients from Vojvodina and their relatives, in addition to HLA DR11(5) in the group of relatives (RR=0.363,PF=0.232). These findings indicate the impact of the HLA testing for CD in clinical practice in order to rule out the possibility to CD in doubtful cases or in at-risk subjects.

Key words: association, coeliac disease, Human Leukocyte Antigens

INTRODUCTION

Coeliac disease (CD) is a common, familial, autoimmune, multifactorial gastrointestinal disease defined as a permanent gluten-sensitive enteropathy characterized by malabsorption and mucosal injury of the small bowel. Symptomatology varies widely from absolute absence of symptoms to pronounced clinical, gastrointestinal, or extradigestive manifestations. It is caused by sensitivity to the dietary protein gluten, which is present in wheat, rye and barley. Symptoms include growth failure, abdominal pain, and diarrhea (VIDALES *et al.,* 2004; NEUHAUSEN *et al.,* 2001). CD can be present at any age and in different clinical forms such as classical, atypical, silent, or latent CD. Classical CD is characterized by chronic diarrhea, abdominal distention, vomiting, muscle wasting and failure to thrive. The timing of presentation of CD may be dependent on the amount and timing of gluten introduction to the diet. Atypical CD presents with extraintestinal manifestations such as unexplained iron deficiency anemia, short stature, osteoporosis, pubertal delay, dental enamel defects, and abnormalities in liver function tests (KULOGLU *et al*., 2008). Recent accurate epidemiologic studies have revealed that CD affects approximately 1% of the general population, both in Europe and in North America. The prevalence of the disease increases among patients with anemia or autoimmune diseases, with short stature, or with Down, Turner, or Williams syndrome. Moreover, CD clusters in families with a prevalence among first-degree relatives ranging from 2.8% to 17.2% in different series (MEGIORNI *et al*., 2009).CD shares many features with autoimmune disorders in general, such as a polygenic mode of inheritance, a strong association with HLA-DQ2 and HLA-DQ8 antigens, the production of a local inflammatory response (lymphocyte infiltration and cytokine production), the presence of autoantibodies in the circulation, female preponderance, and an association with other autoimmune diseases (KUMAR *et al*., 2001). Coeliac disease is caused by an inappropriate intestinal immune response to wheat gluten (consisting of the gliadin and glutenin subcomponents) and the related proteins of rye and barley. Patients with coeliac disease have gluten-reactive $CD4^+$ T cells in their small intestinal mucosa, but healthy controls do not. Most patients with coeliac disease carry the HLA-DQ2 variant DQ2.5, which is encoded by the

DQA1*0501 and DQB1*0201 genes of the DR3-DQ2 haplotype. Most of the few remaining patients express HLA-DQ8. The gluten-reactive T cells of patients with coeliac disease recognize a diverse set of gluten epitopes presented in context of DQ2.5 or DQ8 MHC molecules but not in the context of other MHC class II molecules expressed by the patients. 'Preferential' presentation of gluten peptides by the DQ2.5 and DQ8 molecules thus seems to explain the association of HLA with celiac disease (FALLANG *et al.,* 2009). The genetic influence in the pathogenesis of coeliac disease is indicated by its familial occurrence. Coeliac disease does not develop unless a person has alleles that encode for HLA-DQ2 or HLA-DQ8 proteins, products of two of the HLA genes. However, many people, most of whom do not have coeliac disease, carry these alleles; thus, their presence is necessary but not sufficient for the development of the disease. Studies in siblings and identical twins suggest that the contribution of HLA genes to the genetic component of coeliac disease is less than 50%. Several non-HLA genes that may influence susceptibility to the disease have been identified, but their influence has not been confirmed (GREEN and CELLIER, 2007). In this study, we investigated the frequency of the DR and DQ antigens in individuals with coeliac disease, their first-degree relatives and normal control subjects. We also determined a significant risk and protective factors in investigated groups. In this study, we aimed to determine whether measuring the at-risk HLA antigens can assist in diagnosis of coeliac disease in patients and in their relatives without coeliac disease.

MATERIALS AND METHODS

Subjects and methods

A total of 37 coeliac patients from Vojvodina were studied. Of all patients 70.27% were female and 29.72% male. At-risk subjects were first-degree relatives of patients with CD who presented with CD-associated symptoms (diarrhea, abdominal pain, and constipation) or without it. Two hundred and ten randomly selected healthy individuals from Vojvodina population served as healthy control subjects. The II class HLA typing was performed by microlymphocytotoxicity assay using T and B cells separated by monoclonal antibody labeled immunomagnetic particles (IMB) (VARTDAL *et al.,*1986).

Statistical analysis

HLA DR and DQ phenotype frequencies were calculated by direct counting method, using following formula: $A = n/N$, where n is number of persons with a given antigen and N is total number of persons studied (SHEN *et al.,*2008). Relative risk (RR) for measuring strenght of association with each II class HLA antigen was calculated by the Woolf′s method (ARMITAGE *et al*., 2002), by using following formula: $RR = \frac{P^{+} x C^{-}}{C^{+} x P^{-}}$, where is :

P^{+} = the number of patients who have a given antigen;

C^{-} = the number of healthy persons who do not have a given antigen;

P^- = the number of patients who do not have a given antigen;
C^+ = the number of healthy persons who have a given antigen.

When RR was higher than 1, we calculated the etiologic fraction, while for RR values less than 1, we calculated the preventive fraction. When several antigens with different allele frequencies are associated with the same disease, it is not possible to estimate which of them is more strongly associated with the disease itself solely by means of relative risk; that depends directly on the frequency of the antigen allele. A more accurate estimate of the strength of an association has been made by the calculation of the so-called etiologic fraction that detects among the different antigens associated with a certain disease, which antigen has the stronger genetic association with a hypothetical disease allele. The etiologic fraction (EF) or population attributable risk, was calculated according to the Green′s method, using following formula: $EF = \frac{(FAD - FAP)}{(1 - FAP)}$, where FAD is the frequency of a given HLA antigen in the subgroup of patients and FAP is the frequency of HLA antigen in the control group. The preventive fraction (PF), that gives the percentage of cases that can be prevented if a population is exposed to an intervention, compared to an unexposed population, was calculated according to following formula: $FP = \frac{(1 - RR)xf}{RRx(1 - f) + f}$, where RR is relative risk and f is the frequency of HLA antigen in the subgroup of patients (GREEN *et al*.,1982; CORAZZA *et al.,* 1985).

The association was considered positive if the calculated EFs were higher than 0.15 and negative if calculated PFs were more than 0.15. The Pearson χ^2 goodness-of-fit test was used to valuate Hardy-Weinberg genetic equilibrium for phenotypic data (ARMITAGE, *et al*., 2002).

RESULTS

The distribution of HLA DR and DQ types in CD patients, their first-degree realetives and controls is shown in Table 1. In the control group, HLA DQ5(1) (78.5%),DQ6(1) (45.7%), DR11(5) (36.6%), DQ7(3) (36.1%), DQ2(30%) and DR15(2) (29%) were the most common HLA types observed in II class HLA groups, respectively. In CD patients, HLA DQ2 (67.5%), DR3 (48.6%), DQ6(1) (32.4%), DQ7(3) (29.7%), DR7, DR11(5) and DQ15(2) with the same frequency (24.3%) were the most common HLA types observed in HLA groups DR and DQ, respectively.

In the group of first-degree relatives, the most common DR and DQ antigens were also DQ2 and DR3, both observed in 47.8% of relatives, following with DQ6(1) (34.7%), DQ7(3) and DR15(2) (26%), respectively. All of the HLA loci in CD patients, their relatives and controls were consistent with Hardy-Weinberg equilibrium. The results showing relative risk, etiologic and preventive fraction are ilustrated in Table 2.

Our results demonstrated that there were several HLA class II antigens associated with an increased risk of developing coeliac disease, such as: DQ2

(RR=4.846, EF=0.535), DR3 (RR=6.986, EF=0.361), respectively as well as DR7 (RR=2.106), but without significant association (EF=0.126). In the group of first-degree relatives, RR greater than 1 was found for DR3(RR=1.821, EF=0.351) and DQ2 (RR=1.230,EF=0.254), respectively. On the other hand, we observed significantly decreased frequency of DQ5(1) (RR=0.053,PF=0.742), (RR=0.075,PF=0.727) and DQ6(1) (RR=0.571,PF=0.194),(RR=0.632,PF=0.167) in both investigated groups, as well as DR11(5) (RR=0.363, PF=0.232) in the group of relatives, which reveals that they could be a possible protective factors in investigated groups.

Table 1. ***The distribution of HLA class II antigens in CD patients, their first-degree relatives and in controls***

Antigen	CD patients	Relatives	Controls
DR1	0.081	0.130	0.171
DR3	0.486	0.478	0.195
DR4	0.162	0.086	0.190
DR11(5)	0.243	0.173	0.366
DR12(5)	0	0	0.004
DR13(6)	0.081	0.217	0.166
DR14(6)	0.027	0	0.080
DR7	0.243	0.086	0.133
DR8	0.027	0	0.038
DR9	0	0	0.009
DR10	0	0	0.023
DR15(2)	0.243	0.260	0.290
DR16(2)	0.054	0.086	0.066
Blank	0.351	0.478	0.261
DQ5(1)	0.162	0.217	0.785
DQ6(1)	0.324	0.347	0.457
DQ2	0.675	0.478	0.300
DQ7(3)	0.297	0.260	0.361
DQ8(3)	0.135	0.086	0.152
DQ9(3)	0	0	0.009
DQ4	0.027	0	0.033
Blank	0.378	0.608	0.376

Table 2. Coeliac disease susceptibility with HLA class II antigens

Antigen	CD patients			Relatives		
	RR	EF	PF	RR	EF	PF
DR1	0.427	-	0.098	0.728	-	0.045
DR3	6.986	0.361*	-	1.821	0.351*	-
DR4	0.986	-	0.002	0.402	-	0.112
DR11(5)	0.737	-	0.078	0.363	-	0.232**
DR12(5)	-	-	-	-	-	-
DR13(6)	0.444	-	0.092	1.402	0.061	-
DR14(6)	0.322	-	0.052	-	-	-
DR7	2.106	0.126	-	0.616	-	0.050
DR8	0.721	-	0.009	-	-	-
DR9	-	-	-	-	-	-
DR10	-	-	-	-	-	-
DR15(2)	0.791	-	0.059	0.862	-	0.039
DR16(2)	0.813	-	0.012	1.338	0.021	-
DQ5(1)	0.053	-	0.742**	0.075	-	0.727**
DQ6(1)	0.571	-	0.194**	0.632	-	0.167**
DQ2	4.846	0.535*	-	1.230	0.254*	-
DQ7(3)	0.874	-	0.040	0.622	-	0.136
DQ8(3)	0.873	-	0.019	0.461	-	0.090
DQ9(3)	-	-	-	-	-	-
DQ4	0.815	-	0.004	-	-	-

**=negative association (PF>0.15)

*=positive association(EF>0.15)

DISCUSSION

The genesis and development of CD depend on both genetic and environmental factors. Coeliac disease is an immune-mediated disease where genetic predisposition plays a key role and considerable progress has been made recently in identifying genes that are responsible for CD predisposition. It is well known that CD is strongly associated with specific HLA class II genes known as ***HLA-DQ2*** and ***HLA-DQ8*** located on chromosome 6p21. Approximately 95% of CD patients express ***HLA-DQ2***, and the remaining patients are usually ***HLA-DQ8*** positive. However, the ***HLA-DQ2*** allele is common and is carried by approximately 30% of Caucasian individuals. Thus, ***HLA-DQ2*** or ***HLA-DQ8*** is necessary for disease development but is not sufficient for disease development; its estimated risk effect is only 36-53% (MOUSTAKAS *et al.,* 2000; VIDALES *et al.,* 2004; LIU *et al.,* 2002; VOLTA and VILLANACCI, 2011; MAKI *et al.,* 2003). The genetic susceptibility to CD is confirmed by its high familial incidence (about 10% of first degree relatives of coeliac patients are affected by the disease) and by its strict linkage with some human leukocyte antigen (HLA) class 2 alleles (up to 95% coeliacs are HLA-DQ2 positive with the typical heterodimer DQA1*0501/DQB1*0201, whereas the

remaining 5% are HLA-DQ8 positive HLA-DQB1*0302,(VOLTA and VILLANACCI, 2011). Despite numerous population studies supporting the idea that the HLA region plays the main role in the genetic susceptibility to many multifactorial autoimmune diseases, not enough familial data in the population of Vojvodina are available to quantify the relative contribution of HLA and other genes in the development of these diseases. We presented here a group of paediatric coeliac cases and their relatives together with data from the literature, with the double aim to assess the HLA role on the increased risks of disease in the CD patients and their siblings and to find out the II HLA class specificities that may play a true protective role for the development of coeliac disease. Our results showed that DR3, DQ2 and DR7 were found in higher frequencies in coeliac patients and DR3 and DQ2 in their relatives. Firstly, the higher frequency of HLA B8 in celiac patients has been reported. Later, it was observed that frequency of HLA DR3 is also increased and that the association with HLA B8 simply reflected the linkage disequilibrium between the alleles that coded for these antigens (KULOGLU *et al.,* 2008). In our study, frequency of HLA DQ2 in CD was 67.5% and 47.8% in relatives, which is similar to other reports (MAKI *et al*., 2003; KULOGLU *et al*., 2008; PETRONZELLI *et al.,* 1997). Our study confirmed the strong association of CD patients and their relatives with HLA DQ2 and DR3, which is also in accordance with the results of previous studies (PETRONZELLI *et al.,* 1997; MAKI *et al.,* 2003; VOLTA and VILLANACCI, 2011). The association between HLA DR3/DR7 and CD is explained by the linkage disequilibrium of these alleles with DQ2 allele (CORAZZA *et al.,* 1985; VOJVODIĆ and ADEMOVIĆ-SAZDANIĆ, 2009; VOJVODIĆ and ADEMOVIĆ-SAZDANIĆ, 2011a; VOJVODIĆ and ADEMOVIĆ-SAZDANIĆ, 2011b). Although in our study, the RR for HLA DR7 in coeliac patients was higher than 1, we did not demonstrate an association between DR7 and CD (EF=0.126). The difference of HLA distribution and consequently RR value, may be associated with genetic heterogeneity and geographic region.The positive association between DR3 and DQ2 and susceptibility to coeliac disease is also found in the group of first-degree relatives: for DQ2 (RR=1.230, EF=0.254) and for DR3 (RR=1.821, EF=0.351), but unlike in CD patients, in the group of relatives, DR3 has the strongest genetic association with coeliac disease, since in CD patients EF=0.361 for DR3 and EF=0.535 for DQ2. This findings confirm the previous reports that the first relatives are subjects at risk for CD developing (MEGIORNI *et al*.,2009; VOLTA and VILLANACCI, 2011; LIU *et al.,* 2002). Our results have shown the existence of negative association of DQ5(1) and DQ6(1) antigens with coeliac disease patients as well as their relatives. Stronger negative association was found for DQ5(1) than DQ6(1) in both of groups since PF=0.742 and PF=0.727 for DQ5(1) vs PF=0.194 and PF=0.167 for DQ6(1), respectively. Additionally, in the group of first-degree relatives it is observed that DR11(5) has the lower frequency than control group (RR=0.363, PF=0.232) with significant negative association, showing how much are relatives protected from the coeliac disease by these possible protective HLA factors.

CONCLUSION

In conclusion, this study demonstrated that HLA types are important in the development of CD and DR3 and DQ2 were the most frequent antigens in patients with CD and their relatives in Vojvodina. Our study also showed that a relation may exist between possible protective HLA types and disease development. This result confirms that the HLA antigens are an important genetic background to CD and that the detection of HLA II class antigens can help reinforce or exclude the diagnosis of gluten sensitivity.

ACKNOWLEDGEMENTS

Authors are grateful to staff of Tissue Typing Compartment in the Institute for blood transfusion of Vojvodina, for their great contribution in sample colection and histocompatibility testing.

Received, Juny 16rd2011
Accepted, November 17th 2011

REFERENCES

ARMITAGE, P., G.BERRY and J.N.S. MATTHEWS (2002): Statistical Methods in Medical Research (4th edition). Blackwell Science, Oxford.

CORAZZA, G.R., P. TABACCHI, M.FRISONI, C. PRATI and G. GASBARRINI(1985): DR and non-DR Ia allotypes are associated with susceptibility to coeliac disease. Gut, Volume *26*, pp. 1210-1213.

FALLANG, L-E., E. BERGSENG, K. HOTTA, A. BERG-LARSEN, C-Y. KIM and L.M.SOLLID (2009): Differences in the risk of celiac disease associated with HLA-DQ 2.5 or HLA-DQ2.2 are related to sustained gluten antigen presentation. Nature Immunology, Volume 10, pp.1096-1102.

GREEN, A.(1982): The epidemiologic approach to studies of association between HLA and disease.II Estimation of absolute risk, etiologic and preventive fraction. Tissue Antigens, Volume 19, pp. 259-268.

GREEN, P.H.R. and C.CELLIER.(2007): Celiac disease. The New England Journal of Medicine, Volume *357*, pp.1731-1743.

KULOGLU, Z., T.DOGANCI,A.KANSU, F. DEMIRCEKEN, M. DUMAN, H. TUTKAK, A. ENSARI and N. GIRGIN (2008): HLA types in Turkish children with celiac disease. *The* Turkish Journal of Pediatrics, Volume *50*, pp.515-520.

KUMAR, V., M. RAJADHYAKSHA and J. WORTSMAN (2001): Celiac Disease-Associated Autoimmune Endocrinopathies.Clinical and diagnostic laboratory immunology, Volume *8*, pp. 678–685.

LIU, J., S-H. JUO, P. HOLOPAINEN, J. TERWILLIGER, X. TONG, A. GRUNN, M. BRITO, P. GREEN, K. MUSTALAHI, M. MAKKI, T. C. GILLIAM and J. PARTANEN (2002): Genomewide Linkage Analysis of Celiac Disease in Finnish Families. American Journal of Human Genetics, Volume *70*, pp.51–59.

MAKI, M., K. MUSTALAHTI, J. KOKKONEN, P. KULMALA, M. HAAPLAHTI, T. KARTTUNEN, J.ILONEN,K. LAURILA, I. DAHLBOM, T. HANSSON, P. HOPFL and M. KNIP (2003): Prevalence of Celiac Disease among Children in Finland. The New England Journal of Medicine, Volume *348*, pp.2517-2524.

MEGIORNI, F., B. MORA, M. BONAMICO, M. BARBATO, R. NENNA, G. MAIELLA, P. LULLI and M. C. MAZZILLI (2009): HLA-DQ and risk gradient for celiac disease. Human Immunology , Volume *70*, pp.55-59.

MOUSTAKAS, A.K., Y. VAN DE WAL, J.ROUTSIAS, Y.M.C. KOOY, P. VAN VEELEN, J.W. DRIJFHOUT, F. KONING and G.K.PAPADOPOULOS (2000): Structure of celiac disease-associated HLA-DQ8 and non-associated HLA-DQ9 alleles in complex with two disease-specific epitopes. International Immunology, Volume *12,* pp.1157-1166.

NEUHAUSEN, S.L., M. FEOLO, J. FARNHAM, L. BOOK and J. J. ZONE (2001): Linkage analysis of HLA and candidate genes for celiac disease in a North American family-based study. BMC Medical Genetics*,* Volume *2*, pp.12-17.

PETRONZELLI, F., M. BONAMICO, P. FERRANTE, R. GRILLO, B. MORA, P. MARIANI, I. APOLLONIO, G. GEMME and M. C. MAZZILL.(1997): Genetic contribution of the HLA region to the familial clustering of coeliac disease. Annals of Human Genetics, Volume *61*,pp. 307-317.

SHEN, C., B. ZHU, M. LIU, S. LI (2008): Genetic Polymorphisms at HLA-A, -B, and -DRB1 Loci in Han Population of Xi'an City in China. Croatian Medical Journal, Volume *49*, pp. 476-482

VARTDAL, F., G. GAUDERNACK, S. FUNDERUD, A. BRATLIE, T. LEA, J. UGELSTAD, E. THORSBY (1986): HLA class I and II typing using cells positively selected from blood by immunomagnetic isolation -a fast and reliable technique.Tissue Antigens, Volume *28*, Issue 5, pp. 301–312.

VIDALES, M. C., P. ZUBILLAGA, I. ZUBILLAGA, and M. A. ALFONSO-SANCHEZ (2004): Allele and Haplotype Frequencies for HLA Class II (DQA1 and DQB1) Loci in Patients With Celiac Disease From Spain. Human Immunology*,* Volum*e 65*,pp. 352–358.

VOLTA, U. and V. VILLANACCI (2011): Celiac disease: diagnostic criteria in progress. *Cellular & Molecular Immunology*, Volume *8*, pp. 96–102.

VOJVODIĆ, S. and D. ADEMOVIĆ-SAZDANIĆ (2009): HLA Class II antigens and haplotypes in the Vojvodina population: relationship to other populations.Anthropologi*e,* Volume XLVII/1-2, pp.73-79.

VOJVODIĆ, S. and D. ADEMOVIĆ-SAZDANIĆ (2011a): Study of the HLA class II allele polymorphism and phylogenetic analysis in Vojvodina population. Russian Journal of Genetics, Volume *47*, pp.364-368.

VOJVODIĆ. S. and D. ADEMOVIĆ-SAZDANIĆ (2011b): HLA Class I and Class II Polymorphism in the Population of Vojvodina. Coll. Antropol , in press.

HLA ANTIGENI II KLASE I PREDISPOZICIJA ZA CELIJAKIJU

Svetlana VOJVODIĆ[1], Dušica ADEMOVIĆ-SAZDANIĆ[1]

Zavod za transfuziju krvi Vojvodine, Novi Sad, Srbija

I z v o d

Celijakija je sistemski autoimuni, kompleksni i multifaktorijalno uzrokovan poremećaj koji nastaje kao posledica interakcije genetskih i ekoloških faktora. Jedini potvrđeni genetski faktori rizika za sada su humani lukocitni antigeni. Cilj ovog rada je bio da se proceni distribucija II klase humanih leukocitnih antigena (HLA) kod bolesnika sa celijakijom i da ispita predispozicija za nastanak celijakije u članove njihovih porodica. Vršena je tipizacija HLA antigena DR i DQ lokusa kod 37 pacijenata iz Vojvodine obolelih od celijakije, 23 osobe u prvom stepenu srodstva kao i kod 210 zdrave osoba, serološki standardnim mikrolimfocitotoksičnim testom. HLA DQ5(1), DQ6(1), DR11(5), DQ7(3), DQ2 i DR15 (2) su najčešće zastupljeni antigeni u kontrolnoj grupi. Učestalost HLA DQ2, DR3 i DR7 je bila veća u bolesnika sa celijakijom nego u kontrolnoj grupi. Relativni rizik za HLA DQ2, DR3 i DR7 iznosi 4.846, 6.986 i 2.106, dok je pozitivna udruženost uočena između HLA DQ2 i DR3 i celijakije. Učestalost HLA DQ2, DR3 i DR16(2) bila je veća u osoba u prvom stepenu srodstva sa obolelim od celijakije nego u kontrolnoj grupi, dok je pozitivna asocijacija uočena između HLA DQ2 i DR3. Negativne asocijacije su uočene između HLA DQ5(1) i DQ6(1) i bolesnika sa celijakijom sa teritorije Vojvodine i njihovih srodnika, kao i HLA DR11(5) u grupi srodnika (RR = 0.363, RF = 0.232). Ovi nalazi ukazuju na značaj testiranja HLA antigena i njenu primenu u kliničkoj praksi kod osoba sa ispoljenim simptomima bolesti kao i mogućnost utvrđivanja rizika za nastanak bolesti kod članova njihovih familija.

Primljeno 14. VI. 2011.
Odobreno 17. XI. 2011.